Adolescent Psychosis

Clinical and Scientific Perspectives

Edited by
Ingrid Agartz and Runar Elle Smelror

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ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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ISBN: 978-0-323-89832-4

Publisher: Nikki P. Levy
Acquisitions Editor: Joslyn T. Chaiprasert-Paguio
Editorial Project Manager: Sam Young
Production Project Manager: Selvaraj Raviraj/Punithavathy Govindaradjane
Cover Designer: Mark Rogers

Typeset by TNQ Technologies

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Chapter 1

Introduction to psychotic disorders in adolescence

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Introduction

Psychotic disorders presenting in childhood or adolescence are often referred to as early-onset psychosis (EOP). EOP does not denote a recognized diagnostic entity but is a research term describing the spectrum of psychotic disorders that develop in children and adolescents before 18 years of age. The term "early-onset" was introduced by Werry et al. (1991) embracing childhood-onset (before 13 years of age) and adolescence-onset (from 13 through 17 years of age) psychotic disorders. Fig. 1.1 gives a hierarchical overview of EOP based on diagnoses from the fifth version of the Diagnostic

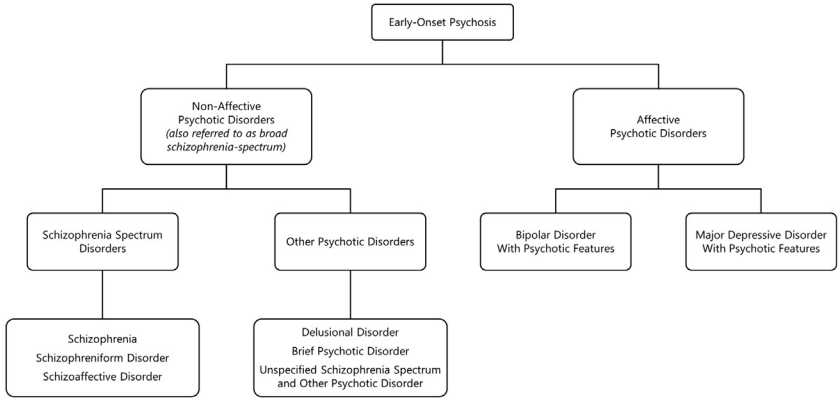

FIGURE 1.1 Hierarchical overview of early-onset psychotic disorders (EOP) based on DSM-5 diagnoses.

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00006-8

and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013).

In Table 1.1 we present diagnostic descriptions for the psychotic disorders included under EOP based on diagnoses from the DSM-5 and the 11th revision of the International Classification of Diseases (ICD-11) (World Health Organization, 2019).

Most studies of EOP have focused on schizophrenia, which is the most prevalent disorder among youth with EOP (75% of cases in a recent French study; Giannitelli et al., 2020). While the incidence of schizophrenia in childhood is very rare (less than 0.04%; Driver et al., 2020), the occurrence increases to about 0.6% during adolescence; Dalsgaard et al., 2020). Despite the relatively low incidence compared to other mental disorders (e.g., anxiety disorders have an incidence of about 6% before 18 years of age) (Dalsgaard et al., 2020), schizophrenia is nevertheless ranked as the second main cause of disease burden in late adolescence (Gore et al., 2011). See Chapter 2 for detailed information about incidence and prevalence, including the importance of sex differences.

Under the EOP umbrella, bipolar disorder with psychotic features is sorted under affective psychotic disorders. The clinical picture is dominated by intermittent periods of depressed or elevated mood (episodes of mania (bipolar I disorder) or hypomania (bipolar II disorder)) (see Table 1.1 for diagnostic descriptions). The incidence rate of bipolar disorder in childhood and adolescence is 0.08%, and it is almost twice as high in girls as in boys (Dalsgaard et al., 2020). Similar to schizophrenia the incidence of bipolar disorder also increases with age (Jensen & Steinhausen, 2016). When psychotic symptoms are considered part of a bipolar disorder, they are by definition related to affective episodes (mania or depression). Pavuluri and colleagues reported that the prevalence of psychotic symptoms varied between 16% and 87.5% in youth with bipolar disorder (Pavuluri et al., 2004).

Clinical characteristics

The fundamental principle of psychosis involves a mental state of distorted perception and thought, resulting in difficulties differentiating between actual and misperceived events (i.e., reality distortion). Persons who experience psychosis may hear voices or see things that are not there (hallucinations), or present ideas and beliefs divergent with reality or the subculture they belong to (delusions). Their family and friends may notice changes in the affected person's behavior, such as withdrawal from social activities, poor grooming, unpredicted agitation, or acting in a peculiar and unusual way.

TABLE 1.1 Diagnostic descriptions of psychotic disorders according to DSM-5 and ICD-11.

Diagnosis	DSM-5 diagnostic description	ICD-11 diagnostic description	DSM-5 versus ICD-11
Non-affective			
Schizophrenia	Minimum two of the following symptoms present for at least one month, in which one must be a-c: (a) delusions; (b) hallucinations; (c) disorganized speech; (d) grossly disorganized behavior; (e) negative symptoms. The disturbance causes impaired functioning and persists for minimum 6 months.	Minimum two of the following symptoms, present for minimum one month, in which at least two must be 1–4: (1) delusions; (2) hallucinations; (3) disorganized thinking; (4) experiences of influence, passivity, or control; (5) negative symptoms; (6) grossly disorganized behavior; (7) psychomotor disturbances.	For diagnosis, DSM-5 requires a total duration of 6 months and impaired functioning. ICD-11 requires a total duration of one month. The 4th ICD symptom (i.e., bizarre delusions) is excluded as a separate criterion in DSM-5 and included under delusions.
Schizophreniform disorder	Minimum two of the symptoms of schizophrenia, in which one must be a–c. Duration of disturbance is at least one month but less than 6 months. No criterion regarding impaired functioning.	Not included in ICD-11.	

Continued

TABLE 1.1 Diagnostic descriptions of psychotic disorders according to DSM-5 and ICD-11.—cont'd

Diagnosis	DSM-5 diagnostic description	ICD-11 diagnostic description	DSM-5 versus ICD-11
Schizoaffective disorder	Meeting the symptom criterion for schizophrenia with concurrent symptoms of a major mood episode during most of the total duration of the disturbance. During the period of illness, delusions or hallucinations must be present for minimum two weeks in the absence of a major mood episode. No formal criterion about impaired functioning.	Meeting the criteria for schizophrenia concurrent with symptoms of a moderate/severe mood episode. The onset of psychotic and mood symptoms must be simultaneous or occur within a few days apart.	DSM-5 requires concurrent psychosis and mood symptoms most of the total duration of illness, while ICD-11 specifies that the concurrent symptoms must occur simultaneously or within a few days apart.
Delusional disorder	Delusions for at least one month without other symptoms of schizophrenia or impaired functioning.	Delusions for at least three months without other symptoms of schizophrenia.	DSM-5 formally requires duration of one month while ICD-11 requires duration of three months.
Brief psychotic disorder (DSM-5), acute and transient psychotic disorder (ICD-11)	Minimum one symptom of schizophrenia from a	Minimum one symptom of schizophrenia, except for negative symptoms, with rapid	ICD-11 requires rapid symptom changes and a

	to c, except for negative symptoms. Duration of disturbance is at least one day and less than one month, with full return to premorbid level of functioning. No formal criterion about impaired functioning.	changes in the nature and intensity of symptoms. Duration of disturbance is less than three months.	duration of less than three months, while DSM-5 does not formally require rapid symptom changes and duration of less than one month.
Unspecified schizophrenia spectrum and other psychotic disorder (DSM-5), schizophrenia or other primary psychotic disorder, unspecified (ICD-11)	Symptoms of schizophrenia spectrum and other psychotic disorder that cause significant distress or impaired functioning predominate but do not meet the full criteria for any of the disorders in the schizophrenia spectrum and other psychotic disorder diagnostic class, or without adequate information to make a specific diagnosis.	Symptoms of schizophrenia or other primary psychotic disorders that cause significant distress or impaired functioning predominate but do not meet the full criteria for any of the disorders in the schizophrenia or other primary psychotic disorders diagnostic class, or without adequate information to make a specific diagnosis.	
Affective			
Bipolar disorder type I with psychotic features	Minimum one manic episode that caused impaired functioning and	Minimum one manic or mixed episode that caused impaired functioning and was	ICD-11 requires either a manic or mixed episode, while only a manic

Continued

TABLE 1.1 Diagnostic descriptions of psychotic disorders according to DSM-5 and ICD-11.—cont'd

Diagnosis	DSM-5 diagnostic description	ICD-11 diagnostic description	DSM-5 versus ICD-11
	was accompanied by delusions and/or hallucinations	accompanied by delusions and/or hallucinations.	episode fulfills the criteria in DSM-5.
Bipolar disorder type II with psychotic features	Minimum one hypomanic episode and one depressive episode that caused impaired functioning and was accompanied by delusions and/or hallucinations.	Minimum one hypomanic episode and one depressive episode that caused impaired functioning accompanied by delusions and/or hallucinations.	
Depressive disorder with psychotic features	Minimum one depressive episode that caused impaired functioning and was accompanied by delusions and/or hallucinations.	Minimum one depressive episode that caused impaired functioning and was accompanied by delusions and/or hallucinations.	

Note: The diagnostic descriptions presented in this table do not incorporate all the diagnostic criteria for the psychotic disorders. See DSM-5 and ICD-11 for full diagnostic criteria.

Data from the American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (*DSM-5*); World Health Organization. (2019). *International classification of diseases, eleventh revision* (*ICD-11*).

Psychotic experiences

Population-based studies suggest that psychotic experiences often appear along a dimensional gradient, ranging from subtle changes in perception and thought in otherwise healthy individuals, to clear-cut hallucinations and delusions with accompanying functional impairments as part of the spectrum of psychotic disorders (Maijer et al., 2018, 2019).

Subclinical psychotic experiences appear more frequently at younger age (Healy et al., 2019; Maijer et al., 2018; Schultze-Lutter et al., 2022) and can complicate a diagnosis of a psychotic disorder in children and adolescents (Schultze-Lutter et al., 2022). For instance, among children between 5 and 12 years of age, 28−65% reported seeing an "imaginary companion" or hallucination-like phenomenon (Pearson et al., 2001). These experiences must be considered within the normal range (Sikich, 2013) and are different from psychotic experiences in at least two aspects: they are voluntary and associated with positive emotions (Jardri et al., 2014). Therefore, a failure to consider the normal developmental trajectories of perception and cognition in children and adolescents when interpreting psychotic experiences may lead to overdiagnosis of severe mental disorders. On the other hand, psychotic-like experiences in community samples of children and adolescents have been associated with increased risk of developing a psychotic or other mental disorders (Healy et al., 2019). Even though hallucinatory experiences in children and adolescents are often transient and self-limiting, they can cause severe distress and dysfunction, and are associated with increased risk of suicidality (Maijer et al., 2019). For more information regarding subclinical psychotic symptoms, see Chapters 2 and 4.

Symptom domains

As with the diagnostic criteria, the clinical symptom descriptions of children and adolescents with EOP largely follow the adult psychosis nomenclature (see Table 1.2). Traditionally, the clinical symptoms of psychotic disorders have been divided into two broad categories: positive symptoms, reflecting an excess or a distortion of normal brain functions; and negative symptoms, reflecting a reduction of normal brain functions and behavior. However, over the years, factor-analytic studies of commonly used psychometric scales for assessing psychotic and associated symptoms, such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), have suggested that the clinical features of psychotic disorders best can be described by at least four or five domains (Wallwork et al., 2012). These domains include positive, negative, disorganized, depressive, and excited symptoms (Wallwork et al., 2012). Both four-factor (McClellan et al., 2002; Petruzzelli et al., 2018; Thakur, Jagadheesan, & Sinha, 2003; Ulloa et al., 2000), and five-factor models (Bunk et al., 1999; Giannitelli et al., 2020; Rapado-Castro et al., 2010) have been

TABLE 1.2 Description of psychotic and affective symptoms.

Positive symptoms	
Hallucinations	Sensory perceptions that appear in the absence of any corresponding external stimulus.
Delusions	False beliefs that are maintained despite conflicting evidence.
Negative symptoms	
Avolition/apathy	Reductions in self-initiated, goal-directed activities due to lack of motivation.
Anhedonia	Reduced experience of pleasure, either "in the moment" (consummatory), or for future anticipated activities (anticipatory).
Asociality	Reduced engagement in social activities and interactions.
Blunted affect	Reduced expression of emotions through facial expressions, intonation of speech, or body gestures.
Alogia	Poverty of speech. Communicates with few words, with little elaboration and spontaneous speech.
Disorganized symptoms	
Disorganized speech	Incoherent speech, loose associations, vague or unrelated answers, idiosyncratic word usage. Formal thought disorder: Disruption in the flow of thought, manifests as disorganized speech.
Disorganized or abnormal motor behavior	Behaving or dressing in a peculiar or childlike manner, unpredictable agitation, or abnormal motor behavior (including catatonic features). Catatonic features: Resistance to instructions (negativism), bizarre rigid postures, lack of verbal responses (mutism), motoric immobility, stupor, excessive and purposeless motor activity, stereotyped movements, echoing of speech or movement.
Affective symptoms	
Depressed mood	Feeling sad, empty, or hopeless. Loss of interest and pleasure. Can involve changes in appetite and weight, sleep disturbances, psychomotor agitation or retardation, loss of

TABLE 1.2 Description of psychotic and affective symptoms.—cont'd

	energy, feelings of worthlessness or guilt, difficulties concentrating or making choices, suicidal ideation.
Elevated mood (hypomania or mania)	Elevated or irritable mood. Increased energy and activity. Can involve a decreased need for sleep, pressure to keep talking, grandiosity, racing thoughts, distractibility, psychomotor agitation, involvement in activities with high-risk of harmful consequences.

Data from the American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (*DSM-5*); Galderisi, S., et al. (2021). EPA guidance on assessment of negative symptoms in schizophrenia. *European Psychiatry: The Journal of the Association of European Psychiatrists, 64*(1), e23.

described when investigating adolescents with EOP. Discrepancies in the different models could be due to the use of different rating scales, the diagnostic distribution in the different studies, or different stages of disease. In a longitudinal study, Rapado-Castro et al. (2010) examined symptom domains, assessed with the PANSS, at baseline, after 4 weeks, and after 6 months, in 99 adolescents with EOP. They found that the symptoms clustered into five domains at the different time points. Moreover, they discovered that the clusters of symptoms within each factor also varied with time, and that the symptoms constituting the negative symptom domain were most consistent across different time points. Another important feature of psychotic disorders is the impaired cognitive functioning, such as reduced processing speed and learning. In both adolescents and adults with psychotic disorders, impaired cognitive functioning is more often reported to be associated with negative and disorganized symptoms, and less with positive symptoms (de Gracia Dominguez et al., 2009; Mørch-Johnsen et al., 2022) See Chapter 6 for cognitive functioning in youth with EOP.

Positive symptoms

In a comprehensive review, Stentebjerg-Olesen and colleagues examined clinical characteristics of 1506 patients (mean age <19 years) with mainly early-onset schizophrenia-spectrum disorders (89%) across 28 individual samples (Stentebjerg-Olesen et al., 2016). They found that hallucinations and delusions were the most frequently reported symptoms, present in 70% and 78% of patients respectively (Stentebjerg-Olesen et al., 2016). Hallucinations can arise from any sensory modality, such as hearing (auditory hallucinations), seeing (visual hallucinations), touch (tactile hallucinations), tasting or smelling (gustatory hallucinations). Hallucinations of hearing voices (auditory verbal hallucinations) were the most frequently reported type of hallucination

among individuals with EOP, found in 82% of patients, while visual, olfactory and other hallucinations combined, were reported in 55% of patients (Stentebjerg-Olesen et al., 2016).

Delusions are grouped based on their content. Delusions of persecution (the person believes they are being followed, spied on, or conspired against) and delusions of reference (the person believes that things in the environment are special cues directed at them) were the most common in youth with EOP (Stentebjerg-Olesen et al., 2016). Delusions can also be related to other themes, such as having special powers or being famous (grandiose), or having religious ideas not shared by others (religious). According to a review by Pavuluri and colleagues, the most common psychotic feature in children with early-onset bipolar disorder were mood congruent, most often grandiose, delusions (Pavuluri et al., 2004).

The presentation of positive psychotic symptoms may vary with age and cognitive developmental stage. For instance, delusions tend to be vaguer and less complex or fixed at a younger age (Russell, 1994; Schultze-Lutter et al., 2022), which can complicate the differential diagnosis of delusions from overvalued ideas found in persons with obsessive-compulsive disorder (Brakoulias & Starcevic, 2011). It has been suggested that in children and adolescents with EOP, multimodal hallucinations are more common than in adults (Schultze-Lutter et al., 2022; Sikich, 2013). In the US National Institute of Mental Health (NIMH) cohort including 117 children (mean age of 14 years) with childhood-onset schizophrenia, David and colleagues found high rates of multimodal hallucinations among the participants. A total of 95% reported having auditory hallucinations (one modality); 80% reported also having visual hallucinations (two modalities); 61% reported an addition of somatic/tactile hallucinations (three modalities); and 30% reported a further addition of olfactory hallucinations (four modalities) (David et al., 2011).

Furthermore, commenting and imperative voices appear to be more common in children and adolescents with EOP than in adults, while conversing voices are more common in adults (Schultze-Lutter et al., 2022; Sikich, 2013).

Negative symptoms

Patients with negative symptoms may show little interest in social activities, express few emotions, and due to a lack of motivation have difficulties initiating routine daily tasks. Negative symptoms can be primary, as part of the disease process, or secondary to other clinical features, for instance positive symptoms, medication side effects, or depression (Galderisi et al., 2021). Distinguishing between primary and secondary negative symptoms can have important clinical implications, as secondary negative symptoms can be relieved by treating their underlying causes.

Five negative symptoms have been defined: blunted affect, alogia, asociality, anhedonia, and avolition/apathy (Kirkpatrick et al., 2006) (see

Table 1.2 for description). Factor-analytic studies of negative symptom rating scales or subscales performed in adults have shown that the negative symptoms most consistently cluster into two factors: an experimental factor including anhedonia, avolition/apathy and asociality; and an expressive factor (diminished expression) including blunted affect and alogia (Blanchard & Cohen, 2006; Galderisi et al., 2021). This two-factor model of negative symptoms was recently supported in adolescents with EOP (Mørch-Johnsen et al., 2022). A current area of research is to investigate whether symptoms included within these two factors have different clinical and biological correlates, and if they require different treatment strategies.

The prevalence of negative symptoms in individuals with EOP varies from 38% to 50% (Downs et al., 2019; Karakuş et al., 2022; Stentebjerg-Olesen et al., 2016). Negative symptoms are difficult to treat, tend to be stable over the course of illness and are associated with a poorer prognosis (Díaz-Caneja et al., 2015; Fusar-Poli et al., 2015; Karakuş et al., 2022). Karakuş and colleagues found that 40% of patients with EOP (mean age 19 years) had persistent negative symptoms, which were associated with several variables related to a more severe illness, such as earlier age of onset, longer duration of untreated psychosis, decreased functioning, and higher frequency of clozapine use (Karakuş et al., 2022). The treatment effects of currently available pharmacological medications on negative symptoms are limited; hence new treatment developments are imperative (Fusar-Poli et al., 2015; Galderisi et al., 2021). See Chapter 12 for information about factors influencing long-term development and outcome.

Disorganized symptoms

Disorganized symptoms involve disorganized thinking (formal thought disorder), speech, and behavior. While delusions refer to a distortion of though content, disorganized thinking involves a disruption in the coherent organization, flow and form of thoughts, observed as disorganized speech. Disorganized thinking, such as illogical thinking, loose associations, incoherence, and poverty of content of speech, is also present in children during their normal language development. However, children with schizophrenia show more of these features than age-matched healthy controls (Caplan et al., 2000).

Childhood language impairments have been shown to precede schizophrenia in adults (Cannon et al., 2002; Fuller et al., 2002; Jones et al., 1994), and in children and adolescents with a diagnosis of schizophrenia (Driver et al., 2020). Language impairments have also been associated with an increased risk of developing psychosis in adolescents with clinical high risk of psychosis (Bearden et al., 2011).

Disorganized behavior can include behaving or dressing in a peculiar or childlike manner. Patients may also present with unpredictable agitation or abnormal motor behavior, including catatonia. Catatonic behavior is a

psychomotor disturbance, summarized in the DSM-5 as a "marked decrease in reactivity to the environment" (see Table 1.2 for included features). Catatonic symptoms are an understudied phenomenon in adolescents with EOP (Waris et al., 2014). Previous studies have shown that catatonia is present in individuals with EOP at different prevalence rates (10−30%) possibly reflecting the investigated populations and the methodology used to characterize catatonic symptoms (Green et al., 1992; Thakur, Jagadheesan, Dutta, et al., 2003; Waris et al., 2014). In the aforementioned review by Stentebjerg-Olesen and colleagues, disorganized thinking was present in 66% and bizarre behavior in 53% of patients with EOP (Stentebjerg-Olesen et al., 2016).

Affective symptoms

Elevated and depressed mood are the defining symptoms of affective disorders, such as bipolar and major depressive disorders. Comorbid affective symptoms in individuals with nonaffective EOP are relatively prevalent. Sanchez-Gistau and colleagues found affective symptoms (depressive and mixed) in 64% of their sample of young people with EOP (Sanchez-Gistau et al., 2015). In another study, Calderon-Mediavilla and colleagues reported that 37% of their sample of youth with EOP had comorbid clinical depression (Calderon-Mediavilla et al., 2021). It is important to pay attention to mood symptoms when assessing symptoms in individuals with EOP as they may have clinical implications in terms of recommended treatment with antidepressant or mood stabilizing medications. See Chapter 11 for information about treatment.

It can be difficult to distinguish depressive symptoms from negative symptoms as they have overlapping features such as anhedonia, reduced goal-directed behavior, and withdrawal from social interactions. Recent guidelines on negative symptoms assessment in adults from the European Psychiatric Association (Galderisi et al., 2021) recommend the use of the Calgary Depression Rating Scale (Addington et al., 1993) for assessing depression in patients with schizophrenia (Lako et al., 2012). Furthermore, the guidelines point to features that may aid in the discrimination between negative symptoms and depression. For instance, the self-reported subjective feelings of depressed mood, guilt, and hopelessness are more associated with depression, while expressive negative symptoms, such as blunted affect, are more suggestive of negative symptoms (Galderisi et al., 2021; Richter et al., 2019).

Suicidal behavior

Suicidal behavior is defined as a continuum from suicidal thoughts (ideation) to plans and attempts (Nock et al., 2008). The simultaneous presence of depressive and psychotic symptoms increases the risk of suicidal behavior (Sanchez-Gistau et al., 2015). In an Irish study, adolescents with major depressive disorder and psychotic symptoms had a 14-fold increased risk of suicidal behavior compared to adolescents with depression without psychotic symptoms (Kelleher et al., 2012). This finding is in line with a recent

systematic review of suicidal behavior in adolescents (aged 10−19 years) with EOP by Barbeito and colleagues. They found that the symptoms that were most closely related to suicidal behavior were depression, distress with psychotic symptoms, fewer negative symptoms at baseline, positive symptoms, and anxiety disorders (Barbeito et al., 2021).

In a prospective cohort study of 1112 school-based adolescents (aged 13−16 years), Kelleher and colleagues investigated suicide attempts in relation to general psychopathology. Among the adolescents with psychopathology and psychotic symptoms (n = 47), 34% reported a suicide attempt after 12 months, compared to 13% of adolescents with psychopathology without psychotic symptoms (n = 146) (Kelleher et al., 2013). Furthermore, compared to the total sample, the adolescents with psychopathology and psychotic symptoms had a nearly 70-fold increased odds of suicide attempts, while no significantly increased odds were found for the adolescents with psychopathology without psychotic symptoms (Kelleher et al., 2013). These findings are in keeping with the review by Barbeito and colleagues, reporting that adolescents with EOP had a 12−72% increased risk of committing suicide across studies (Barbeito et al., 2021).

Diagnostic interviews

Delayed or inaccurate diagnosis can result in longer duration of untreated psychosis, inappropriate or harmful treatment, and unwanted long-term outcomes (Matuschek et al., 2016). Clinician-generated diagnoses show poor inter-rater reliability and validity compared to diagnoses assessed using standardized diagnostic interviews (First, 2015; Jewell et al., 2004; Miller, 2001). A reason for this is the lack of structure as to what questions to ask or how the obtained information is used to arrive at a diagnosis (Summerfeldt et al., 2020). To improve diagnostic procedures, structured clinical interviews designed to minimize the variability in diagnostic assessment, are standard tools used in research and evidence-based clinical practice (Summerfeldt et al., 2020). Moreover, the use of structured interviews has received high acceptance among patients across settings (inpatient, outpatient, and research) and clinicians, which should encourage further use of standardized tools in diagnostic assessment (Suppiger et al., 2009).

In the following, we describe three semi-structured diagnostic interviews that are widely used in clinical and research settings for common psychiatric disorders in children and adolescents, including psychosis. The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) was particularly developed for children and adolescents, whereas the Structured Clinical Interview for DSM (SCID) (Spitzer et al., 1992) and the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) were developed for adults.

Schedule for affective disorders and schizophrenia for school-age children-present and Lifetime version (K-SADS-PL)

The K-SADS-PL (Kaufman et al., 1997) has currently been revised in accordance with changes in the DSM-5 (K-SADS-PL-5). The K-SADS-PL is by many considered the "gold standard" among diagnostic interviews for children and adolescents from 6 to 17 years of age. It assesses current and past psychiatric episodes by combining dimensional and categorical approaches (Kaufman et al., 1997). The interview provides separate child and parent ratings for relevant symptoms and includes the Children's Global Assessment Scale (Shaffer et al., 1983) as a measure of global functioning. The K-SADS-PL is comprised of a screen interview (including a thorough demographic section) and five supplemental interviews, focusing on all relevant child and adolescent disorders. It can take from one to three hours to complete each of the K-SADS-PL interviews, depending on whether the child and parent are interviewed separately or not. The duration of administration can vary considerably between patients. Thus, it may be wise to aim at administration time intervals of 30–60 minutes to ensure that the child has a positive experience throughout the session.

Structured clinical interview for DSM (SCID)

The SCID (Spitzer et al., 1992) is the most widely used structured diagnostic interview for the assessment of DSM disorders in adults (First, 2015), and has recently been updated according to the fifth edition of DSM (SCID-5) (First et al., 2016). The SCID includes both current and lifetime diagnoses. It usually takes approximately 60–90 minutes to complete, depending on the participant's symptoms and psychiatric history. The SCID is developed for adults from 18 years of age but can be used with adolescents from 16 years of age. A child and adolescent version of the SCID for DSM-IV has been developed (the Kid-SCID) (Roelofs et al., 2015). To our knowledge the Kid-SCID is not commonly used in clinical settings or research and has not been revised according to the DSM-5.

Mini-International Neuropsychiatric Interview (M.I.N.I.)

The MINI (Sheehan et al., 1998) is another widely used structured interview for the assessment of common psychiatric disorders in adults. It was developed to bridge the gap between detailed and time-consuming interviews such as the K-SADS-PL and SCID, and the ultrashort screening tests designed for primary care. The MINI takes about 15 minutes to administer and focuses on current symptoms for the most common psychiatric diagnoses while excluding questions about disability and general medical illness. It also comes in a more comprehensive version (MINI-Plus) and a screening version (MINI-Screen),

which takes about 45−60 and 5 minutes to administer, respectively (Sheehan et al., 1998). A version for children and adolescents from 6 to 17 years of age (MINI-KID) has also been developed, which takes about 30−45 minutes to administer (Sheehan et al., 2010). Comparing the MINI-KID to the K-SADS-PL, the developers found good to excellent concordance for most disorders, and the MINI-KID was administered in one third of the time used to complete the K-SADS-PL (Sheehan et al., 2010). In the initial study, the MINI-KID had a high rate of false positive diagnoses for some disorders, including psychosis, but the modules have been updated according to these findings.

Comorbidity

Psychiatric comorbidity

Comorbid syndromes are common in children and adolescents with EOP (Karow et al., 2022). In one study, Ross and colleagues examined 82 children, aged 4−15 years, with schizophrenia or schizoaffective disorder. All but one of the children had at least one comorbid psychiatric illness. The most common comorbid conditions were attention deficit/hyperactivity disorder (ADHD) (84%), oppositional defiant disorder (43%), depression (30%), and separation anxiety disorder (25%) (Ross et al., 2006). These findings are in accordance with the results from a previous study showing that ADHD, oppositional defiant disorder and/or conduct disorder were present in two-thirds of youth with schizophrenia spectrum and bipolar disorders (McClellan & McCurry, 1999). Data from the Philadelphia Neurodevelopmental Cohort (PNC; n = 9498; youth aged 8−21 years) showed that the comorbidity with ADHD was associated with more severe psychotic symptoms in youth with psychosis, but not with greater cognitive impairment (Fox et al., 2021). Interestingly, a Danish nationwide survey and register-based study of 423 adolescents from 13 to 17 years of age showed that food addiction symptomatology was prevalent among adolescents with mental disorders, particularly affective and psychotic disorders (Horsager et al., 2022). See Chapter 5 on delimitations between clinical syndromes.

Somatic comorbidity

Adults with schizophrenia have excess mortality of more than 10 years, largely due to somatic comorbidity with disorders including diabetes type 2 and cardiovascular diseases (Schwarz et al., 2021). In adolescents with EOP, lipids and immune profiles have been found to be abnormal (Szabo et al., 2022; Wedervang-Resell, Friis, Lonning, Smelror, Johannessen, Agartz, et al., 2020; Wedervang-Resell, Friis, Lonning, Smelror, Johannessen, Roponen, 2020), and carotid vessels have shown prearteriosclerotic signs (Bohman et al., 2020). These findings were reported to occur independently from use of antipsychotic

medication. Although these studies need more in-depth follow-up, it is plausible that the abnormalities will develop into future cardiovascular morbidity and adverse somatic health outcomes. There are no studies of cardiometabolic risk prediction algorithms in individuals below 35 years of age with psychosis, and most algorithms have not included antipsychotic medication (Perry et al., 2021). Existing cardiometabolic prediction algorithms for adults tend to underestimate risk in young individuals, and new tailored algorithms or recalibration of the existing ones is warranted (Perry et al., 2020). In a large-scale Swedish comorbidity study, children aged 3−18 years with psychiatric disorders, were, across conditions and age, at remarkably high risk for concurrent somatic illness (Agnafors et al., 2019). At this young age, psychotic conditions were mainly associated with asthma, bowel disorders and myalgia, although the number of children with psychosis was low (Agnafors et al., 2019). The immune system's role in neurodevelopment and EOP is presented in Chapter 7.

The neurodevelopmental hypothesis of schizophrenia

The history of the neurodevelopmental hypothesis of schizophrenia has been traced back to the ground-breaking work of Barbara Fish in 1957 (Jablensky et al., 2017) on the fetal development and early predictors of schizophrenia risk (Fish, 1957). The hypothesis was further developed in 1987 by Weinberger (1987) and by Murray et al. (1987). The neurodevelopmental hypothesis postulates that the combined effects of genetic risk and an early brain lesion acquired during pregnancy or at birth increase the risk of developing schizophrenia (Jablensky et al., 2017). Although never proven, the neurodevelopmental model of schizophrenia has become broadly recognized in contemporary schizophrenia research. As an interesting follow-up of the neurodevelopmental hypothesis, recent studies have shown that placental genes expressed during fetal life might affect early synapse development and brain maturation during sensitive developmental windows with implications for neural growth (Ursini et al., 2018, 2021). Ursini et al. (2018, 2021) found that a higher placental genomic risk for schizophrenia and a history of early life complications (particularly in males) was associated with altered early brain growth and function. This could point to a neurodevelopmental path of risk for schizophrenia.

Genetic and environmental influence

The biological mechanisms underlying psychotic disorders are not fully understood. In adults, genetic research supports that schizophrenia and bipolar disorder lie on an extended neurodevelopmental continuum with neurodevelopmental disorders such as intellectual disability, autism spectrum disorder and ADHD (see Fig. 1.2) (Craddock & Owen, 2010; Forsyth & Asarnow, 2020; Morris-Rosendahl & Crocq, 2020). This hypothetical continuum model might be as or even more relevant for the early-onset cases (Morris-Rosendahl & Crocq, 2020).

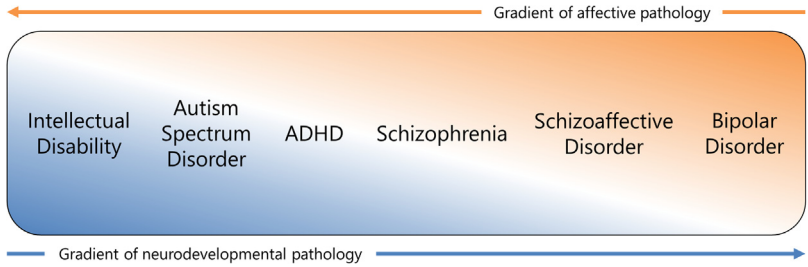

FIGURE 1.2 Hypothetical neurodevelopmental continuum across psychiatric syndromes. Illustration of the hypothesized neurodevelopmental relationship between clinical syndromes with gradients of neurodevelopmental and affective contributions to disturbance. *Modified from Fig. 1 in Craddock, N., & Owen, M. J. (2010). The Kraepelinian dichotomy - going, going … but still not gone.* British Journal of Psychiatry, 196*(2), 92–95 and Fig. 1 in Morris-Rosendahl, D. J., & Crocq, M. A. (2020). Neurodevelopmental disorders-the history and future of a diagnostic concept.* Dialogues in Clinical Neuroscience, 22*(1), 65–72.*

Compared to the typical age of onset of psychotic disorders in early adulthood, studies of individuals with EOP report stronger genetic load with more rare gene variants or highly penetrant variants (Asarnow & Forsyth, 2013; Hilker et al., 2017). As such, they represent biological phenotypes that can be informative for the psychosis pathophysiology and highlight the importance of studying individuals with EOP. Chapter 3 presents information of genetic research in youth with EOP.

Genes are considered to play a large part in the origin of disorders such as ADHD, autism spectrum disorder, and schizophrenia (Smoller et al., 2013; Tamminga et al., 2013), likely in complex interactions with the environment (Wahbeh & Avramopoulos, 2021). As an example, Stepniak and colleagues investigated the effect of accumulated environmental risk factors (cannabis use, neuro- or psychotrauma, urbanicity, migration, and one perinatal complication) on the age at onset of schizophrenia in 750 men (mean age 31 years). They found that the age at onset was nearly a decade earlier in those with four or more risk factors than in those with no environmental risk, and that cannabis use was the most important factor (Stepniak et al., 2014). Chapters 4 and 12 give information about substance abuse and EOP.

Another risk factor that has been studied in psychosis development is exposure to infections. As an example, a Danish population-based cohort study investigated the association between all treated infections since birth and the subsequent risk of development of any treated mental disorder during childhood and adolescence. The risk of mental disorders after infections increased in a dose–response association and with the temporal proximity of the last infection (Köhler-Forsberg et al., 2019). This was shown in a wide range of disorders including schizophrenia spectrum disorders. More information about risk factors for psychosis development can be found in Chapter 4.

Clinical heterogeneity

The clinical presentation of psychotic disorders, including EOP, is heterogeneous, as is the longitudinal course and outcome. Patients fulfilling the criteria for the same diagnosis may present with different symptoms and problems, and their course of illness may differ greatly. Psychotic and affective symptoms are also shared across the diagnostic entities. The difficulty in determining the disease origins could be due both to phenotypic heterogeneity and to high biological variability within the psychosis spectrum (Arango et al., 2021). This encourages research into the phenomenology and potential biological underpinnings of psychotic and mood symptom domains across the diagnostic spectrum of psychotic disorders. Different approaches have been suggested to address the issues of clinical heterogeneity and biological variability. The "reverse phenotyping" or "genotype-first" is an approach where genetic markers drive new phenotypic definitions, so that phenotypes are distinguished by allele sharing, rather than the traditional descriptive diagnostic categories (Stessman et al., 2014). Another approach is the US NIMH Research Domain Criteria (RDoC) (Insel et al., 2010). The RDoC was launched to better capture the underlying mechanisms of dysfunction and address the heterogeneity and comorbidity of mental disorders by investigating behavioral domains rather than diagnostic categories (Insel et al., 2010).

Future directions

Developmental trajectories

It is important to conduct longitudinal follow-up studies in children and adolescents with EOP as they are too limited today. National or international population and health registries constitute great sources for outcome research, as well as for health monitoring and planning, and these need to be further developed. The understanding of developmental and disease trajectories, from fetal life through the life course, can help outcome prediction and underlines the need for continuity from adolescent to adult psychiatric care. Furthermore, the overlap between affective and nonaffective psychotic disorders, and neurodevelopmental disorders, need to be better understood. The same is true for diagnostic categories which can be refined depending on age trajectories and symptom overlap. Regarding pubertal and sexual development, more knowledge is needed on how sex hormones and sexual maturity are related to psychosis onset and development. Gender diversity is an important consideration, and different genders might need separate studies and their own conceptualized frameworks.

Interdisciplinary studies

Interdisciplinary scientific collaborations and use of multimodal methodologies can hopefully inform on useful new phenotypes and find the missing link between the biological causes and their clinical disease manifestations. The combination of methods from computational psychiatry, clinical and demographic registry data, and advanced neuroimaging, gene, and biomarker discovery has several advantages: it can increase the potential for novel knowledge about clinical characteristics, risk factors, and brain phenotypes across the spectrum of psychosis and related neurodevelopmental disorders in adolescents. Further, it can help stratifying among heterogeneous clinical phenomenology to discover meaningful subtypes of disorders. One ambition is to combine individual clinical cohorts into very large samples, since EOP samples to date are comparatively size small.

Experimental approaches

It is now possible for scientists to experimentally test for biological mechanisms, and not only statistical associations, which is a big step forward. Stem cell model systems or patient-derived brain organoids can be used to test for effects of for instance hypoxia, genes, and drug exposures on developing neural cell systems. One hypothesis in schizophrenia is that patient-derived neurons show fewer excitatory synapses or disrupted synaptogenesis, with subsequent downregulation of neurotransmitter and synapse markers (Courchesne et al., 2019). Indeed, reduced density of dendritic spines has been a consistent finding in the postmortem brain in adults with schizophrenia (Glausier & Lewis, 2013) and results from postmortem positron emission tomography show lower synaptic vesicle density in several brain regions (Radhakrishnan et al., 2021). The reduced synaptic density in postmortem cortical brain tissue from patients with schizophrenia is suggestive of increased synapse elimination (pruning). Using a reprogrammed in vitro stem cell model of microglia-mediated synapse engulfment, Sellgren and colleagues could show an increased synaptic elimination in patient-derived neural cultures (Sellgren et al., 2019). Synaptic elimination is an important process for cognitive development (synaptic specialization) in adolescence, and cognitive health in this developmental phase is of great importance for the individual's future functioning. Excessive synaptic elimination during adolescence might be reflected in the cortical brain abnormalities found in brain imaging studies of schizophrenia and bipolar disorder, as described in Chapters 8–10.

Uncovering early life processes by focusing on placental genes and fetal life function in the context of psychotic disorders might be one way forward. Maternal immune activation can affect fetal processes, and maternal infections and stress have shown to be risk factors for neurodevelopmental outcomes including schizophrenia (Aguilar-Valles et al., 2020; Ganguli & Chavali, 2021).

In a model study of individuals with autism spectrum disorder, Courchesne and colleagues suggested that prenatal and early postnatal pathogenic processes could lead to the clinical heterogeneity that characterizes autism spectrum disorder. These processes could generate information for individual and group level explanations (Courchesne et al., 2019). This hypothetical model could also serve as a model for studying psychosis syndromes, considering their polygenicity, clinical heterogeneity, and susceptibility to environmental risk. It could offer individualized scientific explanations and lead way toward clinically purposeful treatment.

Another avenue toward discovery is the study of risk exposures in animal models. Gene−environment interactions have been explored, but combinations of environmental (prenatal) risk factors remain to be studied (Eyles, 2021).

Clinical and societal responsibility

How can society contribute to provide a more secure, better adjusted, and predictable environment for young individuals with different degrees of symptoms characteristic of psychosis? We envision even larger scientific leaps in the future. Mental health of children and adolescents needs to be prioritized and prevention strategies need to be developed and promoted with support in the family, schools, and community. Mental health focus for young people needs promotion and visibility, and services need financial resources. New advancements should encourage implementation into the clinic, or promotion among policy makers for improved mental health prevention strategies and better treatments. Educational approaches are important, and schools and clinics can develop programs for improving mental health among youth. Clinical outcome is dynamic and can give reason for a positive and reassuring attitude that is important to communicate to the adolescent and care team. To convey optimism and encourage positive visibility are also important to reduce the stigma associated with psychotic disorders in general, including youth with EOP.

We know many of the societal risk factors that need addressing, such as cannabis use, underprivileged home environment, poverty, and demographic migration. With the increase in social media use, and "fake news" breakthroughs as we have witnessed the recent years, the importance of correct media communication of research (the why and how), its effects and consequences, cannot be overstated. Lastly, future research should go global and not be limited to the Global North, or wealthier population strata.

Ethical considerations

Use of digital monitoring and detection, and the wealth of personal information in particularly genetic studies give rise to ethical considerations regarding

individuals with difficulty to understand and interpret information and with impaired judgmental capacity.

The kind of studies summarized above could be informative at the individual level, in accordance with "personalized" medicine, but the study methods also bring new ethical challenges that need to be handled with care. Ethical considerations are further discussed in Chapter 13.

Conclusion

EOP is an umbrella term used in research to describe nonaffective and affective psychotic disorders with onset before 18 years of age. The clinical diagnoses for youth follow the same diagnostic criteria as for adults, but symptom manifestations can show other nuances, particularly in the younger individuals. Only some of the diagnostic instruments are developed specifically for children and adolescents. The comorbidity in individuals with EOP is high and its long-term outcome warrants further investigation. The origins of psychosis development are complex with both genetic and environmental influences, and although interactions have not been firmly clarified, hypotheses have been developed. Children and adolescents who develop EOP represent a heightened biological vulnerability for psychosis that could uncover new knowledge about the pathophysiology of psychosis development in general. To include youth with EOP in scientific studies is advantageous considering the short time between diagnosis and recruitment, the limited substance, alcohol, or nicotine use, and the controlled pharmacological use compared to adult patients. Most importantly, continued research into psychotic disorders in children and adolescence is warranted to improve the treatment and care for young people suffering from these disorders.

Acknowledgments

This work was supported by the South-Eastern Norway Regional Health Authority (2019−099). Ingrid Agartz received lecturer honorarium from Lundbeck AS. The other authors report no conflicts of interest.

References

Addington, D., Addington, J., & Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: The Calgary depression scale. *British Journal of Psychiatry, 163*(22), 39−44. https://doi.org/10.1192/s0007125000292581

Agnafors, S., Norman Kjellström, A., Torgerson, J., & Rusner, M. (2019). Somatic comorbidity in children and adolescents with psychiatric disorders. *European Child and Adolescent Psychiatry, 28*(11), 1517−1525. https://doi.org/10.1007/s00787-019-01313-9

Aguilar-Valles, A., Rodrigue, B., & Matta-Camacho, E. (2020). Maternal immune activation and the development of dopaminergic neurotransmission of the offspring: Relevance for

schizophrenia and other psychoses. *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.00852

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Arango, C., Dragioti, E., Solmi, M., Cortese, S., Domschke, K., Murray, R. M., Jones, P. B., Uher, R., Carvalho, A. F., Reichenberg, A., Shin, J. I. I., Andreassen, O. A., Correll, C. U., & Fusar-Poli, P. (2021). Risk and protective factors for mental disorders beyond genetics: An evidence-based atlas. *World Psychiatry, 20*(3), 417−436. https://doi.org/10.1002/wps.20894

Asarnow, R. F., & Forsyth, J. K. (2013). Genetics of childhood-onset schizophrenia. *Child and Adolescent Psychiatric Clinics of North America, 22*(4), 675−687. https://doi.org/10.1016/j.chc.2013.06.004

Barbeito, S., Vega, P., Sánchez-Gutiérrez, T., Becerra, J. A., González-Pinto, A., & Calvo, A. (2021). A systematic review of suicide and suicide attempts in adolescents with psychotic disorders. *Schizophrenia Research, 235*, 80−90. https://doi.org/10.1016/j.schres.2021.07.029

Bearden, C. E., Wu, K. N., Caplan, R., & Cannon, T. D. (2011). Thought disorder and communication deviance as predictors of outcome in youth at clinical high risk for psychosis. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(7), 669−680. https://doi.org/10.1016/j.jaac.2011.03.021

Blanchard, J. J., & Cohen, A. S. (2006). The structure of negative symptoms within schizophrenia: Implications for assessment. *Schizophrenia Bulletin, 32*(2), 238−245. https://doi.org/10.1093/schbul/sbj013

Bohman, H., Agartz, I., Mansouri, S., Naessen, T., & Lundberg, M. (2020). Preclinical atherosclerosis in adolescents with psychotic or bipolar disorders investigated with carotid high-frequency ultrasound. *Brain and Behavior, 10*(12). https://doi.org/10.1002/brb3.1862

Brakoulias, V., & Starcevic, V. (2011). The characterization of beliefs in obsessive-compulsive disorder. *Psychiatric Quarterly, 82*(2), 151−161. https://doi.org/10.1007/s11126-010-9157-8

Bunk, D., Eggers, C., & Klapal, M. (1999). Symptom dimensions in the course of childhood-onset schizophrenia. *European Child and Adolescent Psychiatry, 8*(S1), S29−S35. https://doi.org/10.1007/pl00010688

Calderon-Mediavilla, M., Vila-Badia, R., Dolz, M., Butjosa, A., Barajas, A., Del Cacho, N., Sánchez, B., Pardo, M., Baños, I., Usall, J., Ochoa, S., Araya, S., Arranz, B., Arteaga, M., Asensio, R., Autonell, J., Baños, I., Bañuelos, M., Barajas, A., … Vila-Badia, R. (2021). Depressive symptoms and their relationship with negative and other psychotic symptoms in early onset psychosis. *European Child and Adolescent Psychiatry, 30*(9), 1383−1390. https://doi.org/10.1007/s00787-020-01618-0

Cannon, M., Caspi, A., Moffitt, T. E., Harrington, H., Taylor, A., Murray, R. M., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: Results from a longitudinal birth cohort. *Archives of General Psychiatry, 59*(5), 449−456. https://doi.org/10.1001/archpsyc.59.5.449

Caplan, R., Guthrie, D., Tang, B., Komo, S., & Asarnow, R. F. (2000). Thought disorder in childhood schizophrenia: Replication and update of concept. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(6), 771−778. https://doi.org/10.1097/00004583-200006000-00016

Courchesne, E., Pramparo, T., Gazestani, V. H., Lombardo, M. V., Pierce, K., & Lewis, N. E. (2019). The ASD living biology: From cell proliferation to clinical phenotype. *Molecular Psychiatry, 24*(1), 88−107. https://doi.org/10.1038/s41380-018-0056-y

Craddock, N., & Owen, M. J. (2010). The Kraepelinian dichotomy - going, going… but still not gone. *British Journal of Psychiatry, 196*(2), 92−95. https://doi.org/10.1192/bjp.bp.109.073429

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B. B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K. B., Timmerman, A., Schendel, D., McGrath, J. J., Mortensen, P. B., & Pedersen, C. B. (2020). Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. *JAMA Psychiatry, 77*(2), 155−164. https://doi.org/10.1001/jamapsychiatry.2019.3523

David, C. N., Greenstein, D., Clasen, L., Gochman, P., Miller, R., Tossell, J. W., Mattai, A. A., Gogtay, N., & Rapoport, J. L. (2011). Childhood onset schizophrenia: High rate of visual hallucinations. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(7), 681−686. https://doi.org/10.1016/j.jaac.2011.03.020. e3.

Díaz-Caneja, C. M., Pina-Camacho, L., Rodríguez-Quiroga, A., Fraguas, D., Parellada, M., & Arango, C. (2015). Predictors of outcome in early-onset psychosis: A systematic review. *NPJ Schizophrenia, 1*(1). https://doi.org/10.1038/npjschz.2014.5

Downs, J., Dean, H., Lechler, S., Sears, N., Patel, R., Shetty, H., Hotopf, M., Ford, T., Kyriakopoulos, M., Diaz-Caneja, C. M., Arango, C., MacCabe, J. H., Hayes, R. D., & Pina-Camacho, L. (2019). Negative symptoms in early-onset psychosis and their association with antipsychotic treatment failure. *Schizophrenia Bulletin, 45*(1), 69−79. https://doi.org/10.1093/schbul/sbx197

Driver, D. I., Thomas, S., Gogtay, N., & Rapoport, J. L. (2020). Childhood-onset schizophrenia and early-onset schizophrenia spectrum disorders: An update. *Child and Adolescent Psychiatric Clinics of North America, 29*(1), 71−90. https://doi.org/10.1016/j.chc.2019.08.017

Eyles, D. W. (2021). How do established developmental risk-factors for schizophrenia change the way the brain develops? *Translational Psychiatry, 11*(1). https://doi.org/10.1038/s41398-021-01273-2

First, M. B. (2015). In R. L. Cautin, & S. O. Lilienfeld (Eds.), *Structured clinical interview for the DSM (SCID)*. https://doi.org/10.1002/9781118625392.wbecp351

First, M. B., Williams, J., Karg, R., & Spitzer, R. L. (2016). *Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV)*. American Psychiatric Association.

Fish, B. (1957). The detection of schizophrenia in infancy. *Journal of Nervous and Mental Disease, 125*(1), 1−24. https://doi.org/10.1097/00005053-195701000-00001

Forsyth, J. K., & Asarnow, R. F. (2020). Genetics of childhood-onset schizophrenia 2019 update. *Child and Adolescent Psychiatric Clinics of North America, 29*(1), 157−170. https://doi.org/10.1016/j.chc.2019.08.007

Fox, V., Sheffield, J. M., & Woodward, N. D. (2021). Attention-deficit/hyperactivity disorder in youth with psychosis spectrum symptoms. *Schizophrenia Research, 237*, 141−147. https://doi.org/10.1016/j.schres.2021.08.027

Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B. C., & Andreasen, N. C. (2002). Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *American Journal of Psychiatry, 159*(7), 1183−1189. https://doi.org/10.1176/appi.ajp.159.7.1183

Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., & McGuire, P. (2015). Treatments of negative symptoms in schizophrenia: Meta-analysis of 168 randomized placebo-controlled trials. *Schizophrenia Bulletin, 41*(4), 892−899. https://doi.org/10.1093/schbul/sbu170

Galderisi, S., Mucci, A., Dollfus, S., Nordentoft, M., Falkai, P., Kaiser, S., Giordano, G. M., Vandevelde, A., Nielsen, M., Glenthøj, L. B., Sabé, M., Pezzella, P., Bitter, I., & Gaebel, W. (2021). EPA guidance on assessment of negative symptoms in schizophrenia. *European*

Psychiatry: The Journal of the Association of European Psychiatrists, 64(1), e23. https://doi.org/10.1192/j.eurpsy.2021.11

Ganguli, S., & Chavali, P. L. (2021). Intrauterine viral infections: Impact of inflammation on fetal neurodevelopment. *Frontiers in Neuroscience, 15*. https://doi.org/10.3389/fnins.2021.771557

Giannitelli, M., Levinson, D. F., Cohen, D., Xavier, J., & Laurent-Levinson, C. (2020). Developmental and symptom profiles in early-onset psychosis. *Schizophrenia Research, 216*, 470−478. https://doi.org/10.1016/j.schres.2019.10.028

Glausier, J. R., & Lewis, D. A. (2013). Dendritic spine pathology in schizophrenia. *Neuroscience, 251*, 90−107. https://doi.org/10.1016/j.neuroscience.2012.04.044

Gore, F. M., Bloem, P. J. N., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., Sawyer, S. M., & Mathers, C. D. (2011). Global burden of disease in young people aged 10-24 years: A systematic analysis. *The Lancet, 377*(9783), 2093−2102. https://doi.org/10.1016/S0140-6736(11)60512-6

de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J. P., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin, 135*(1), 157−171. https://doi.org/10.1037/a0014415

Green, W. H., Padron-Gayol, M., Hardesty, A. S., & Bassiri, M. (1992). Schizophrenia with childhood onset: A phenomenological study of 38 cases. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(5), 968−976. https://doi.org/10.1097/00004583-199209000-00027

Healy, C., Brannigan, R., Dooley, N., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: A systematic review and meta-analysis. *Psychological Medicine, 49*(10), 1589−1599. https://doi.org/10.1017/S0033291719000485

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2017). Is an early age at illness onset in schizophrenia associated with increased genetic susceptibility? Analysis of data from the nationwide Danish twin register. *EBioMedicine, 18*, 320−326. https://doi.org/10.1016/j.ebiom.2017.04.002

Horsager, C., Færk, E., Gearhardt, A. N., Lauritsen, M. B., & Østergaard, S. D. (2022). Food addiction comorbid to mental disorders in adolescents: A nationwide survey and register-based study. Eating and weight disorders - studies on anorexia. *Bulimia and Obesity, 27*(3), 945−959. https://doi.org/10.1007/s40519-021-01212-6

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748−751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jablensky, A., McNeil, T. F., & Morgan, V. A. (2017). Barbara fish and a short history of the neurodevelopmental hypothesis of schizophrenia. *Schizophrenia Bulletin, 43*(6), 1158−1163. https://doi.org/10.1093/schbul/sbx094

Jardri, R., Bartels-Velthuis, A. A., Debbané, M., Jenner, J. A., Kelleher, I., Dauvilliers, Y., Plazzi, G., Demeulemeester, M., David, C. N., Rapoport, J., Dobbelaere, D., Escher, S., & Fernyhough, C. (2014). From phenomenology to neurophysiological understanding of hallucinations in children and adolescents. *Schizophrenia Bulletin, 40*(Suppl. l_4), S221−S232. https://doi.org/10.1093/schbul/sbu029

Jensen, C. M., & Steinhausen, H. C. (2016). Time trends in lifetime incidence rates of first-time diagnosed bipolar and depressive disorders across 16 years in Danish psychiatric hospitals: A nationwide study. *Journal of Clinical Psychiatry, 77*(12), e1570−e1575. https://doi.org/10.4088/JCP.15m10276

Jewell, J., Handwerk, M., Almquist, J., & Lucas, C. (2004). Comparing the validity of clinician-generated diagnosis of conduct disorder to the diagnostic interview schedule for children. *Journal of Clinical Child and Adolescent Psychology, 33*(3), 536–546. https://doi.org/10.1207/s15374424jccp3303_11

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *The Lancet, 344*(8934), 1398–1402. https://doi.org/10.1016/S0140-6736(94)90569-X

Karakuş, O. B., Ermiş, Ç., Tunçtürk, M., Yüksel, A. S., Alarslan, S., Sağlam, Y., Görmez, V., & Karaçetin, G. (2022). Identifying clinical and psychological correlates of persistent negative symptoms in early-onset psychotic disorders. *Clinical Child Psychology and Psychiatry*, 1–15. https://doi.org/10.1177/13591045221075531

Karow, A., Luedecke, D., Schöttle, D., Rohenkohl, A., Schimmelmann, B., Gallinat, J., & Lambert, M. (2022). Charakteristika von Psychosen in der Adoleszenz – longitudinale Daten der Integrierten Versorgung. *Der Nervenarzt, 93*(4), 331–340. https://doi.org/10.1007/s00115-022-01276-4

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Kelleher, I., Corcoran, P., Keeley, H., Wigman, J. T. W., Devlin, N., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2013). Psychotic symptoms and population risk for suicide attempt a prospective cohort study. *JAMA Psychiatry, 70*(9), 940–948. https://doi.org/10.1001/jamapsychiatry.2013.140

Kelleher, I., Lynch, F., Harley, M., Molloy, C., Roddy, S., Fitzpatrick, C., & Cannon, M. (2012). Psychotic symptoms in adolescence index risk for suicidal behavior: Findings from 2 population-based case-control clinical interview studies. *Archives of General Psychiatry, 69*(12), 1277–1283. https://doi.org/10.1001/archgenpsychiatry.2012.164

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., & Marder, S. R. (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin, 32*(2), 214–219. https://doi.org/10.1093/schbul/sbj053

Köhler-Forsberg, O., Petersen, L., Gasse, C., Mortensen, P. B., Dalsgaard, S., Yolken, R. H., Mors, O., & Benros, M. E. (2019). A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry, 76*(3), 271–279. https://doi.org/10.1001/jamapsychiatry.2018.3428

Lako, I. M., Bruggeman, R., Knegtering, H., Wiersma, D., Schoevers, R. A., Slooff, C. J., & Taxis, K. (2012). A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *Journal of Affective Disorders, 140*(1), 38–47. https://doi.org/10.1016/j.jad.2011.10.014

Maijer, K., Begemann, M. J. H., Palmen, S. J. M. C., Leucht, S., & Sommer, I. E. C. (2018). Auditory hallucinations across the lifespan: A systematic review and meta-analysis. *Psychological Medicine, 48*(6), 879–888. https://doi.org/10.1017/S0033291717002367

Maijer, K., Hayward, M., Fernyhough, C., Calkins, M. E., Debbané, M., Jardri, R., Kelleher, I., Raballo, A., Rammou, A., Scott, J. G., Shinn, A. K., Steenhuis, L. A., Wolf, D. H., & Bartels-

Velthuis, A. A. (2019). Hallucinations in children and adolescents: An updated review and practical recommendations for clinicians. *Schizophrenia Bulletin, 45*(Suppl. ment_1), S5−S23. https://doi.org/10.1093/schbul/sby119

Matuschek, T., Jaeger, S., Stadelmann, S., Dölling, K., Grunewald, M., Weis, S., von Klitzing, K., & Döhnert, M. (2016). Implementing the K-SADS-PL as a standard diagnostic tool: Effects on clinical diagnoses. *Psychiatry Research, 236*, 119−124. https://doi.org/10.1016/j.psychres.2015.12.021

McClellan, J., & McCurry, C. (1999). Early onset psychotic disorders: Diagnostic stability and clinical characteristics. *European Child and Adolescent Psychiatry, 8*(S1), S13−S19. https://doi.org/10.1007/pl00010686

McClellan, J., McCurry, C., Speltz, M. L., & Jones, K. (2002). Symptom factors in early-onset psychotic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(7), 791−798. https://doi.org/10.1097/00004583-200207000-00010

Miller, P. R. (2001). Inpatient diagnostic assessments: 2. Interrater reliability and outcomes of structured vs. unstructured interviews. *Psychiatry Research, 105*(3), 265−271. https://doi.org/10.1016/S0165-1781(01)00318-3

Mørch-Johnsen, L., Smelror, R. E., Andreou, D., Barth, C., Johannessen, C., Wedervang-Resell, K., Wortinger, L. A., Díaz, R., Victoria, G., Ueland, T., Andreassen, O. A., Myhre, A. M., Rund, B. R., Ulloa, R. E., & Agartz, I. (2022). Negative symptom domains are associated with verbal learning in adolescents with early onset psychosis. *Frontiers in Psychiatry, 12*. https://doi.org/10.3389/fpsyt.2021.825681

Morris-Rosendahl, D. J., & Crocq, M. A. (2020). Neurodevelopmental disorders-the history and future of a diagnostic concept. *Dialogues in Clinical Neuroscience, 22*(1), 65−72. https://doi.org/10.31887/DCNS.2020.22.1/macrocq

Murray, R. M., Lewis, S. W., & Lecturer, L. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal (Clinical Research Ed.), 295*(6600), 681−682. https://doi.org/10.1136/bmj.295.6600.681

Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and suicidal behavior. *Epidemiologic Reviews, 30*(1), 133−154. https://doi.org/10.1093/epirev/mxn002

Pavuluri, M. N., Herbener, E. S., & Sweeney, J. A. (2004). Psychotic symptoms in pediatric bipolar disorder. *Journal of Affective Disorders, 80*(1), 19−28. https://doi.org/10.1016/S0165-0327(03)00053-3

Pearson, D., Burrow, A., FitzGerald, C., Green, K., Lee, G., & Wise, N. (2001). Auditory hallucinations in normal child populations. *Personality and Individual Differences, 31*(3), 401−407. https://doi.org/10.1016/S0191-8869(00)00145-8

Perry, B. I., Osimo, E. F., Upthegrove, R., Mallikarjun, P. K., Yorke, J., Stochl, J., Perez, J., Zammit, S., Howes, O., Jones, P. B., & Khandaker, G. M. (2021). Development and external validation of the psychosis metabolic risk calculator (PsyMetRiC): A cardiometabolic risk prediction algorithm for young people with psychosis. *The Lancet Psychiatry, 8*(7), 589−598. https://doi.org/10.1016/S2215-0366(21)00114-0

Perry, B. I., Upthegrove, R., Crawford, O., Jang, S., Lau, E., McGill, I., Carver, E., Jones, P. B., & Khandaker, G. M. (2020). Cardiometabolic risk prediction algorithms for young people with psychosis: A systematic review and exploratory analysis. *Acta Psychiatrica Scandinavica, 142*(3), 215−232. https://doi.org/10.1111/acps.13212

Petruzzelli, M. G., Margari, L., Bosco, A., Craig, F., Palumbi, R., & Margari, F. (2018). Early onset first episode psychosis: Dimensional structure of symptoms, clinical subtypes and related

neurodevelopmental markers. *European Child and Adolescent Psychiatry, 27*(2), 171−179. https://doi.org/10.1007/s00787-017-1026-7

Radhakrishnan, R., Skosnik, P. D., Ranganathan, M., Naganawa, M., Toyonaga, T., Finnema, S., Hillmer, A. T., Esterlis, I., Huang, Y., Nabulsi, N., Carson, R. E., & D'Souza, D. C. (2021). In vivo evidence of lower synaptic vesicle density in schizophrenia. *Molecular Psychiatry, 26*(12), 7690−7698. https://doi.org/10.1038/s41380-021-01184-0

Rapado-Castro, M., Soutullo, C., Fraguas, D., Arango, C., Payá, B., Castro-Fornieles, J., González-Pinto, A., Parellada, M., Graell, M., Baeza, I., & Bombin, I. (2010). Predominance of symptoms over time in early-onset psychosis: A principal component factor analysis of the positive and negative syndrome scale. *Journal of Clinical Psychiatry, 71*(3), 327−337. https://doi.org/10.4088/JCP.08m04845yel

Richter, J., Hölz, L., Hesse, K., Wildgruber, D., & Klingberg, S. (2019). Measurement of negative and depressive symptoms: Discriminatory relevance of affect and expression. *European Psychiatry, 55*, 23−28. https://doi.org/10.1016/j.eurpsy.2018.09.008

Roelofs, J., Muris, P., Braet, C., Arntz, A., & Beelen, I. (2015). The structured clinical interview for DSM-IV childhood diagnoses (Kid-SCID): First psychometric evaluation in a Dutch sample of clinically referred youths. *Child Psychiatry and Human Development, 46*(3), 367−375. https://doi.org/10.1007/s10578-014-0477-z

Ross, R. G., Heinlein, S., & Tregellas, H. (2006). High rates of comorbidity are found in childhood-onset schizophrenia. *Schizophrenia Research, 88*(1−3), 90−95. https://doi.org/10.1016/j.schres.2006.07.006

Russell, A. T. (1994). The clinical presentation of childhood-onset schizophrenia. *Schizophrenia Bulletin, 20*(4), 631−646. https://doi.org/10.1093/schbul/20.4.631

Sanchez-Gistau, V., Baeza, I., Arango, C., González-Pinto, A., De La Serna, E., Parellada, M., Graell, M., Paya, B., Llorente, C., & Castro-Fornieles, J. (2015). The affective dimension of early-onset psychosis and its relationship with suicide. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 56*(7), 747−755. https://doi.org/10.1111/jcpp.12332

Schultze-Lutter, F., Kindler, J., Ambarini, T. K., & Michel, C. (2022). Positive psychotic symptoms in childhood and adolescence. *Current Opinion in Psychology, 45*, 101287. https://doi.org/10.1016/j.copsyc.2021.11.007

Schwarz, E., Alnæs, D., Andreassen, O. A., Cao, H., Chen, J., Degenhardt, F., Doncevic, D., Dwyer, D., Eils, R., Erdmann, J., Herrmann, C., Hofmann-Apitius, M., Kaufmann, T., Koutsouleris, N., Kodamullil, A. T., Khuntia, A., Mucha, S., Nöthen, M. M., Paul, R., … Meyer-Lindenberg, A. (2021). Identifying multimodal signatures underlying the somatic comorbidity of psychosis: The COMMITMENT roadmap. *Molecular Psychiatry, 26*(3), 722−724. https://doi.org/10.1038/s41380-020-00915-z

Sellgren, C. M., Gracias, J., Watmuff, B., Biag, J. D., Thanos, J. M., Whittredge, P. B., Fu, T., Worringer, K., Brown, H. E., Wang, J., Kaykas, A., Karmacharya, R., Goold, C. P., Sheridan, S. D., & Perlis, R. H. (2019). Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nature Neuroscience, 22*(3), 374−385. https://doi.org/10.1038/s41593-018-0334-7

Shaffer, D., Gould, M. S., Brasic, J., Fisher, P., Aluwahlia, S., & Bird, H. (1983). A Children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*(11), 1228−1231. https://doi.org/10.1001/archpsyc.1983.01790100074010

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*(20), 22−33.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., Milo, K. M., Stock, S. L., & Wilkinson, B. (2010). Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *Journal of Clinical Psychiatry, 71*(3), 313−326. https://doi.org/10.4088/JCP.09m05305whi

Sikich, L. (2013). Diagnosis and evaluation of hallucinations and other psychotic symptoms in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America, 22*(4), 655−673. https://doi.org/10.1016/j.chc.2013.06.005

Smoller, J. W., Craddock, N., Kendler, K., Lee, P. H., Neale, B. M., Nurnberger, J. I., Ripke, S., Santangelo, S., & Sullivan, P. F. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet, 381*, 1371−1379. https://doi.org/10.1016/S0140-6736(12)62129-1

Spitzer, R. L., Williams, J. B. W., Gibbon, M., & First, M. B. (1992). The structured clinical interview for DSM-III-R (SCID): I: History, rationale, and description. *Archives of General Psychiatry, 49*(8), 624−629. https://doi.org/10.1001/archpsyc.1992.01820080032005

Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, P. (2016). Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: A systematic review. *Journal of Child and Adolescent Psychopharmacology, 26*(5), 410−427. https://doi.org/10.1089/cap.2015.0097

Stepniak, B., Papiol, S., Hammer, C., Ramin, A., Everts, S., Hennig, L., Begemann, M., & Ehrenreich, H. (2014). Accumulated environmental risk determining age at schizophrenia onset: A deep phenotyping-based study. *The Lancet Psychiatry, 1*(6), 444−453. https://doi.org/10.1016/S2215-0366(14)70379-7

Stessman, H. A., Bernier, R., & Eichler, E. E. (2014). A genotype-first approach to defining the subtypes of a complex disease. *Cell, 156*(5), 872−877. https://doi.org/10.1016/j.cell.2014.02.002

Summerfeldt, L. J., Ovanessian, M. M., & Antony, M. M. (2020). In M. M. Antony, & D. H. Barlow (Eds.), *Structured and semistructured diagnostic interviews* (3rd ed.). The Guilford Press.

Suppiger, A., In-Albon, T., Hendriksen, S., Hermann, E., Margraf, J., & Schneider, S. (2009). Acceptance of structured diagnostic interviews for mental disorders in clinical practice and research settings. *Behavior Therapy, 40*(3), 272−279. https://doi.org/10.1016/j.beth.2008.07.002

Szabo, A., O'Connell, K. S., Ueland, T., Sheikh, M. A., Agartz, I., Andreou, D., Aukrust, P., Boye, B., Bøen, E., Drange, O. K., Elvsåshagen, T., Engh, J. A., Hope, S., Collier Høegh, M., Joa, I., Johnsen, E., Kroken, R. A., Vik Lagerberg, T., Lekva, T., … Djurovic, S. (2022). Increased circulating IL-18 levels in severe mental disorders indicate systemic inflammasome activation. *Brain, Behavior, and Immunity, 99*, 299−306. https://doi.org/10.1016/j.bbi.2021.10.017

Tamminga, C. A., Ivleva, E. I., Keshavan, M. S., Pearlson, G. D., Clementz, B. A., Witte, B., Morris, D. W., Bishop, J., Thaker, G. K., & Sweeney, J. A. (2013). Clinical phenotypes of psychosis in the bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). *American Journal of Psychiatry, 170*(11), 1263−1274. https://doi.org/10.1176/appi.ajp.2013.12101339

Thakur, A., Jagadheesan, K., Dutta, S., & Sinha, V. K. (2003). Incidence of catatonia in children and adolescents in a paediatric psychiatric clinic. *Australian and New Zealand Journal of Psychiatry, 37*(2), 200−203. https://doi.org/10.1046/j.1440-1614.2003.01125.x

Thakur, A., Jagadheesan, K., & Sinha, V. K. (2003). Psychopathological dimensions in childhood and adolescent psychoses: A confirmatory factor analytical study. *Psychopathology, 36*(4), 190−194. https://doi.org/10.1159/000072788

Ulloa, R. E., Birmaher, B., Axelson, D., Williamson, D. E., Brent, D. A., Ryan, N. D., Bridge, J., & Baugher, M. (2000). Psychosis in a pediatric mood and anxiety disorders clinic: Phenomenology and correlates. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(3), 337−345. https://doi.org/10.1097/00004583-200003000-00016

Ursini, G., Punzi, G., Chen, Q., Marenco, S., Robinson, J. F., Porcelli, A., Hamilton, E. G., Mitjans, M., Maddalena, G., Begemann, M., Seidel, J., Yanamori, H., Jaffe, A. E., Berman, K. F., Egan, M. F., Straub, R. E., Colantuoni, C., Blasi, G., Hashimoto, R., … Weinberger, D. R. (2018). Convergence of placenta biology and genetic risk for schizophrenia. *Nature Medicine, 24*(6), 792−801. https://doi.org/10.1038/s41591-018-0021-y

Ursini, G., Punzi, G., Langworthy, B. W., Chen, Q., Xia, K., Cornea, E. A., Goldman, B. D., Styner, M. A., Knickmeyer, R. C., Gilmore, J. H., & Weinberger, D. R. (2021). Placental genomic risk scores and early neurodevelopmental outcomes. *Proceedings of the National Academy of Sciences, 118*(7). https://doi.org/10.1073/pnas.2019789118

Wahbeh, M. H., & Avramopoulos, D. (2021). Gene-environment interactions in schizophrenia: A literature review. *Genes, 12*(12), 1850. https://doi.org/10.3390/genes12121850

Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., & Dickinson, D. (2012). Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. *Schizophrenia Research, 137*(1−3), 246−250. https://doi.org/10.1016/j.schres.2012.01.031

Waris, P., Lindberg, N., Kettunen, K., Lipsanen, J., & Tani, P. (2014). Catatonic features in adolescents with schizophrenia with and without a comorbid pervasive developmental disorder. *Child and Adolescent Psychiatry and Mental Health, 8*(1). https://doi.org/10.1186/1753-2000-8-16

Wedervang-Resell, K., Friis, S., Lonning, V., Smelror, R. E., Johannessen, C., Agartz, I., Ulven, S. M., Holven, K. B., Andreassen, O. A., & Myhre, A. M. (2020). Lipid alterations in adolescents with early-onset psychosis may be independent of antipsychotic medication. *Schizophrenia Research, 216*, 295−301. https://doi.org/10.1016/j.schres.2019.11.039

Wedervang-Resell, K., Friis, S., Lonning, V., Smelror, R. E., Johannessen, C., Reponen, E. J., Lyngstad, S. H., Lekva, T., Aukrust, P., Ueland, T., Andreassen, O. A., Agartz, I., & Myhre, A. M. (2020). Increased interleukin 18 activity in adolescents with early-onset psychosis is associated with cortisol and depressive symptoms. *Psychoneuroendocrinology, 112*, 104513. https://doi.org/10.1016/j.psyneuen.2019.104513

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44*(7), 660−669. https://doi.org/10.1001/archpsyc.1987.01800190080012

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 457−465. https://doi.org/10.1097/00004583-199105000-00017

World Health Organization. (2019). *International classification of diseases, eleventh revision (ICD-11)*. World Health Organization. https://doi.org/https://icd.who.int/browse11.

Chapter 2

The epidemiology of early-onset psychosis

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Introduction

Psychiatric epidemiology has been defined as "the science of public mental health" (Susser et al., 2006). The importance of the field is increasingly acknowledged due to reports from the World Health Organization indicating that mental disorders are among the leading causes of disease burden and disability worldwide (Murray & Lopez, 1996; World Health Organization, 2001). Psychiatric epidemiology has played a critical role in advancing the study of mental disorders. First, the field has promoted the development of systematic classification systems of mental health symptoms and disorders. Second, it has provided evidence for the high prevalence and persistence of psychiatric phenomena in general nonhelp seeking community samples. Lastly, it has elucidated the contribution of genetic and environmental mechanisms underlying risk of mental health problems (Susser et al., 2006).

In this chapter, we discuss the epidemiology of psychosis in adolescence at different levels, from the clinical disorder to the subclinical symptom level. A major part of the available literature comes from studies of individuals with early-onset schizophrenia (EOS) and early-onset psychosis (EOP). With regard to psychosis, early-onset is defined as the onset of a psychotic disorder before 18 years of age (Werry et al., 1991). There are no specific diagnostic criteria for early-onset psychosis; therefore, most studies use the criteria for schizophrenia and other psychotic disorders from the Diagnostic Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) or the International Classification of Diseases (ICD) (World Health Organization, 2019). EOP usually includes nonaffective and affective psychotic

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00004-4

disorders, such as bipolar and depressive disorders with psychotic features. However, there is substantial variation across studies in the age range of onset and diagnostic criteria used. According to most definitions used in the literature, early-onset means an onset between 0 and 17 years of age, with very early- or childhood-onset before age 13 years and adolescent-onset between 13 and 17 years (Bo & Haahr, 2015; Werry et al., 1991). Here, we will primarily focus on youth aged 13−17 years old with EOS and EOP, even though some of the studies may have included individuals with an onset before age 13 and after age 17 years. In addition to the outcomes at the disorder level, we will also discuss the occurrence of psychotic-like experiences (PLE) in adolescence. PLE or subclinical psychotic symptoms are subtle hallucinations and delusions that are relatively common in the general population (Kelleher & Cannon, 2011). Unlike the attenuated psychosis syndrome, most PLE are transient experiences that do not require mental health treatment. There is substantial evidence, however, suggesting that they exist on a continuum with psychotic disorder (Van Os et al., 2009).

We have divided this chapter into three main parts: First, we describe the epidemiology of EOS and EOP based on general population studies. We devote a separate paragraph to studies from the Global South, which are grossly underrepresented. Other paragraphs cover a discussion of the literature on affective psychosis including bipolar disorder, sex differences, and diagnostic stability. In the second part, we discuss the incidence and prevalence of PLE in adolescence, and in the third part, we discuss different methodological considerations and the availability of different data sources. Lastly, we provide a summary and conclusions.

The incidence and prevalence of adolescent psychosis

Common terms to explain outcomes in the general population include incidence and prevalence. Incidence reflects the number of *new cases* of a condition in a specific population (population at risk) over a defined interval of time, for example, 15 cases of schizophrenia per 100,000 persons per year. Prevalence is defined as the number of cases of a condition that exist in a defined population *at a specific point in time* (point prevalence) or *during a specific period* (period prevalence). Various epidemiological study designs may produce reliable incidence and prevalence estimates such as birth cohorts, population-based registers or surveys, and first-contact incidence studies (i.e., studies in which all people seeking help for a specific condition in a specified catchment areas are identified). These will be the main focus in this chapter.

In the general population, the adult lifetime prevalence of psychotic disorders is estimated between 0.5% (Jablensky et al., 2000) and 3.06% (Perälä et al., 2007). The number of new cases of psychotic disorders worldwide, as reported in a recent meta-analysis, was estimated at 27 per 100,000 (0.027%) (Jongsma et al., 2019). Studies show great heterogeneity, depending on where

and how they were conducted, with higher rates of incidence reported in population register studies compared to first-contact designs (Jongsma et al., 2019). The number of epidemiological studies investigating adolescents with EOP in the age range 13−17 years is limited. Earlier studies have shown that the prevalence of EOS was approximately nine per 100,000 (0.009%) at 13 years (Remschmidt et al., 1994). Gillberg et al. (1986) used the wider diagnostic criteria of EOP based on DSM−III−R criteria (American Psychiatric Association, 1987) and included schizophrenia, schizophreniform disorder, affective psychosis, atypical, and substance-induced psychosis. They reported the same number of cases at 13 years as Remschmidt et al. (1994), and an increase in cases during adolescence, with a peak of 176 cases per 100,000 (0.18%) at 18 years. They found that the prevalence of EOP in adolescence was about 10 times higher than in childhood, and about a quarter of the prevalence in adults (Gillberg et al., 1986). These studies suggest that the real prevalence of EOP is probably higher, since the former study only reported EOS, excluding other psychotic disorders (Remschmidt et al., 1994), and the latter study only included in-patients admitted to a psychiatric clinic, excluding outpatients.

Despite the steep increase of these diagnoses during adolescence, Häfner found that EOS represents less than 4% of all schizophrenia diagnoses (Häfner, 1998). However, a more recent meta-analysis estimated the proportion of EOS that developed before age 18 years to 8.2% which rose to 47.4% at age 25 (Solmi et al., 2022). When considering a broader category including both schizophrenia-spectrum and other primary psychotic disorders (not secondary to a medical condition, substance use or a mood disorder) based on ICD-11 criteria (Gaebel, 2012), the proportion of young people with an onset before 18 years was considerably higher, at 12.3% (Solmi et al., 2022). These data indicate that about a 10th of cases with schizophrenia debuted during adolescence, although incidence peaks slightly later, at age 20 years, with a median age of onset of all cases at 25 years (Solmi et al., 2022). This age peak is similar to what has been shown using earlier data (Häfner, 1998).

Population-based epidemiological studies

One of the largest population-based studies reporting on the prevalence of adolescent psychosis is the Avon Longitudinal Study of Parents and Children (ALSPAC), a British birth cohort study (Boyd et al., 2013). The presence of a psychotic disorder was established based on the occurrence of definite psychotic experiences at least once per month over the previous 6 months, that caused severe distress and functional impairment. The psychotic symptoms were assessed using the Psychosis-Like Symptoms Interview (Horwood et al., 2008), a semistructured interview covering three main domains of positive psychotic symptoms: hallucinations, delusions (e.g., persecutory beliefs) and bizarre symptoms (e.g., beliefs about thought broadcasting). Based on data

from the ALSPAC study, Zammit et al. (2013) reported that in a sample of 4724 participants aged 18 years, 1.7% had developed a psychotic disorder between the ages of 12 and 18 years. Most of these adolescents (75%) reported visual or auditory hallucinations as their most common symptom. Only 12.8% of the adolescents with a psychotic disorder had previously sought professional help for their psychotic symptoms. Having experienced psychotic symptoms at the age of 12 was predictive of a psychotic disorder at age 18 years (Zammit et al., 2013).

A population-based English study reported on hospitalization incidence of children and adolescents. Incidence increased from around 0.02 per 100,000 in children under 12 years, to about 2.6 per 100,000 in the age group of 13−17 years (Seminog et al., 2021). With increasing age, incidence rates increased, with the majority (>90%) of individuals with EOS being 14 years and older. Furthermore, Scottish data reporting on the prevalence of EOP suggests a 3-year prevalence in the general population of 5.9 per 100,000 (Boeing et al., 2007).

A Canadian retrospective cohort study of 193,400 adolescents born between 1990 and 1998 found that 0.76% were diagnosed with a nonaffective psychotic disorder between the ages of 13 and 19 years (Magee et al., 2022). Incidence rates increased with higher age from 12 to 17 per 100,000, especially in males. The risk of having a psychotic disorder was elevated in low-income families and neighborhoods, if a parent had health service contact for a mental disorder, and in more recent birth cohorts. Unexpectedly, the risk was reduced among children of immigrants compared to children of nonmigrants (Magee et al., 2022). Another Canadian population-based study estimated the incidence of EOS based on data from physician billings, hospitalizations, pharmacies, and public health clinics from 2004 to 2006, and reported a cumulative incidence of first-episode schizophrenia spectrum disorders of 25 cases per 100,000 at age 18 years (Anderson et al., 2012). Large increases in incidence were found between 14 and 18 years. Since these estimates are much higher than what has been found in other studies, the authors reason that many cases may be missed in studies using clinical samples. They argue that administrative databases may be more useful resources for studying the rarer types of mental disorders such as EOS (Anderson et al., 2012).

In Italy, an epidemiologically based survey was conducted among the general population, examining risk of psychosis in relation to age, sex, immigration status, urbanicity, and socioeconomic deprivation. The study was conducted between 2005 and 2007 within the framework of the Psychosis Incident Cohort Outcome Study (PICOS) (Lasalvia et al., 2014) and comprised of a total number of 3,077,555 person-years, that is, the total population in the study catchment area multiplied by the number of years of recruitment. The incidence rates for all psychotic disorders for adolescents aged 15−19 years, was 11.9 per 100,000 person-years. For nonaffective psychosis, the incidence was slightly lower, at 10.3, and for schizophrenia it was half, at 5.9 per person-

years. For affective psychosis the incidence rate was 1.6 per 100,000 person years, including 1.2 and 0.4 per 100,000 for bipolar disorder and major depressive disorder with psychotic features, respectively. The incidence rates of psychotic disorders peaked in the age span 20–29 years, with 30.3 per 100,000 person-years (Lasalvia et al., 2014).

The English naturalistic cohort study, known as the Social Epidemiology of Psychoses in East Anglia (SEPEA) study (Kirkbride et al., 2017), with a total of 2,021,663 person-years, reported even higher incidence rates of EOP. The incidence was 45.8 per 100,000 in 16- and 17-year-olds, and 57.2 in 18- and 19-year-olds. Highest incidence rates were found for nonaffective psychosis with approximately 35 per 100,000 in 16- and 17-year-olds and approximately 50 per 100,000 in 18- and 19-year-olds. Considerably fewer cases with affective psychosis were reported, with less than 10 per 100,000 for both age groups (Kirkbride et al., 2017). Similarly, in the Jerusalem Perinatal Study, a population-based cohort derived from all births in Israel between 1964 and 1976, the incidence of schizophrenia-spectrum disorders was examined in different age bands (Kleinhaus et al., 2011). Between the ages of 10–14 years the incidence was 6.6 per 100,000. This rapidly increased to 53 per 100,000 between the ages of 15–19 years and reached a peak incidence of 62.5 per 100,000 between the ages of 20–24 (Kleinhaus et al., 2011).

In conclusion, population-based studies report substantial heterogeneity in the incidence and prevalence of EOS and EOP which is at least partially explained by the type of study design and sampling strategies. Studies consistently indicate a significant increase of around 10 times more cases during adolescence (age 12–18 years) compared to psychosis with earlier onset (<12 years of age), and a peak of incidences in the early twenties.

Studies from the Global South

Only a few studies from the Global South report incidence data on EOP or EOS. The Chilean First-Episode of Schizophrenia Program included individuals aged 10–64 years, reporting the incidence of nonaffective psychotic disorders (González-Valderrama et al., 2020). They found a major increase between the ages of 15 and 19 years, reaching rates of 57.6 per 100,000 person-years in boys and 29.5 per 100,000 person-years in girls (González-Valderrama et al., 2020). An Iranian population based study including 33,264 children and adolescents aged 6–18 years showed that the likelihood of being diagnosed with EOP increased with age: 0.1% between ages 6–9 years; 0.3% for ages 10–13 years; and 0.4% between the ages 15–18 years (Alavi et al., 2021). The overall incidence of psychosis in the same sample aged 6–18 years was 0.26% (Mohammadi et al., 2019). Adjorlolo and Anum reviewed the literature on psychosis in Africa, including studies from South Africa, Kenya, and Nigeria. They concluded that the prevalence rates of EOP in these African countries were generally lower than in the Global North

(Adjorlolo & Anum, 2021). However, they did not report any prevalence numbers for EOP (as opposed to PLE, presented later in the chapter). Moreover, it should be mentioned that the African studies used often locally developed clinical instruments and much more limited sample sizes (with the smallest sample including 45 participants, and the largest 2963 participants) compared to the large cohort studies from the Global North (e.g., PICOS, SEPEA, and ALSPAC cohorts).

Affective psychotic disorders

Affective psychotic disorders are mood disorders, such as bipolar and major depressive disorders, accompanied by psychotic features (e.g., hallucinations and/or delusions).

Studies indicate that affective psychotic disorders are less prevalent than nonaffective psychosis in adolescence. In the previously described Italian epidemiological survey, the annual incidence rates among adolescents from 15 to 19 years were 1.6 per 100,000 person-years for affective and 10.3 for nonaffective psychosis (Lasalvia et al., 2014). Similarly, among Danish youth aged 15–24 years, the incidence of bipolar disorder was 4.6 per 100,000 person-years, which is about half of the incidence of acute and transient psychotic disorders (9.0) and about a third of schizophrenia cases (16.4) (Castagnini & Foldager, 2013). Söderlund et al. (2015) linked data from two Swedish national registers (Statistics Sweden and The National Board of Health and Welfare), comprising the birth years of 1955–76. Investigating the incidence of schizophrenia, other nonaffective psychoses and bipolar disorder in adults aged 18–30 years, they reported three times lower rates of affective psychotic disorders compared with nonaffective psychosis (Söderlund et al., 2015). The US National Comorbidity Survey Replication Adolescent Supplement (NCS-A) survey included a sample of 10,123 adolescents aged 13–18 years, and found a prevalence of bipolar disorder (type I and II) of 2.9% (Merikangas et al., 2010). The prevalence among the older adolescents (17 and 18 year-olds) was nearly twice as high as in the younger group (13 and 14 year-olds) (Defilippis & Wagner, 2013; Merikangas et al., 2010). Unfortunately, no prevalence numbers were reported in these studies. Although less steep, this increase resembles the increase found in EOS and EOP.

Van Meter and colleagues synthesized findings from 12 studies (6 from the United States, five from other countries in the Global North and one from Mexico), including 16,222 youth between 7 and 21 years of age. Three of the studies included children under age 11 years and two of the studies included adolescents older than 18 years. The results indicated a prevalence for bipolar disorder of 1.8% in the total sample, and 2.7% in samples over 12 years old (Van Meter et al., 2011). This reflects increased prevalence rates with higher age in adolescence. A Dutch study on the incidence of bipolar disorder in the general population corroborated this finding,

showing a peak in incidence between 15 and 24 years of age, a similar age of onset pattern as observed in nonaffective psychotic disorders (Kroon et al., 2013).

In sum, the incidence of nonaffective psychosis, including schizophrenia is generally higher in adolescence compared with affective psychosis, including bipolar disorder. Age seems to play a role in the incidence of nonaffective psychosis with a significant increase of cases during the period of adolescence, gradually increasing after the age of 12 years, with a steep increase around 18 years. Numbers peak shortly after age 20. Few studies have examined affective disorders with and without psychotic features separately. During adolescence and young adulthood, the incidence of bipolar disorder also increases with age, a pattern that resembles that of schizophrenia, although the increase with age tends to be less steep. The year of the study also seems to influence the incidence rates. However, studies are inconclusive, with one study reporting an increased incidence (Magee et al., 2022) and another a decreased incidence during the period of data collection (Seminog et al., 2021), which span between 8 and 16 years. Because the vast majority of studies has been conducted in the Global North, it is difficult to make meaningful comparisons across countries and regions.

Sex differences

In psychiatry, sex and gender are often used interchangeably while they are different concepts. Sex refers to a biological construct referring to the physical differences between people who are male, female or intersex. Gender is a predominantly social construct that reflects how a person identifies. Here, we will use the term sex for consistency.

Whether there are sex differences in the incidence of adult psychotic disorders is an ongoing debate. While it was initially assumed that men and women were as likely to be diagnosed with psychotic disorders, more recent studies suggest an elevated risk for men compared to women (Ochoa et al., 2012; Riecher-Rössler et al., 2018). Epidemiological research on the sex distribution of particularly individuals with EOP is scarce. Cohorts of help-seeking individuals with first-episode psychosis generally report a preponderance of boys and young men. In the well-known Australian Early Psychosis Prevention and Intervention Center (EPPIC), approximately two-thirds of young people who developed a psychotic disorder before age 17 years were men, which was similar to individuals with an onset between 18 and 30 years of age (Amminger et al., 2011).

In one of the most extensive birth cohort studies (1995−2016) on youth mental health to date, Dalsgaard and colleagues estimated age- and sex-specific incidence rates of being diagnosed with any mental disorder during childhood and adolescence in Denmark. Including all youth from age 0−18 years, they found a higher incidence of EOS in girls (0.76%) than boys (0.48%) (Dalsgaard et al., 2020). The incidence rate of EOS before age 12

years was low for both sexes, after which it increased for girls more steeply than for boys.

In a population-based administrative database of physician billings, hospitalizations, pharmacies, and public health clinics in Montreal, Canada, researchers found the opposite. The cumulative incidence of schizophrenia-spectrum disorders at age 18 years was about three times higher in boys (25 per 100,000 per year) compared to girls (8 per 100,000 per year) (Anderson et al., 2012). At age 25, the incidence for men was still more than twice as high as for women. In an earlier study using the nationwide admission data from Denmark, schizophrenia with onset in mid- and late-adolescence (age 15−17 years) was twice as common in boys than in girls (Thomsen, 1996). In a more recent study, Okkels and colleagues explored changes in the diagnosed incidence of schizophrenia with an onset before age 18 years based on data from the Danish Psychiatric Central Research Register from 1971 to 2010. They observed that the age-standardized incidence rate was higher for boys than girls from 1971 to 1994 but a reversal occurred between 1994 and 2010 with a higher incidence rate in girls compared to boys (Okkels et al., 2013). This is consistent with the findings from the recent nationwide Danish cohort study (Dalsgaard et al., 2020). It is unclear whether these reflect true changes in incidence over time or whether they can be attributed to changes in case ascertainment.

Based on English hospital admission and outpatient data, Seminog and colleagues examined changes in the sex distribution of EOS during different age periods. Their findings also suggested more cases in girls than in boys up to the age of 13 years, although sample sizes for the youngest age groups (8−13 years) were small (Seminog et al., 2021). From age 14 years, the number of EOS cases were higher in boys compared to girls. When comparing the years of data collection, there was a decrease in the incidence of EOS between 2001 and 2016. However, the incidence only decreased in boys while it increased in girls (Seminog et al., 2021). Of note, these findings are based on hospital admission rates and therefore impacted by selection bias. An increasing preponderance of boys in the incidence of EOS with age has also been reported in other studies (Kleinhaus et al., 2011). In conclusion, although the limited empirical evidence is inconsistent, most studies still suggest a higher incidence of EOS and other nonaffective psychotic disorders in boys compared to girls. Yet, the extent of the sex difference appears to vary by diagnostic category (schizophrenia spectrum vs. broader category of EOP), age at illness onset (early vs. mid-late adolescence), geographical context, type of case ascertainment (first hospital admission vs. in- and outpatient), and time period of data collection.

Importantly, there are several issues to consider when interpreting the findings on sex differences. Some studies only reported hospital admission data, which tend to include a disproportionate selection of boys with more severe symptoms and externalizing problems (Häfner, 2019; Häfner et al.,

1994; Talonen et al., 2017). Moreover, research has shown that the use of different diagnostic criteria has a substantial impact on the incidence of psychosis across sex. For instance, using a more restrictive definition as the outcome such as narrowly defined schizophrenia leads to a higher number of exclusions of women than men (Castle et al., 1993). This is in line with previous systematic reviews and meta-analyses indicating that men are at higher risk of nonaffective psychotic disorder than women are, while rates of affective psychosis are generally similar across sexes (Aleman et al., 2003; Jongsma et al., 2019; Kirkbride et al., 2017; McGrath et al., 2004).

Another issue is clinician bias in diagnosing psychotic disorders. In a well-known experimental study, psychiatrists were instructed to assign diagnoses to case vignettes that were identical except the pronoun ("he" vs. "she"). The results indicated that vignettes with female pronouns were much less likely to be assigned a diagnosis of schizophrenia than vignettes with male pronouns (Høye et al., 2006). The clinical presentation of girls may also differ from boys. Girls tend to exhibit more affective symptoms, while boys are more likely to present with negative symptoms and social isolation (Brand et al., 2022). Together, clinician bias and differences in clinical presentation may contribute to the underestimation of girls with psychotic illness in research studies, while clinically, they may lead to longer durations of untreated psychosis, treatment delays and underdiagnosing of psychotic disorders in girls compared to boys (Brand et al., 2022).

Diagnostic stability

Psychotic disorders in youth often cooccur with and evolve into other mental conditions. In a longitudinal study in the US, McClellan and McCurry followed 51 children and adolescents with EOP over 2 years. They found that the diagnostic stability between the first clinical diagnosis and the research diagnosis given about 2 years later at study entry was only 50% (McClellan & McCurry, 1999). There was also substantial variation between diagnoses. The authors found much lower diagnostic stability among youth diagnosed with a psychotic disorder, not otherwise specified (NOS) (36%) than among those diagnosed with schizophrenia (66%) or bipolar disorder (77%) (McClellan & McCurry, 1999). Although the variation between these diagnoses might have been expected, there might also have been a difference in stability if the research diagnosis would have been given at the same time as the clinical diagnosis. The diagnostic stability between the research diagnoses assessed using standardized instruments at study entry and after one- and 2-year follow-up was high (90% agreement). Among youth with schizophrenia-spectrum or bipolar disorder, up to two-thirds of individuals had comorbid diagnoses of attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and/or conduct disorder, while about one-third had a comorbid substance abuse disorder (McClellan & McCurry, 1999).

Two Spanish studies reported comparable results regarding overall diagnostic stability among youth aged 9–18 years with EOP. Diagnostic agreement over the course of 2-year follow-up varied between 64% (Castro-Fornieles et al., 2011) and 54% (Fraguas et al., 2008). It was high in schizophrenia spectrum disorders (90% or more), moderate to high in bipolar disorder (71%–92%), and relatively low for people with an initial diagnosis of schizoaffective disorder (50%), depressive disorder (38%), and psychotic disorder NOS (12%). Youth with more negative symptoms and lower general functioning at the initial clinical evaluation were more likely to be diagnosed with schizophrenia at follow-up (Castro-Fornieles et al., 2011; Fraguas et al., 2008).

A few studies have followed adolescents to adult life. In an influential study, Hollis included 110 patients with EOP from the Maudsley Hospital in London and followed 85% of the cohort more than 11 years after the first contact with mental health services. Diagnostic stability was high for individuals diagnosed with schizophrenia (80%) and affective psychoses (83%), while it was low for schizoaffective disorder (33%) (Hollis, 2000). High diagnostic stability of schizophrenia and affective psychotic disorders was also reported in a Swedish cohort of youth with a mean follow-up period of more than 10 years (Jarbin & Von Knorring, 2003).

Altogether, the highest diagnostic agreement is found for schizophrenia and bipolar disorder, both at the short and longer term. Other diagnoses including psychotic disorder NOS and schizoaffective disorder are more likely to evolve into other diagnoses over time, mainly schizophrenia, while a major depressive disorder with psychotic features is more likely to evolve into a bipolar disorder (Jarbin & Von Knorring, 2003; Schwartz et al., 2000). Findings from several longitudinal studies suggest that most diagnostic changes occur in the first year of follow-up, a finding consistent with research on the evolution of adult-onset psychosis (Bromet et al., 2005).

There may be various explanations for the diagnostic instability especially in the beginning of the illness phase. Traditionally, most studies have labeled diagnostic changes as evidence of misdiagnosis at the initial clinical evaluation. Indeed, misdiagnosis could be a result of hesitancy by clinicians to assign a stigmatizing label such as schizophrenia, especially at young age. Using structured diagnostic instruments to ascertain diagnoses also appeared to improve diagnostic stability (McClellan & McCurry, 1999). However, there is also strong evidence indicating that the course of psychiatric symptoms and clinical presentation may change over time while adolescents move through different phases of social, behavioral and neural development (Ochoa et al., 2012). Importantly, symptoms at an early age are less specific and show great overlap with a number of developmental disorders, including autism spectrum and ADHD (Siebald et al., 2016). Thus, applying the "adult criteria" to children and adolescents with a suspected psychotic disorder can be problematic.

Replication and reconsideration of diagnosis is therefore recommended after several years of follow-up (Remschmidt & Theisen, 2005).

Incidence and prevalence of psychotic symptoms in adolescence

Whereas psychotic disorders are relatively rare in adolescence, PLE are common phenomena. In a large representative Australian sample of 1998 adolescents (age 14−17 years), the 12-month prevalence of PLE ranged from 3.3% to 14.0% depending on the type of experience (Hielscher et al., 2018), with receiving special messages showing the lowest, and auditory hallucinations the highest prevalence. Dolphin et al. (2015) reported lifetime prevalence estimates between 10.4% and 13.7% in an Irish sample of 5910 adolescents, aged 12−19 years. The prevalence of auditory verbal hallucinations in a population-based sample of 16−19 year-old Norwegian adolescents (n = 9,646, 46.4% male) was 10.6%, in which 5.3% of the adolescents that experienced hallucinations indicated that they were troubled by the voices (Kompus et al., 2015). In the ALSPAC cohort described earlier, 9.2% of adolescents were rated as having either suspected (4.3%) or definite (4.9%) psychotic experiences (Zammit et al., 2013). The majority (62.8%) reported only one experience, while 21.0% reported two experiences, 8.8% reported three, and 7.4% reported four or more different types of experiences (Sullivan et al., 2020; Thompson et al., 2020; Zammit et al., 2013). Of these experiences, auditory and visual hallucinations were the most common, while 1.7% reported persecutory delusions (Zammit et al., 2013). The incidence of PLE peaked around 18 years of age (Sullivan et al., 2020). Among 553 adolescents in Ghana, the lifetime prevalence estimates of PLE were similarly around 10% using the answer category of "nearly always" on the Community Assessment of Psychic Experiences questionnaire (Konings et al., 2006), except for much higher percentages for two items related to grandiose thinking (Adjorlolo & Anum, 2021). Estimates appear higher for specific subgroups, such as adolescents seeking help for nonpsychotic psychopathology (Brandizzi et al., 2014; Pontillo et al., 2018) and ethnic minorities (Adriaanse et al., 2015; El Bouhaddani et al., 2019).

A systematic review summarizing 19 population studies reported a median prevalence of psychotic symptoms of 17% in childhood (age 9−12) and 7.5% among adolescents aged 13−18 years (Kelleher, Connor, et al., 2012). Compared to an estimated median prevalence of 5% in adult studies (Van Os et al., 2009), this suggests that prevalence declines with increasing age from childhood to adulthood. Similarly, the attenuated psychosis syndrome occurs more frequently in adolescent compared to adult samples (Schultze-Lutter et al., 2014). In line with this, PLE in adolescence are often transitory and not necessarily clinically significant. However, for a subgroup of adolescents, the PLE do bear clinical significance. These adolescents often report multiple

PLE or PLE with impact, or in combination with other risk factors, such as low self-esteem, suicidal ideation, cannabis-use, and nonpsychotic psychopathology such as depression and anxiety (Dolphin et al., 2015; Kelleher, Connor, et al., 2012). While the prevalence of PLE tends to decline from childhood to adolescence to adulthood, their clinical significance increases with age as is evident from associations with other forms of psychopathology as well as increased need for care (Kelleher, Connor, et al., 2012; Kelleher, Keeley, et al., 2012).

Methodological considerations

Several lines of studies from different data sources shed light on the epidemiology of EOP and psychotic symptoms in adolescence. Concerning EOP, a number of studies have used administrative claims data, hospital admission or nationwide psychiatric registry data including in- and outpatient services. Nationwide registry data are almost exclusively available in Scandinavian countries, and they provide an incredibly rich and important data source, especially for a relatively rare condition like EOP. It requires a large background population to produce a sufficient number of cases to provide reliable incidence and prevalence estimates. A limitation of registry data is that it is difficult to verify the validity of the diagnoses and research is restricted to the variables available in routine clinical data collection. This emphasizes the importance of examining the validity of clinical information in registries by comparing these data to variables retrieved from patient cohorts using systematic, validated research instruments.

Only a few prospective cohort studies have included consecutive cases of EOP. The Spanish Child and Adolescent First-Episode Psychosis Study (CAFEPS) is a longitudinal multicenter study that aims to evaluate a wide range of clinical, genetic, and prognostic characteristics of young people aged 9–17 years who presents with first-episode psychosis (Castro-Fornieles et al., 2007). The Norwegian Thematically Organized Psychosis Study for Youth (Youth-TOP) and the Swedish Stockholm Child and Adolescent Psychosis Study (SCAPS) are two other studies including consecutive cases of EOP and healthy controls. They include adolescents with psychotic disorders and at clinical high risk from 12 to 18 years with follow-up after 3 years. The studies collect clinical and cognitive data, structural and functional brain scans, biomarkers, and genetic data (Smelror, 2019). Given that EOP is relatively rare, prospective studies take up a large amount of financial and logistical resources to identify and follow a representative cohort of patients. The majority of studies that include individuals with EOP collected data retrospectively using chart review. It is important to have prospective data which can be obtained from the national birth registries. Another common approach using data from first-episode psychosis programs has been to retrospectively divide participants into early-onset or adult-onset psychosis based on structured instruments

that systematically identify the age of illness onset, such as the Interview for the Retrospective Assessment of the Onset of Schizophrenia (Häfner et al., 1992). Given that these types of studies have not been set up to identify adolescents with EOP, it is possible that this group experiences more health barriers to care and is less likely to enter specialized psychosis services.

A major limitation of the overall body of epidemiological evidence is the lack of representation. The vast majority of epidemiological studies on EOP and psychotic symptoms in adolescence are from Europe, North America, and Australia. Therefore, the generalizability of the study findings is limited to these socio-geographical contexts. More research is needed from other continents, specifically South America, Asia, and Africa. Furthermore, the inconsistency in the literature regarding nomenclature, use of diagnostic criteria, sex differences in the incidence of psychosis throughout adolescence and early adulthood warrant further investigation. The same is recommended for bipolar disorder with and without psychotic symptoms, and the overlap with other neurodevelopmental syndromes. Together, these future avenues may deepen our understanding of the underlying social processes that may play a role in the etiology of EOP.

Future directions

First, we propose some methodological considerations. Considering the developmental stages of childhood and adolescence, and the differences in presentation of psychosis compared to adult samples, validated tools specifically targeting these developmental groups would be a considerable step forward in identifying EOP. This will potentially increase the validity of the clinical information and facilitate comparison between studies.

Using online, digital methods in these age groups might be specifically useful, since adolescents are apt users of digital devices, and in Western countries, many adolescents own or have access to mobile phones or computers. These methods might increase the propensity to participate in studies, since it may overcome the selection bias of participants due to their location, and the inequality of help seeking for those who need mental health support. Possibly, this may also be used in studies in the Global South, where geographic distances to health care are often long and an obstacle to accessibility. Psychiatric health care may also not be available, or not affordable when available. There has been a recent increase in the use of virtual reality, which might be used as a diagnostic tool, providing more ecologically valid situations than questionnaires.

Second, for the existing cohorts and studies, stratification of age groups will be a useful addition, considering the changes of incidence during different developmental stages, such as adolescence. This is also of particular interest for studies targeting sex differences, given that prevalence and incidence vary across sexes and age groups. Reliable incidence estimates in large cohorts of

youth that are followed longitudinally are indispensable for explaining sources of incidence variation. This will be instrumental for service planning and for the identification of appropriate targets for early intervention.

Third, the wealth of prospectively collected data that nation-wide population-based data registries provide could be synthesized and coupled with other registry data. Examples of population-based registries are multi-generation registry, medical birth registry on pregnancy and births, patient diagnosis registries, and registries for sociodemographic and academic data, immigration, school performance, clinical records of patients and drug prescription, and cause of death. The registry data can be made available to use for approved scientific purposes, as in Scandinavia.

Lastly, based on the low generalizability of the presented data, and the underrepresentation of studies in the Global South, future research could explore cross-country and cross-cultural variation in the epidemiological landscape of psychosis in adolescence. Using the same study methods in different countries will increase comparison and generalizability, and let putative cross-cultural differences be addressed in a meaningful way.

Conclusions

The progressive increase in incidence of psychotic disorders between 13 and 18 years of age is remarkable. Nonaffective psychosis including schizophrenia is more commonly diagnosed than affective (e.g., bipolar) disorders with psychotic features. The diagnostic stability of schizophrenia and bipolar disorder is high. PLE are common in adolescence. Their prevalence declines from childhood to adolescence and adulthood, while their clinical significance increases with age. Overall, the epidemiology of EOP is characterized by substantial variation by sex, age, and geographical location, as well as by various factors associated with research design and the nature of the data source. Digital tools may offer new possibilities for data capture on a global scale. With about a quarter of psychosis cases being adolescent onset, it is extremely important to have reliable data on incidence, to adequately intervene and treat these individuals still in development.

References

Adjorlolo, S., & Anum, A. (2021). Positive and negative psychosis risk symptoms among adolescents in Ghana. *International Journal of Adolescence and Youth, 26*(1), 307−320. https://doi.org/10.1080/02673843.2021.1933110

Adriaanse, M., Van Domburgh, L., Hoek, H. W., Susser, E., Doreleijers, T. A. H., & Veling, W. (2015). Prevalence, impact and cultural context of psychotic experiences among ethnic minority youth. *Psychological Medicine, 45*(3), 637−646. https://doi.org/10.1017/S0033291714001779

Alavi, S. S., Mohammadi, M. R., Hooshyari, Z., Kalhori, S. M., Salehi, M., Salmanian, M., Khaleghi, A., Zarafshan, H., Ahmadi, A., Kamali, K., & Ahmadi, N. (2021). Epidemiology of

psychotic disorders based on demographic variables in iranian children and adolescents. *Iranian Journal of Psychiatry, 16*(1), 1−12. https://doi.org/10.18502/ijps.v16i1.5372

Aleman, A., Kahn, R. S., & Selten, J. P. (2003). Sex differences in the risk of schizophrenia: Evidence from meta-analysis. *Archives of General Psychiatry, 60*(6), 565−571. https://doi.org/10.1001/archpsyc.60.6.565

American Psychiatric Association. (1987). *DSM III-R diagnostic and statistical manual of mental disorders* (3rd ed.). American Psychiatric Association. Text Revision.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

Amminger, G. P., Henry, L. P., Harrigan, S. M., Harris, M. G., Alvarez-Jimenez, M., Herrman, H., Jackson, H. J., & Mcgorry, P. D. (2011). Outcome in early-onset schizophrenia revisited: Findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study. *Schizophrenia Research, 131*(1−3), 112−119. https://doi.org/10.1016/j.schres.2011.06.009

Anderson, K. K., Fuhrer, R., Abrahamowicz, M., & Malla, A. K. (2012). The incidence of first-episode schizophrenia-spectrum psychosis in adolescents and young adults in Montreal: An estimate from an administrative claims database. *Canadian Journal of Psychiatry, 57*(10), 626−633. https://doi.org/10.1177/070674371205701007

Boeing, L., Murray, V., Pelosi, A., McCabe, R., Blackwood, D., & Wrate, R. (2007). Adolescent-onset psychosis: Prevalence, needs and service provision. *British Journal of Psychiatry, 190*, 18−26. https://doi.org/10.1192/bjp.190.1.18

Bo, S., & Haahr, U. H. (2015). Early-onset psychosis and child and adolescent schizophrenia. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 4*(1), 1−3. https://doi.org/10.21307/sjcapp-2016-001

El Bouhaddani, S., van Domburgh, L., Schaefer, B., Doreleijers, T. A. H., & Veling, W. (2019). Psychotic experiences among ethnic majority and minority adolescents and the role of discrimination and ethnic identity. *Social Psychiatry and Psychiatric Epidemiology, 54*(3), 343−353. https://doi.org/10.1007/s00127-019-01658-1 2013.12060768

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2013). Cohort profile: The 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology, 42*(1), 111−127. https://doi.org/10.1093/ije/dys064

Brand, B. A., de Boer, J. N., Dazzan, P., & Sommer, I. E. (2022). Towards better care for women with schizophrenia-spectrum disorders. *The Lancet Psychiatry, 9*(4), 330−336. https://doi.org/10.1016/S2215-0366(21)00383-7

Brandizzi, M., Schultze-Lutter, F., Masillo, A., Lanna, A., Curto, M., Lindau, J. F., Solfanelli, A., Listanti, G., Patanè, M., Kotzalidis, G., Gebhardt, E., Meyer, N., Di Pietro, D., Leccisi, D., Girardi, P., & Fiori Nastro, P. (2014). Self-reported attenuated psychotic-like experiences in help-seeking adolescents and their association with age, functioning and psychopathology. *Schizophrenia Research, 160*(1−3), 110−117. https://doi.org/10.1016/j.schres.2014.10.005

Bromet, E. J., Naz, B., Fochtmann, L. J., Carlson, G. A., & Tanenberg-Karant, M. (2005). Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. *Schizophrenia Bulletin, 31*(3), 639−649. https://doi.org/10.1093/schbul/sbi030

Castagnini, A., & Foldager, L. (2013). Variations in incidence and age of onset of acute and transient psychotic disorders. *Social Psychiatry and Psychiatric Epidemiology, 48*(12), 1917−1922. https://doi.org/10.1007/s00127-013-0726-7

Castle, D. J., Wessely, S., & Murray, R. M. (1993). Sex and schizophrenia: Effects of diagnostic stringency, and associations with premorbid variables. *British Journal of Psychiatry, 162*(MAY), 658−664. https://doi.org/10.1192/bjp.162.5.658

Castro-Fornieles, J., Baeza, I., de la Serna, E., Gonzalez-Pinto, A., Parellada, M., Graell, M., Moreno, D., Otero, S., & Arango, C. (2011). Two-year diagnostic stability in early-onset first-episode psychosis. *Journal of Child Psychology and Psychiatry, 52*(10), 1089−1098. https://doi.org/10.1111/j.1469-7610.2011.02443.x

Castro-Fornieles, J., Parellada, M., Gonzalez-Pinto, A., Moreno, D., Graell, M., Baeza, I., Otero, S., Soutullo, C. A., Crespo-Facorro, B., Ruiz-Sancho, A., Desco, M., Rojas-Corrales, O., Patiño, A., Carrasco-Marin, E., & Arango, C. (2007). The child and adolescent first-episode psychosis study (CAFEPS): Design and baseline results. *Schizophrenia Research, 91*(1−3), 226−237. https://doi.org/10.1016/j.schres.2006.12.004

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B. B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K. B., Timmerman, A., Schendel, D., McGrath, J. J., Mortensen, P. B., & Pedersen, C. B. (2020). Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. *JAMA Psychiatry, 77*(2), 155−164. https://doi.org/10.1001/jamapsychiatry.2019.3523

Defilippis, M. S., & Wagner, K. D. (2013). Bipolar depression in children and adolescents. *CNS Spectrums, 18*(4), 209−213. https://doi.org/10.1017/S1092852913000217

Dolphin, L., Dooley, B., & Fitzgerald, A. (2015). Prevalence and correlates of psychotic like experiences in a nationally representative community sample of adolescents in Ireland. *Schizophrenia Research, 169*(1−3), 241−247. https://doi.org/10.1016/j.schres.2015.09.005

Fraguas, D., De Castro, M. J., Medina, O., Parellada, M., Moreno, D., Graell, M., Merchán-Naranjo, J., & Arango, C. (2008). Does diagnostic classification of early-onset psychosis change over follow-up? *Child Psychiatry and Human Development, 39*(2), 137−145. https://doi.org/10.1007/s10578-007-0076-3

Gaebel, W. (2012). Status of psychotic disorders in ICD-11. *Schizophrenia Bulletin, 38*(5), 895−898. https://doi.org/10.1093/schbul/sbs104

Gillberg, C., Wahlström, J., Forsman, A., Hellgren, L., & Gillberg, I. C. (1986). Teenage psychoses - epidemiology, classification and reduced optimality in the pre-, peri- and neonatal periods. *Journal of Child Psychology and Psychiatry, 27*(1), 87−98. https://doi.org/10.1111/j.1469-7610.1986.tb00624.x

González-Valderrama, A., Jongsma, H. E., Mena, C., Castañeda, C. P., Nachar, R., Undurraga, J., Crossley, N., Aceituno, D., Iruretagoyena, B., & Gallardo, C. (2020). The incidence of non-affective psychotic disorders in Chile between 2005 and 2018: Results from a national register of over 30 000 cases. *Psychological Medicine*, 1−10.

Häfner, H. (1998). Onset and course of the first schizophrenic episode. *The Kaohsiung Journal of Medical Sciences, 14*(7), 413−431.

Häfner, H. (2019). From onset and prodromal stage to a life-long course of schizophrenia and its symptom dimensions: How sex, age, and other risk factors influence incidence and course of illness. *Psychiatry Journal, 2019*, 1−15. https://doi.org/10.1155/2019/9804836

Häfner, H., Maurer, K., Löffler, W., Fätkenheuer, B., Heiden, W. A. D., Riecher-Rössler, A., Behrens, S., & Gattaz, W. F. (1994). The epidemiology of early schizophrenia. *British Journal of Psychiatry, 164*(S23), 29−38. https://doi.org/10.1192/s0007125000292714

Häfner, H., Riecher-Rössler, A., Hambrecht, M., Maurer, K., Meissner, S., Schmidtke, A., Fätkenheuer, B., Löffler, W., & van der Heiden, W. (1992). IRAOS: An instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research, 6*(3), 209−223. https://doi.org/10.1016/0920-9964(92)90004-O

Hielscher, E., Connell, M., Lawrence, D., Zubrick, S. R., Hafekost, J., & Scott, J. G. (2018). Prevalence and correlates of psychotic experiences in a nationally representative sample of Australian adolescents. *Australian and New Zealand Journal of Psychiatry, 52*(8), 768−781. https://doi.org/10.1177/0004867418785036

Hollis, C. (2000). Adult outcomes of child- and adolescent-onset schizophrenia: Diagnostic stability and predictive validity. *American Journal of Psychiatry, 157*(10), 1652−1659. https://doi.org/10.1176/appi.ajp.157.10.1652

Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., Lewis, G., Menezes, P., Thompson, A., Wolke, D., Zammit, S., & Harrison, G. (2008). IQ and non-clinical psychotic symptoms in 12-year-olds: Results from the ALSPAC birth cohort. *British Journal of Psychiatry, 193*(3), 185−191. https://doi.org/10.1192/bjp.bp.108.051904

Høye, A., Rezvy, G., Hansen, V., & Olstad, R. (2006). The effect of gender in diagnosing early schizophrenia. *Social Psychiatry and Psychiatric Epidemiology, 41*(7), 549−555. https://doi.org/10.1007/s00127-006-0066-y

Jablensky, A., McGrath, J., Herrman, H., Castle, D., Gureje, O., Evans, M., Carr, V., Morgan, V., Korten, A., & Harvey, C. (2000). Psychotic disorders in urban areas: An overview of the study on low prevalence disorders. *Australian and New Zealand Journal of Psychiatry, 34*(2), 221−236. https://doi.org/10.1046/j.1440-1614.2000.00728.x

Jarbin, H., & Von Knorring, A. L. (2003). Diagnostic stability in adolescent onset psychotic disorders. *European Child and Adolescent Psychiatry, 12*(1), 15−22. https://doi.org/10.1007/s00787-003-0300-z

Jongsma, H. E., Turner, C., Kirkbride, J. B., & Jones, P. B. (2019). International incidence of psychotic disorders, 2002−17: A systematic review and meta-analysis. *The Lancet Public Health, 4*(5), e229−e244. https://doi.org/10.1016/S2468-2667(19)30056-8

Kelleher, I., & Cannon, M. (2011). Psychotic-like experiences in the general population: Characterizing a high-risk group for psychosis. *Psychological Medicine, 41*(1), 1−6. https://doi.org/10.1017/S0033291710001005

Kelleher, I., Connor, D., Clarke, M. C., Devlin, N., Harley, M., & Cannon, M. (2012). Prevalence of psychotic symptoms in childhood and adolescence: A systematic review and meta-analysis of population-based studies. *Psychological Medicine, 42*(9), 1857−1863. https://doi.org/10.1017/S0033291711002960

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M. C., Harley, M., Arseneault, L., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: Evidence from four population-based studies. *British Journal of Psychiatry, 201*(1), 26−32. https://doi.org/10.1192/bjp.bp.111.101543

Kirkbride, J. B., Hameed, Y., Ankireddypalli, G., Ioannidis, K., Crane, C. M., Nasir, M., Kabacs, N., Metastasio, A., Jenkins, O., Espandian, A., Spyridi, S., Ralevic, D., Siddabattuni, S., Walden, B., Adeoye, A., Perez, J., & Jones, P. B. (2017). The epidemiology of first-episode psychosis in early intervention in psychosis services: Findings from the social epidemiology of psychoses in east Anglia [SEPEA] Study. *American Journal of Psychiatry, 174*(2), 143−153. https://doi.org/10.1176/appi.ajp.2016.16010103

Kleinhaus, K., Harlap, S., Perrin, M., Manor, O., Weiser, M., Lichtenberg, P., & Malaspina, D. (2011). Age, sex and first treatment of schizophrenia in a population cohort. *Journal of Psychiatric Research, 45*(1), 136−141. https://doi.org/10.1016/j.jpsychires.2010.05.010

Kompus, K., Løberg, E. M., Posserud, M. B., & Lundervold, A. J. (2015). Prevalence of auditory hallucinations in Norwegian adolescents: Results from a population-based study. *Scandinavian Journal of Psychology, 56*(4), 391−396. https://doi.org/10.1111/sjop.12219

Konings, M., Bak, M., Hanssen, M., Van Os, J., & Krabbendam, L. (2006). Validity and reliability of the CAPE: A self-report instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatrica Scandinavica, 114*(1), 55−61. https://doi.org/10.1111/j.1600-0447.2005.00741.x

Kroon, J. S., Wohlfarth, T. D., Dieleman, J., Sutterland, A. L., Storosum, J. G., Denys, D., de Haan, L., & Sturkenboom, M. C. (2013). Incidence rates and risk factors of bipolar disorder in the general population: A population-based cohort study. *Bipolar Disorders, 15*(3), 306−313. https://doi.org/10.1111/bdi.12058

Lasalvia, A., Bonetto, C., Tosato, S., Zanatta, G., Cristofalo, D., Salazzari, D., Lazzarotto, L., Bertani, M., Bissoli, S., De Santi, K., Cremonese, C., De Rossi, M., Gardellin, F., Ramon, L., Zucchetto, M., Amaddeo, F., Tansella, M., Ruggeri, M., Brambilla, P., … Santi, M. (2014). First-contact incidence of psychosis in north-eastern Italy: Influence of age, gender, immigration and socioeconomic deprivation. *British Journal of Psychiatry, 205*(2), 127−134. https://doi.org/10.1192/bjp.bp.113.134445

Magee, C., Guhn, M., Puyat, J. H., Gadermann, A., & Oberle, E. (2022). Diagnosed incidence of non-affective psychotic disorders amongst adolescents in British Columbia and sociodemographic risk factors: A retrospective cohort study. *The Canadian Journal of Psychiatry, 67*(4), 296−305. https://doi.org/10.1177/07067437211055412

McClellan, J., & McCurry, C. (1999). Early onset psychotic disorders: Diagnostic stability and clinical characteristics. *European Child and Adolescent Psychiatry, 8*(S1), S13−S19. https://doi.org/10.1007/pl00010686

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine, 2*(1). https://doi.org/10.1186/1741-7015-2-13

Merikangas, K. R., He, J. P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., & Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the national comorbidity survey replication-adolescent supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(10), 980−989. https://doi.org/10.1016/j.jaac.2010.05.017

Mohammadi, M. R., Ahmadi, N., Khaleghi, A., Mostafavi, S. A., Kamali, K., Rahgozar, M., Ahmadi, A., Hooshyari, Z., Alavi, S. S., Molavi, P., Sarraf, N., Hojjat, S. K., Mohammadzadeh, S., Amiri, S., Arman, S., Ghanizadeh, A., Ahmadipour, A., Ostovar, R., Nazari, H., … Fombonne, E. (2019). Prevalence and correlates of psychiatric disorders in a national survey of Iranian children and adolescents. *Iranian Journal of Psychiatry, 14*(1), 1−15. https://doi.org/10.18502/ijps.v14i1.418

Murray, C. J. L., & Lopez, A. D. (Eds.). (1996). *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: Summary.* World Health Organization.

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment, 2012*, 1−9. https://doi.org/10.1155/2012/916198

Okkels, N., Vernal, D. L., Jensen, S. O. W., McGrath, J. J., & Nielsen, R. E. (2013). Changes in the diagnosed incidence of early onset schizophrenia over four decades. *Acta Psychiatrica Scandinavica, 127*(1), 62−68. https://doi.org/10.1111/j.1600-0447.2012.01913.x

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppä, T., Härkänen, T., Koskinen, S., & Lönnqvist, J.

(2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry, 64*(1), 19–28. https://doi.org/10.1001/archpsyc.64.1.19

Pontillo, M., De Luca, M., Pucciarini, M. L., Vicari, S., & Armando, M. (2018). All that glitters is not gold: Prevalence and relevance of psychotic-like experiences in clinical sample of children and adolescents aged 8–17 years old. *Early Intervention in Psychiatry, 12*(4), 702–707. https://doi.org/10.1111/eip.12370

Remschmidt, H. E., Schulz, E., Martin, M., Warnke, A., & Trott, G. E. (1994). Childhood-onset schizophrenia: History of the concept and recent studies. *Schizophrenia Bulletin, 20*(4), 727–745. https://doi.org/10.1093/schbul/20.4.727

Remschmidt, H. E., & Theisen, F. M. (2005). Schizophrenia and related disorders in children and adolescents. *Journal of Neural Transmission, Supplement, 69*, 121–141. https://doi.org/10.1007/3-211-31222-6_7

Riecher-Rössler, A., Butler, S., & Kulkarni, J. (2018). Sex and gender differences in schizophrenic psychoses—a critical review. *Archives of Women's Mental Health, 21*(6), 627–648. https://doi.org/10.1007/s00737-018-0847-9

Schultze-Lutter, F., Michel, C., Ruhrmann, S., & Schimmelmann, B. G. (2014). Prevalence and clinical significance of DSM-5-attenuated psychosis syndrome in adolescents and young adults in the general population: The Bern Epidemiological At-Risk (BEAR) Study. *Schizophrenia Bulletin, 40*(6), 1499–1508. https://doi.org/10.1093/schbul/sbt171

Schwartz, J. E., Fennig, S., Tanenberg-Karant, M., Carlson, G., Craig, T., Galambos, N., Lavelle, J., & Bromet, E. J. (2000). Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Archives of General Psychiatry, 57*(6), 593–600. https://doi.org/10.1001/archpsyc.57.6.593

Seminog, O., Hoang, U., Goldacre, M., & James, A. (2021). National record-linkage study of hospital admissions for schizophrenia in childhood and adolescence in England. *European Child and Adolescent Psychiatry*. https://doi.org/10.1007/s00787-021-01817-3

Siebald, C., Khandaker, G. M., Zammit, S., Lewis, G., & Jones, P. B. (2016). Association between childhood psychiatric disorders and psychotic experiences in adolescence: A population-based longitudinal study. *Comprehensive Psychiatry, 69*, 45–52. https://doi.org/10.1016/j.comppsych.2016.05.004

Smelror, R. E. (2019). *Cognitive and clinical characteristics in adolescent non-affective early-onset psychosis and healthy controls* (Ph.D. Thesis). University of Oslo.

Söderlund, J., Wicks, S., Jörgensen, L., & Dalman, C. (2015). Comparing cohort incidence of schizophrenia with that of bipolar disorder and affective psychosis in individuals born in Stockholm County 1955–1967. *Psychological Medicine, 45*(16), 3433–3439. https://doi.org/10.1017/s0033291715001336

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry, 27*(1), 281–295. https://doi.org/10.1038/s41380-021-01161-7

Sullivan, S. A., Kounali, D., Cannon, M., David, A. S., Fletcher, P. C., Holmans, P., Jones, H., Jones, P. B., Linden, D. E. J., Lewis, G., Owen, M. J., O'Donovan, M., Rammos, A., Thompson, A., Wolke, D., Heron, J., & Zammit, S. (2020). A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *American Journal of Psychiatry, 177*(4), 308–317. https://doi.org/10.1176/appi.ajp.2019.19060654

Susser, E., Schwartz, S., Morabia, A., & Bromet, E. J. (2006). *Psychiatric epidemiology: Searching for the causes of mental disorders*. Oxford University Press.

Talonen, S., Väänänen, J., & Kaltiala-Heino, R. (2017). Gender differences in first onset Schizophrenia spectrum psychoses. *Nordic Journal of Psychiatry, 71*(2), 131−138. https://doi.org/10.1080/08039488.2016.1245783

Thompson, A. D., Jones, H. J., Heron, J., Hibbeln, J., Sullivan, S., & Zammit, S. (2020). Omega-3 and Omega-6 fatty acids and risk of psychotic outcomes in the ALSPAC birth cohort. *Schizophrenia Research, 224*, 108−115. https://doi.org/10.1016/j.schres.2020.09.018

Thomsen, P. H. (1996). Schizophrenia with childhood and adolescent onset - a nationwide register-based study. *Acta Psychiatrica Scandinavica, 94*(3), 187−193. https://doi.org/10.1111/j.1600-0447.1996.tb09847.x

Van Meter, A. R., Moreira, A. L. R., & Youngstrom, E. A. (2011). Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *Journal of Clinical Psychiatry, 72*(9), 1250−1256. https://doi.org/10.4088/JCP.10m06290

Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine, 39*(2), 179−195. https://doi.org/10.1017/S0033291708003814

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 457−465. https://doi.org/10.1097/00004583-199105000-00017

World Health Organization. (2001). *The world health report: 2001: Mental health: New understanding, new hope*. World Health Organization. https://apps.who.int/iris/handle/10665/42390.

World Health Organization. (2019). *International classification of diseases, eleventh revision (ICD-11)*. World Health Organization. https://icd.who.int/browse11.

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., Jones, P. B., Lewis, S., Sullivan, S., Wolke, D., & Lewis, G. (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry, 170*(7), 742−750. https://doi.org/10.1176/appi.ajp.2013.12060768

Chapter 3

Genetics of psychotic disorders with focus on early-onset psychosis

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Introduction

Psychosis is characterized by specific symptoms of abnormal thoughts and perceptions, primarily delusions, and hallucinations. These psychotic symptoms are present across different psychiatric diagnoses, which are named psychotic disorders. They typically include schizophrenia and bipolar disorder, but psychotic symptoms are also common in other conditions such as severe depression (Benard et al., 2020). A subtype of psychotic disorders develops before the age of 18 years, termed early-onset psychosis (EOP) (Díaz-Caneja et al., 2015), while childhood-onset schizophrenia (COS) is defined by the onset of schizophrenia before the age of 13 years (Fernandez et al., 2019). In addition, psychotic symptoms can also be induced by medication (Jensen & Abba-Aji, 2020) and substance use (Fiorentini et al., 2021), and appear in neurological disorders (Chendo et al., 2022).

The German psychiatrist Emil Kraepelin was one of the first to describe psychotic disorders. He proposed a dichotomy between dementia praecox (later termed schizophrenia) and manic depressive disorder (later termed bipolar disorder) and described an increased frequency of dementia praecox within families (Kraepelin, 1919). Later, a more converging understanding of the disorders has been proposed, where affective and psychotic disorders might be understood as conditions on an expanded psychiatric continuum with partly overlapping clinical and etiological characteristics (Möller, 2003). Psychotic disorders usually begin in adolescence or early adulthood, often

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00005-6

preceded by prodromal symptoms such as social withdrawal and cognitive decline (Fusar-Poli et al., 2012).

The lifetime risk for schizophrenia has been reported to 1% across gender, time, and geography (Owen et al., 2016), and the lifetime risk for bipolar disorder to 1.3% for men and 1.8% for women (Pedersen et al., 2014). COS on the other hand is a very rare condition, with a prevalence less than one in 10,000 individuals (<0.01%) (Burd & Kerbeshian, 1987). A large twin study found a lifetime prevalence of psychotic symptoms in 7.1% in young adults (age range 18−38 years), indicating that the presence of psychotic symptoms is more common than psychotic disorders fulfilling diagnostic criteria (Couvy-Duchesne et al., 2018).

Genetic epidemiology

Twin studies have shown a high heritability for schizophrenia (approximately 80%) (Sullivan et al., 2003) and bipolar disorder (approximately 60%−70%) (Edvardsen et al., 2008; Johansson et al., 2019). A high heritability (>80%) is also suggested for COS comparing the concordance rates between monozygotic and dizygotic twins, indicating that the genetic susceptibility might be even stronger in this subgroup (Forsyth & Asarnow, 2020; Kallmann & Roth, 1956). While large-scale multicenter studies have been carried out for adults with schizophrenia and bipolar disorder, comparable large sample sizes have not been reachable for youth with early-onset schizophrenia due to its rarity. However, there is evidence for a considerable overlap with the genetic etiology for individuals with adult-onset schizophrenia as well as other neurodevelopmental disorders such as autism spectrum disorder and intellectual disability (Forsyth & Asarnow, 2020).

Family studies

Family studies were initiated after the observation that severe mental disorders seemed to aggregate within families. A large number of family studies have been carried out for patients with schizophrenia and bipolar disorder, confirming familial accumulation of severe mental illness.

A Swedish population-based register study included more than nine million individuals, of them 35,985 individuals diagnosed with schizophrenia and 40,487 individuals diagnosed with bipolar disorder. This study reported 9 times higher risk of schizophrenia and approximately 8 times higher risk of bipolar disorder in full-siblings. Furthermore, the study reported an estimated heritability of 64% for schizophrenia and 59% for bipolar disorder (Lichtenstein et al., 2009).

A review of family studies of individuals with schizophrenia found an almost 10 times higher risk for schizophrenia in first-degree relatives compared to relatives of a matched control group, and it was suggested that the

increased prevalence of schizophrenia in relatives was mainly due to genetic factors rather than shared environment (Kendler & Diehl, 1993). The lifetime risk for schizophrenia in parents of individuals with COS has been reported to be considerably higher than the risk for schizophrenia in the general population and the parents of individuals with COS had in average an earlier age at onset (Asarnow et al., 2001).

In addition to an increased risk for schizophrenia observed in relatives to a person with schizophrenia, an aggregation of other conditions and personality traits has been observed. A familial predisposition for schizophrenia, schizotypal, and avoidant personality disorders in parents of individuals with COS has been reported (Asarnow et al., 2001). Accordingly, parents of individuals with adult-onset schizophrenia have shown a higher prevalence of schizotypal-, schizoid-, avoidant-, and paranoid personality disorders, schizoaffective disorder and nonaffective psychosis (Kendler et al., 1993a,b). Shared familial liability of other personality- and psychiatric disorders in individuals with childhood- and adult-onset schizophrenia supports a shared genetic susceptibility for these disorders.

Based on Swedish registry data, first-degree relatives of a person with bipolar disorder have approximately 6–8 times higher risk of developing bipolar disorder compared to relatives without an affected family member. Further, for second- and third-degree relatives the risk was reported to be 2.2–3.3 and 1.6 times higher, respectively (Song et al., 2015). A family study of childhood-onset mood disorders including bipolar disorder reported a more than two times higher prevalence of mood disorders in first-degree relatives compared with first-degree relatives of adult-onset mood disorders (Neuman et al., 1997). This might indicate a higher genetic susceptibility in early-onset affective disorders.

An increased prevalence of other neurobiological abnormalities is also reported in nonpsychotic family members of individuals with COS (Forsyth & Asarnow, 2020). Among nonpsychotic relatives of patients with schizophrenia, abnormal magnetic resonance imaging (MRI) findings, aberrant electric brain activity and impaired cognitive functioning have been described to be more prevalent compared with individuals without an affected relative (Allen et al., 2009; Forsyth & Asarnow, 2020; Owens et al., 2016). The term endophenotype is sometimes used to describe heritable neurobiological abnormalities, characterized by a cosegregation (the tendency to be inherited together) with an illness within a family and state independence (as a stable trait across time) (Gottesman & Gould, 2003). An endophenotype is further characterized by a higher prevalence within unaffected family members of a person with a psychotic disorder compared to the general population. It has been suggested that these phenotypes might be closer to underlying pathophysiological mechanisms compared to the complex psychiatric phenotypes, thus representing identifiable features deconstructed from the complex phenotype with more

identifiable underlying genetics (Gottesman & Gould, 2003; Gottesman & Shields, 1973).

Twin and adoption studies

The comparison of the presence of disease in monozygotic and dizygotic twin pairs is a well-established design to explore the relative contribution of genetic and environmental risk factors for a condition. A Nationwide Danish study included 31,524 twin pairs with psychiatric register diagnoses and reported that the concordance rate (i.e., the probability that both twins develop the same disease) for schizophrenia is 33% in monozygotic twins and 7% in dizygotic twins, and calculated the heritability estimate to 79% (Hilker et al., 2018). A large meta-analysis including data from 12 twin studies estimated the heritability for schizophrenia to be 81%, whereas the contribution from shared environmental factors was estimated to 11% (Sullivan et al., 2003). For bipolar spectrum disorders, the concordance rate has been reported to be 42% for monozygotic twins and 11% for dizygotic twins (Edvardsen et al., 2008). A study of twins with early-onset schizophrenia (age under 15 years) found a concordance rate of 88% for monozygotic twins and 22% dizygotic twins, and a high estimated heritability of 85%, indicating a substantial genetic susceptibility for early-onset schizophrenia (Kallmann & Roth, 1956). Consistent with this finding, a more recent Danish twin study found that younger age at onset of schizophrenia was associated with a higher genetic vulnerability (Hilker et al., 2017).

A recent Swedish National Adoption Study evaluated the contribution from genetic and environmental factors to parent-offspring transmission of bipolar disorder and cross-generational association with nonaffective psychotic disorders (Kendler et al., 2020). Their findings suggest that genes are largely responsible for transmission of bipolar disorder across generations, but evidence for a modest effect of raring was also found. On the other hand, the parent−offspring transmission between bipolar disorder and nonaffective psychotic disorders was found to be entirely genetic (Kendler et al., 2020).

Molecular genetics

Systematic research and systematization of hereditary traits date back to Gregor Mendel (1822−84), who is known for his contribution to the science of genetics. The relationship between a hereditary component (genotype) and the clinical expression (phenotype) is described as having Mendelian inheritance if it follows recognizable, predictable rules such as autosomal dominant, autosomal recessive, sex-linked, or mitochondrial. Our genome consists of 46 chromosomes, of which 22 pairs of autosomes and one pair of sex chromosomes (X and Y). For an autosomal dominant inherited phenotype, it is sufficient to have a genetic change in one of two gene copies, and offspring of an

affected person will have 50% probability to inherit the genetic variant and might develop the phenotype. In autosomal recessive inheritance, a disease-causing variant must be present in both gene copies for a phenotype to develop. People with a disease-causing variant in only one of two gene copies will be healthy carriers. Dominant and recessive inheritance are also present for the sex chromosomes, whereas the mitochondria are only inherited from the mother. Most common disorders, including psychiatric disorders, however, have multifactorial etiology where both multiple genes and the environment confer risk to develop a condition.

The human chromosomes as carriers of hereditary traits were first identified in the late nineteenth century. The chromosomes are dynamic structures that consist of deoxyribonucleic acid (DNA) and proteins which together are called chromatin. Chromatin exists in a less condensed form (euchromatin) when genes are transcribed (the process of reading DNA to RNA) and a more condensed form when genes are not transcribed (heterochromatin). Complex genetic and epigenetic mechanisms contribute to the regulation of gene transcription.

The human genome was first sequenced in 2003 as part of the Human Genome Project and consists of three billion nucleotide base pairs (Collins et al., 2003; Lander et al., 2001). The number of genes has been debated, but it is reported to be approximately 20,000 protein coding genes and 20,000 nonprotein coding genes (Willyard, 2018). The sequence of four types of nucleotide base pairs, adenine (A), cytosine (C), guanine (G), and thymine (T) forms the recipes for the proteins produced by the cells. Only approximately 1% of the genome, the exome, encodes proteins (Ng, Turner, et al., 2009). Part of the remaining DNA sequence is translated to noncoding RNA transcripts. These noncoding transcripts might have regulatory functions on the chromatin structure and gene transcription with implications for normal human physiology, as well as for the development of disease (Qiu et al., 2021).

During the last decades, our knowledge of the genomic structure and variance, and the relationship with disease has rapidly increased. There are different kinds of genetic variation and the 1000 Genome Project (an initiative working to provide an overview over different kinds of genetic variation across populations) has identified that a typical human genome differs from a reference genome at 4.1 million to five million sites (Auton et al., 2015). The major part of the variation consists of common sequence variants called single nucleotide polymorphisms (SNPs) with a frequency $>1\%$ and short insertions or deletions (<50 base pairs). Single nucleotide variants (SNV) with a frequency less than 1% and structural variants are also prevalent in a typical genome (Auton et al., 2015). Structural variants can be of different type and size and comprises translocations, inversions, and copy number variants (CNV). CNVs such as deletions, duplications, and triplications might be of different size, from submicroscopic to involve whole chromosomes

(aneuploidy, such as monosomy/trisomy). CNVs might either be unique or recurrent; the latter often arises as a result from unequal crossing over in meiosis (nonallelic homologous recombination) due to segmental duplications in the genome (Liu et al., 2012). Large databases for normal variation in the DNA sequence are publicly available, such as Genome Aggregation Database (GnomAD) (Karczewski et al., 2020).

Sequence variants, indels (insertions or deletions of nucleotides), structural variants, and CNVs can either be inherited from a parent or have arisen de novo. The number of de novo variants increases with parental age, and the fathers' age contributes to a larger increase in de novo variants compared with the age of the mother (Jónsson et al., 2017). The annotation of the functional and molecular consequence of a genetic variant might be challenging and specific guidelines for interpretation of sequence variants and CNVs have been established (Brandt et al., 2020; Richards et al., 2015).

In addition to quantitative and qualitative differences in DNA, molecular mechanisms for gene regulation such as imprinting and epigenetic changes contribute to differences in human health. Most genes are expressed regardless of location on a maternally or paternally inherited chromosome. Imprinting refers to a regulatory process of gene expression through DNA and/or chromatin modification (Franklin et al., 1996). Some genes are imprinted only if they are inherited from the father or mother, and dysregulation of this process is a known cause of different imprinting disorders, such as Prader–Willi syndrome (Cassidy & Schwartz, 1998; Eggermann et al., 2015). Epigenetics refers to a process of DNA modifications such as methylation of nucleotides or histone modifications, both affecting the expression of genes (Gayon, 2016). Some epigenetic features are inherited through generations, while others are not (Gayon, 2016), and it is evidence for environmental impact on the individual epigenetic profile (Cavalli & Heard, 2019).

Methods

Specific technological methods are applied to detect different kinds of genetic variation in clinical diagnostics and research. In the following section, common methods and the relevance and findings in patients with psychotic disorders will be presented.

Linkage studies

Genetic linkage studies aim to detect the chromosomal location or gene responsible for a disease or trait, by exploring the cosegregation of a phenotype and a chromosomal marker during meiosis. Genetic linkage analysis has been a powerful tool used for mapping Mendelian traits, whereas other methods have been more suitable for detecting variants of modest effects associated with complex traits (Ott et al., 2015). For rare, monogenic

disorders, the technology has successfully recognized several disease-causing genes and chromosomal regions (Hall et al., 1990; Webb et al., 1998).

Linkage studies have been carried out both for individuals with bipolar disorder and schizophrenia (Barnett & Smoller, 2009; Ng, Levinson, et al., 2009), as well as in adolescents with early-onset schizophrenia (Gadelha et al., 2012). The method is less powerful to detect genetic variants of small to moderate effect sizes characterized by reduced penetrance, or variants associated with polygenic phenotypes, such as psychotic disorders (Risch, 2000). The interpretation of linkage analyses of suspected monogenic etiologies for EOP might also be complicated by phenocopies (an apparently equal/similar phenotype with another (multifactorial) etiology). Thus, the methodology has not disentangled a large part of the genetic contribution for severe mental disorders in general, nor in EOP.

Candidate gene studies

Association studies are designed to explore candidate genes for an association with a disease or trait by comparing frequencies of a genetic variant and a phenotype between relevant patients and matched healthy control subjects. A large number of association studies of small to moderate size have been carried out for individuals with psychotic disorders, initially exploring candidate genes based on plausible hypotheses for etiology.

A meta-analysis of a large number of association studies have been performed for adults with schizophrenia and bipolar disorder (Gatt et al., 2015). The candidate studies were generally underpowered to detect small effect sizes, and the results were generally not valid or reproducible.

Genome-wide association studies

Whereas association studies involve the examination of selected genes, the technology of genome-wide association studies (GWAS) allows the examination of hundreds to millions of DNA polymorphisms across the genome. GWAS is used in a large extent to identify correlations between SNPs and common, complex disorders or traits (Hirschhorn & Daly, 2005). The large number of SNPs in a GWAS analysis increases the risk of false positive findings (type 1 error). Thus a stringent threshold for statistical genome-wide significance level is essential ($P < 5 \times 10^{-8}$).

The hypothesis-free and hypothesis generating design has been beneficial enabling the identification of novel disease-causing genes and achievement of new insight into pathophysiological mechanisms (Tam et al., 2019). Because of linkage disequilibrium, referring to the tendency of variants to be inherited together, GWAS is able to capture a large part of the common variation in the genome. The knowledge of linkage disequilibrium and haplotypes enables the

calculation or imputation of additional common and rare variants (Kong et al., 2008).

International collaborations, such as the Psychiatric Genomics Consortium (PGC), has substantially increased the power and enabled the detection of variants with small effect sizes (Ripke et al., 2020).

Novel polygenic analytical approaches

Polygenic risk score (PRS)

The understanding of the individual small contribution from single common variants motivated the development of a statistical model for combining the effect of many common variants into a polygenic risk score (PRS) which is applied on GWAS data for individuals with schizophrenia and bipolar disorder (Purcell et al., 2009). PRS for schizophrenia has shown to be able to distinguish between a group of patients and a group of healthy controls in independent samples (Pardiñas et al., 2018; Ripke et al., 2014), but the sensitivity and specificity is not sufficient to be a useful clinical tool to assess individual risk for schizophrenia (Murray et al., 2021; Purcell et al., 2009; Smeland & Andreassen, 2021). The calculation and comparison of PRS for different phenotypes has enabled the exploration of genetic overlap between disorders and features.

Heritability estimations

It is estimated that 30%–50% of the genetic liability to schizophrenia is accounted for by common variants using tools such as LD score regression or MiXeR (Bulik-Sullivan et al., 2015; Frei et al., 2019; Ripke et al., 2014), which estimate SNP-based heritability using GWAS summary statistics and linkage disequilibrium data. Statistical power calculations for GWAS have estimated that a sample of approximately 860,000 individuals is needed to explain 50% of the SNP-heritability (Smeland, Frei, et al., 2020).

Enrichment analysis

As GWAS deliver large amounts of associations between individual SNPs and a phenotype, the interpretation work is substantial. Gene set enrichment analysis or functional enrichment analysis use statistical methods to identify enrichment or depletion of groups of genes or protein families, which enables the identification of functional biological pathways involved in the pathophysiology of a disorder (Subramanian et al., 2005). This has been advantageous in the psychosis research both by confirming suspected pathways, such as the involvement of essential genes for synaptic function and neurotransmission, and the identification of new pathways, such as the involvement of the immune system (Ripke et al., 2014).

Copy number variants

Giemsa-band standard karyotyping or light microscopic chromosome analysis enables the detection of aneuploidy (abnormal number of chromosomes), structural rearrangements such as translocations and large inversions and CNVs larger than 3−10 megabases. Microarray-based genomic copy number analyses have a higher resolution and enable the detection of submicroscopic CNVs across the genome. The technology is frequently used in the clinical diagnostics for neurodevelopmental disorders, as well as in research. Additional technologies are suitable to detect CNVs, such as multiplex ligation-dependent probe amplification (MLPA) for detection of smaller duplications and deletions in specific genes or chromosomal regions and whole genome sequencing with CNV calling.

Whole exome/genome sequencing

Sequencing refers to a method determining the nucleotide order (A/C/G/T) in the DNA and can be applied on a single variant, one or several genes, and the whole exome or genome. Sequencing techniques enable the detection of both common and rare variants. The time and cost for sequencing genes and genomes have been cut down drastically over the last 10 years. This enables whole exome and genome sequencing tools to be more frequently used both in clinical diagnostics and research. In diagnostics, the use of targeted gene panels or the use of parental DNA samples in whole exome and genome sequencing analyses are commonly used options to support the selection of relevant genes and interpretation of the results. Recently, the Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium reported several rare variants associated with schizophrenia identified by whole exome sequencing (Singh et al., 2020).

Pharmacogenetics and pharmacogenomics

Genetic variation might not only confer risk to develop a psychotic disorder, but also explain variation in the metabolism of different kinds of medication. The topic is extensive and relevant both for early- and adult-onset psychosis as well as for other psychiatric disorders.

Pharmacogenetics refers to the effect of a genetic variant on variability in a drug response. This is often reflected by variation in therapeutic response and serum level of the medication and the extent of adverse side effects. Several enzymes within the cytochrome (CYP) P450-system are important for the metabolism of different kinds of medications. In psychiatry, variants in *CYP2C19* and *CYP2D6* are the most relevant and the incidence of variants in these genes varies worldwide (Kirchheiner et al., 2004; Koopmans et al., 2021). For a more extensive discussion, see Chapter 11. Pharmacogenomics denotes more broadly the variability in a drug response caused by the genome.

The variability in a drug response is also influenced by nongenetic factors such as age, sex, weight, diet, smoking, and comorbid disorders.

Genetic architecture of early-onset psychosis

Genetic studies have been carried out for adults with psychotic disorders such as schizophrenia and bipolar disorder in large scale, and gained new insight into the polygenic architecture of these conditions (Ripke et al., 2020; Stahl et al., 2019). The rarity of early-onset schizophrenia has made similar large-scale studies unachievable, but informative studies have been carried out for this subgroup as well.

The genetic architecture of schizophrenia as well as EOP as a subgroup is considered complex and highly polygenic. A *common disease-common variant* hypothesis and a *common disease-rare variant* hypothesis have been suggested (Sullivan et al., 2012). The first hypothesis refers to an additive effect of a large number of common variants with individual low risk. The second hypothesis refers to the presence of rare variants such as de novo SNVs and CNVs with high penetrance. As for most common disorders, both hypotheses are supported in the literature, as rare and highly penetrant variants have been identified in a few percentage of patients (Cosemans et al., 2020; Lowther et al., 2017).

Common variants

In the recent years, several large international multicenter GWAS have been carried out, exploring common variants across the genome in patients and healthy controls. A large GWAS from PGC in 2014 included 36,989 patients with schizophrenia and 113,075 controls, and reported 108 genome-wide significant loci with individual very low risk for disease (odds ratio <1.3) (Ripke et al., 2014). SNP annotation of the 108 loci revealed that 75% were located in protein-coding genes. Several of these were expressed in the brain and 10 loci were nonsynonymous variants altering the amino-acid sequence (Ripke et al., 2014). A more recent GWAS from the PGC schizophrenia working group included an even larger sample of 69,369 patients with schizophrenia and 236,642 controls (Ripke et al., 2020). They reported common variants at 270 genetic loci associated with schizophrenia. Identified variants were enriched in genes expressed in the central nervous system (CNS). Despite large sample sizes, identified SNPs in current GWAS only explain a small fraction of the heritability.

The PGC bipolar disorder working group has published results from a large GWAS including 20,352 patients and 31,358 controls, with a follow-up sample consisting of 9,412 patients and 137,760 controls (Stahl et al., 2019). This study identified 30 genome-wide significant loci, including genes that encode

ion channels, transporters of neurotransmitters, as well as genes important for synaptic functioning.

In a recent GWAS from the PGC bipolar disorder working group with 41,917 individuals with bipolar disorder and 371,549 controls, more than 64 genetic loci were associated with bipolar disorder (Mullins et al., 2020). Genetic studies of early-onset bipolar disorder are sparse. A recent study investigated 35 loci previously associated with bipolar disorder or associated characteristics, in a sample of 114 patients with adolescent bipolar disorder and 101 healthy controls. The results revealed four significant loci implicated in dopamine neurotransmission, inflammation, oxidative stress, and neuronal development (Dimick et al., 2020). The findings indicate at least partly shared genetic susceptibility and underlying pathophysiological mechanisms between early- and adult-onset affective disorders.

As the largest GWAS samples include patients with large variability in age at onset, it is possible to compare GWAS data between patients with the earliest and latest age at onset. As a result, researchers have distinguished between early- and late-onset age groups based on a multi-SNP risk score and revealed specific loci associated with the earliest age at onset (Woolston et al., 2017).

Application of PRS from the PGC schizophrenia working group on patients with COS and their healthy siblings revealed both a higher score in the patient group compared to their siblings, but also a higher score compared with patients with adult-onset schizophrenia (Ahn et al., 2016). This indicates a more salient genetic risk in individuals with early-onset compared with later-onset disease (Ahn et al., 2016). Further, application of PRS from the PGC schizophrenia working group on a large population-based sample of children aged 7–9 years, revealed an association with both cognitive and social abilities, emotional regulation, and behavior (Riglin et al., 2017).

Rare variants

Rare sequence variants have also been associated with the risk of COS (Asarnow & Forsyth, 2013). Due to their rareness or even uniqueness, their individual relevance for disease risk might be challenging to determine.

Exome analysis of 17 patients with sporadic (i.e., single affected case compared to multiple cases within a family) COS and their parents found enrichment of de novo variants in genes with lower tolerance for variation (Ambalavanan et al., 2016). Patients with schizophrenia both with and without intellectual disability have shown to carry a significant burden of rare, damaging variants located in genes with low tolerability for loss of function variants (Singh et al., 2017). Advanced paternal age (often defined as ≥ 50 years) has been associated with an increased risk of schizophrenia in offspring and an increased number of de novo variants has been a suggested explanation,

but there is still no consensus regarding the mechanisms (Khachadourian et al., 2021).

Exome-based analyses of patients with schizophrenia and controls have revealed a higher burden of rare, disruptive variants in patients (Purcell et al., 2014). Exome analysis of 12,332 unrelated Swedish individuals, including 4877 patients with schizophrenia, detected an increased prevalence of protein-compromising ultrarare variants in patients, where annotation of the variants revealed that they were concentrated in brain-expressed genes (Genovese et al., 2016). A recent meta-analysis of whole exome sequencing data from 24,248 individuals with schizophrenia and 97,322 controls identified ultra-rare variants in coding regions of 10 genes conferring high risk for schizophrenia (odds ratios 3−50), and 32 genes at a False Discovery Rate of <5% (Singh et al., 2020).

Recent studies have combined family-based linkage analysis with exome sequencing, enabling the identification of rare variants. The application of this method in patients with bipolar disorder has revealed rare missense variants in three genes expressed in the brain (*NRBF2, PCDH15* and *ANK3*) (Toma et al., 2021). For the latter, also common variants have been identified in GWAS (Ferreira et al., 2008).

The knowledge of the contribution from SNVs for early-onset schizophrenia was recently reviewed and 31 SNVs were identified in the 36 studies fulfilling the inclusion criteria (Fernandez et al., 2019). The SNVs were primarily located in genes with relevance for brain development and function, and they were located on 12 autosomes and the X chromosome.

Inherited or de novo SNVs have been identified in sequencing studies of patients with COS, such as *FXYD1*, *FXYD6-FXYD2*, *FXYD6*, *GPR153*, *GTF2IRD1*, *ITGA6*, *LUZP4*, *OPHN1*, *PCDH19*, *RPS6KA3*, *RYR2*, *SEZ6*, *TTBK1*, *UPF3B*, and *ATP1A3* (Fernandez et al., 2019). Several missens variants (amino acid substitutions in the protein) have been reported in the brain expressed ATPase Na+/K+ transporting Alpha-3 Polypeptide gene (*ATP1A3*) in boys with COS (Fernandez et al., 2019). Some of the boys had additional clinical features, such as autism spectrum disorder or psychomotor delay.

Copy number variants in psychotic disorders

Enrichment of both duplications and deletions, and CNVs covering a single or multiple genes have been found in patients with schizophrenia (Szatkiewicz et al., 2020). A large study of 21,094 patients with schizophrenia and 20,227 controls found enrichment of CNVs in patients with schizophrenia and enrichment of CNVs including genes important for synaptic functioning and neurobehavioral phenotypes in mice (Marshall et al., 2017). Eight loci were genome-wide significant, including 1q21.1, 2p16.3 (*NRXN1*), 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2 and 22q11.2 (Marshall et al., 2017).

A substantial minority of about 2.5% of patients with schizophrenia carry large, deleterious, and recurrent CNVs, previously associated with schizophrenia (Rees et al., 2014). A 22q11.2 deletion has been reported to be the strongest molecular risk factor for schizophrenia and 41% of young adult carriers of a 22q11.2 deletion (age 26–35 years) have been reported with a schizophrenia spectrum disorder, of which 28% with schizophrenia more strictly defined (Schneider et al., 2014).

Structural variant calling in whole genome sequencing data has been carried out in a sample of 1162 patients with schizophrenia and 936 controls. This study revealed an increased number of ultrarare structural (including CNVs) variants affecting the boundaries of topologically associated domains (TADs) in patients with schizophrenia, indicating a possible dysregulation of gene expression (Halvorsen et al., 2020).

CNV burden and PRS for schizophrenia have been evaluated in a sample of 6353 patients with bipolar disorder, including 579 patients with schizoaffective disorder, bipolar type. In this study, the CNV burden was only found to be higher among the patients with schizoaffective disorder and did not differ between the group of patients with bipolar disorder and controls (Charney et al., 2019).

The knowledge of the contribution from CNVs for the development of early-onset schizophrenia was recently reviewed and 72 cytogenetic abnormalities including 66 CNVs, were identified in the 36 studies fulfilling the inclusion criteria (Fernandez et al., 2019). The cytogenetic abnormalities involved 16 autosomes and both sex chromosomes. Some of these had a higher frequency and clinical significance, such as 2p16.3, 3q29, 15q13.3, and 22q11.21 deletions; and 2p25.3, 3p25.3, and 16p11.2 duplications. In a sample of 126 patients with COS, 12% were found to carry at least one of 46 CNVs previously associated with adult-onset schizophrenia or other neurodevelopmental disorders and 4% the recurrent 22q11.2 deletion, which is considerably higher compared to individuals with adult-onset schizophrenia (Ahn et al., 2014). Further, some of the identified CNVs detected in patients with COS had previously only been reported in individuals with intellectual disability or autism, illustrating the phenotypic variability associated with several of these CNVs. Thus, a larger proportion of patients with COS carry a more penetrant, detectable genetic risk factor compared with individuals with later onset schizophrenia, some of them associated with other medical or psychiatric comorbidities.

Imprinting disorders, epigenetics, and psychosis

The rare imprinting disorder Prader–Willi syndrome is caused by loss of expression of specific genes on the paternal copy of chromosome 15. The same genes on the maternal copy of chromosome 15 are normally not expressed. Prader–Willi syndrome, and especially genetic subtypes where two copies of the maternal chromosome 15 is present (maternal uniparental disomy 15), is

associated with a high risk for psychotic episodes and affective psychotic disorders (Aman et al., 2018; Boer et al., 2002).

Epigenetic factors have been a proposed contributing mechanism in the relationship between childhood trauma and bipolar disorder (Aas et al., 2016) and a potential contributing explanation for the gene × environment interaction observed in schizophrenia (Wagh et al., 2021). A recent review exploring epigenetic factors from postmortem brain tissue and peripheral tissue from individuals with schizophrenia has proposed that these features represent important mechanisms in the pathophysiology of schizophrenia and might serve as biomarkers in precision medicine strategies in the future (Khavari & Cairns, 2020).

Genetic overlap

Evidence from large GWAS for neurodevelopmental disorders such as schizophrenia and bipolar disorder shows a considerable genetic overlap (Smeland, Bahrami, et al., 2020). A strong genetic correlation has been confirmed between patients with bipolar disorder type 1 and schizophrenia, as well as between patients with bipolar disorder type 2 and major depression (Lee et al., 2013). The proportions of shared gene variants between individuals with schizophrenia, bipolar disorder, major depression, and autism spectrum disorder are modeled in a recent review suggesting considerable overlap, where most variants confer a risk for several psychiatric conditions, albeit with different effect sizes (Smeland, Frei, et al., 2020). Further, common loci from GWAS have shown overlap between schizophrenia and volumes of several brain regions including hippocampus, putamen, and intracranial volume (Smeland et al., 2018).

Several CNVs with high penetrance are associated with neuropsychiatric disorders such as schizophrenia, autism spectrum disorder, and intellectual disability (Kushima et al., 2018; Rees et al., 2016). A few CNVs previously associated with schizophrenia have also been associated with the risk of bipolar disorder (1q21.1 and 16p11.2 duplication and 3q29 deletion) (Green et al., 2016), but there is evidence for a lesser contribution from large CNVs to the risk of bipolar disorder compared with autism spectrum disorder and schizophrenia (Green et al., 2016; Sullivan & Geschwind, 2019). Several CNVs associated with different neuropsychiatric disorders might also be present in healthy subjects in accordance with reduced penetrance and the presence of modulating genetic and environmental factors (Rosenfeld & Patel, 2017).

A large study of CNVs implicated in intellectual disability revealed significant enrichment in patients with schizophrenia compared with controls (Rees et al., 2016). Further, individuals with COS have been shown to carry a higher burden of CNVs associated with psychiatric and neurodevelopmental phenotypes compared with healthy controls and patients with adult-onset schizophrenia (Ahn et al., 2014; Walsh et al., 2008).

There are now several lines of evidence suggesting overlapping genetic influence between individuals with schizophrenia and individuals with autism spectrum disorder. Genetic overlap of common variants has been shown between individuals with COS and autism spectrum disorder (Ahn et al., 2016). More than 90% of CNVs associated with COS have also been reported in patients with an autism spectrum disorder (Fernandez et al., 2019). This is also reflected in a high reported prevalence of comorbid autism in individuals with COS (Rapoport et al., 2009). For individuals with adult-onset schizophrenia and autism spectrum disorder, the overlap of common variants is less evident compared with the genetic overlap of common variants associated with schizophrenia, bipolar disorder, and major depressive disorder (Lee et al., 2013).

To summarize, psychotic disorders are highly polygenic and accumulating evidence supports the contribution of both common and rare variants for disease risk. Youth with EOP show substantial genetic overlap with individuals with adult-onset schizophrenia, and there is some support of a higher heritability in general as well as a higher frequency of highly penetrant CNVs in COS. Further, there is evidence for a genetic overlap represented by both common and rare variants with other neurodevelopmental disorders including autism. The identification of shared genetic etiology for complex phenotypes might increase the understanding of unique and shared pathophysiological mechanisms and inform nosology and treatment recommendations (Visscher et al., 2017).

From genetic loci to disease mechanisms

Central hypotheses for pathophysiological mechanisms for schizophrenia include dysregulation of neurotransmitters such as dopamine (Howes & Kapur, 2009), glutamate (Moghaddam & Javitt, 2012), GABA (Nakazawa et al., 2012), and serotonin (Pourhamzeh et al., 2021). It has further been suggested that a disturbance in the balance between inhibitory and excitatory stimuli and involvement of several neurotransmitters and neural networks contribute to a psychotic phenotype (Finucane et al., 2018; Lieberman & First, 2018). In accordance with a neurodevelopmental model, there is evidence for genetic and environmental impact on synaptic formation and connectivity (Ripke et al., 2020; Weinberger, 1987).

The GWAS from the PGC schizophrenia working group, previously referred to, found 270 genetic loci associated with schizophrenia (Ripke et al., 2020). Several loci associated with schizophrenia are located within genes relevant for neurotransmission such as the dopamine receptor 2 (*DRD2*), genes encoding voltage-gated calcium channel subunits (*CACNA1C*, *CACNB2*, and *CACNA1I*), genes encoding glutamate receptors (*GRIA1*, *GRM3,* and *GRIN2A*), serine racemase (*SRR*), a ion transporter (*CLCN3*), and a putative amino acid transporter (*SLC38A7*). Enrichment analyses have revealed an

overrepresentation of genes expressed in the CNS (Finucane et al., 2018; Ripke et al., 2020) including multiple neurotransmitter systems, specifically within glutamatergic neurons and genes relevant for neurotransmission and neuronal excitability (Devor et al., 2017). Ultra-rare variants conferring high risk for schizophrenia identified in the recent meta-analysis of exome data from the SCHEMA consortium also have greatest expression in neurons in the CNS with diverse molecular functions related to the synapses (Singh et al., 2020).

Evidence from genetic studies implicates the involvement of the immune system in the pathogenesis of schizophrenia (Ripke et al., 2014), such as the classical complement cascade and complement factor 4 (Sekar et al., 2016). The immune system is central in the removing of pathogens, but also to maintain a healthy neuronal development by the elimination of immature synapses (pruning) (Stevens et al., 2007), further supporting a neurodevelopmental hypothesis. A role of genomic risk associated with placental gene expression in interaction with prenatal complications has been suggested to affect early neurodevelopment and risk for schizophrenia in males (Ursini et al., 2018, 2021). This hypothesis has been contested and not confirmed by others (Vassos & Murray, 2022), but several critical issues including different level of details leave the two studies not directly comparable (Ursini & Weinberger, 2022).

For bipolar disorder, GWAS support a role of *ANK3* and *CACNA1C*, both genes involved in ion channel functioning (Ferreira et al., 2008). *ANK3* encodes AnkyrinG belonging to a group of membrane proteins called ankyrins, where *ANK3* is involved in different cellular processes and modulates sodium channels (Bennett & Healy, 2009). AnkyrinG is supposed to have important functions for neuronal signaling (Iqbal et al., 2013). *CACNA1C* encodes part of a calcium channel involved in axon potential and gene expression in the brain (Hofmann et al., 2014). Other genes relevant for calcium channels, synaptic signaling and brain-expressed genes have been identified in recent large GWAS (Mullins et al., 2020; Stahl et al., 2019).

For patients with EOP, the same large-scale GWAS exploring potential pathways have not been carried out. The application of PRS for schizophrenia and autism has, however, shown large overlap in common variants (Ahn et al., 2016). The elevated frequency of rare de novo variants in genes relevant for brain development and function (Fernandez et al., 2019) and the higher prevalence of rare CNVs associated with several neurodevelopmental phenotypes (Ahn et al., 2014), support a neurodevelopmental hypothesis for EOP. Several variants have been described in the *ATP1A3* gene in patients with COS (Fernandez et al., 2019). The gene encodes alpha-3 catalytic subunit of the Na+/K(+)-ATPase transmembrane ion pump and is exclusively expressed in the brain (Rosewich et al., 2012). Rare disease-causing variants in *ATP1A3* are related to alternating hemiplegia of childhood (Heinzen et al., 2012), CAPOS

syndrome (Demos et al., 2014) and dystonia (de Carvalho Aguiar et al., 2004), illustrating the importance of the gene for normal brain function.

The biological consequences of the interplay between common and rare gene variants, as well as environmental factors remain challenging to elucidate. The interpretation of genetic findings into plausible etiological and pathophysiological mechanisms must be carried out with caution because of the broad interpretation of the loci of interest based on GWAS results and incomplete knowledge of the function and interaction of several genes and proteins identified in both GWAS and whole exome/genome sequencing studies (Smeland, Frei, et al., 2020). As identified individual common variants only account for a small fraction of risk, it will be important to clarify the combinatorial effect of multiple common and rare genetic risk variants and the environmental impact on the liability to develop psychosis.

Clinical implications

The recent years have given us new insight into the complex etiology of psychotic disorders. The translation of psychiatric genomics might have several clinical implications and will also give rise to central ethical dilemmas (Kong et al., 2017). The International consortium of psychiatric genetics (ISPG) has recently published their view on ethical, legal, and social issues regarding genetic testing in psychiatry to contribute to a wise integration of the knowledge of genetic risk, maximizing the benefits and reducing potential negative impact for patients (Lázaro-Muñoz et al., 2019). The consortium encourages active participation from researchers in the field of psychiatric genetics through their communication and terminology to reduce stigma and increase the insight into neurodiversity.

The insight into underlying etiological mechanisms is expected to help the development of new therapeutic options and contribute to classifications into clinical relevant subgroups, which might inform personalized treatment (Mullins et al., 2020; Smeland, Frei, et al., 2020).

In general, the insight into the genetic vulnerability for psychosis might increase acceptance and reduce stigma and self-blame in the patients and their family members, but in a tradition of genetic exceptionalism there is also potential to increase stigma and hopelessness (Kong et al., 2017). Knowledge of genetic risk might motivate an optimization of modifiable environmental risk factors for persons with an elevated risk.

Based on current knowledge, a few percent of patients with schizophrenia, including EOP, have a rare, highly penetrant genetic/chromosomal variant which might be of importance for the relevant patients. It may help to increase the awareness of relevant comorbidities, such as congenital heart disease, hypocalcemia, immunodeficiency, and other neurodevelopmental disorders in patients with a 22q11.2 deletion (Goldmuntz, 2020). Medical comorbidity and the presence of monogenic causes of childhood- and early-onset schizophrenia

have recently been reviewed. A significant minority (12.5%) were found to have relevant and potentially treatable causes for their psychotic condition demanding systematic medical evaluation of these patients (Giannitelli et al., 2018). Among the reported conditions are different inborn errors of metabolism, genetic syndromes, autoimmune and infectious encephalitis, endocrine disorders, and other neurological disorders. Information regarding highly penetrant variants might be relevant for genetic counseling regarding familial risk. A consensus regarding the indication for genetic testing for highly penetrant genetic variants in EOP is needed, and the presence of additional neurodevelopmental features or intellectual disability will increase the diagnostic yield.

In recent years, there has been intense research focusing on the development and refinement of more efficient polygenic risk algorithms with the aim of translating genetic information into clinical tools. For example, one application in psychiatry could be earlier and more precise identification of individuals with clinical high-risk of developing psychosis. However, given the low power of current psychiatric GWAS, current PRSs still explain too little risk variance to yield a clinically meaningful prediction (Wray et al., 2021). With the expected increase in genetic variance explained for psychiatric disorders, due to larger GWAS in the coming decade (Smeland, Frei, et al., 2020), this is likely to change with potential transformative effects on clinical psychiatry.

Practices regarding pharmacogenetic testing vary between different institutions, but efforts are being made to establish consensus recommendations (Caudle et al., 2020). Until recently, pharmacogenetic testing in psychiatry was mainly carried out when the serum level of a medication, the therapeutic effect, or extent of adverse side effects was unexpected for the prescribed dose. Currently, this type of testing is being used in earlier phases of treatment, and it is expected that it will increasingly be used to optimize treatment before start in the coming years. More knowledge regarding the interplay between specific pharmacogenetic variants and pharmacogenomics as well as nongenetic factors might enhance the usefulness of pharmacogenetic testing in clinical psychiatry.

Conclusion

EOP is a genetic complex phenotype where both common low penetrant and rare highly penetrant variants might contribute to disease risk in combination with environmental factors. Most knowledge is based on individuals with schizophrenia in general, reflecting the common form of adult-onset schizophrenia. However, the knowledge about the genetic architecture of EOP is increasing and confirms a substantial overlap with adult-onset psychotic disorders, particularly schizophrenia, as well as with other neurodevelopmental disorders such as autism spectrum disorder. The annotation of the variants

associated with schizophrenia in general and EOP specifically indicates a dysfunction in pathways such as synaptic neurotransmission, neurodevelopment, and the immune system. Both polygenic risk for schizophrenia and autism spectrum disorder and a higher burden of large CNVs in patients with COS support a stronger contribution from genetic factors in this subgroup. Thus, understanding more of the underlying genetic vulnerability for this subgroup might be informative in our insight into the heterogeneous group of psychotic disorders in general.

Increasing knowledge of the genetic architecture of youth with EOP will have important clinical relevance to inform guidelines for the indication and extension of genetic testing and counseling in this group. A wise integration of the knowledge about the biological contribution to the susceptibility for psychotic disorders might lessen stigmatization for patients and their family. Confirmed genetic diagnoses achievable in a significant minority might offer an explanation to the family, have relevance for family planning, and inform on follow-up regarding comorbidities and treatment.

Acknowledgments

O.A.A. is a consultant to HealthLytix, and has received speaker's honorarium from Lundbeck and Sunovion. O.B.S. and K.V.W. declare no competing interests. The work was supported by grants from Research Council of Norway (223273, *273291*), *EU's H2020 RIA grant #* 847776 CoMorMent. KG Jebsen Foundation.

References

Aas, M., Henry, C., Andreassen, O. A., Bellivier, F., Melle, I., & Etain, B. (2016). The role of childhood trauma in bipolar disorders. *International Journal of Bipolar Disorders, 4*(1), 1−10. https://doi.org/10.1186/s40345-015-0042-0

Ahn, K., An, S. S., Shugart, Y. Y., & Rapoport, J. L. (2016). Common polygenic variation and risk for childhood-onset schizophrenia. *Molecular Psychiatry, 21*(1), 94−96. https://doi.org/10.1038/mp.2014.158

Ahn, K., Gotay, N., Andersen, T. M., Anvari, A. A., Gochman, P., Lee, Y., Sanders, S., Guha, S., Darvasi, A., Glessner, J. T., Hakonarson, H., Lencz, T., State, M. W., Shugart, Y. Y., & Rapoport, J. L. (2014). High rate of disease-related copy number variations in childhood onset schizophrenia. *Molecular Psychiatry, 19*(5), 568−572. https://doi.org/10.1038/mp.2013.59

Allen, A. J., Griss, M. E., Folley, B. S., Hawkins, K. A., & Pearlson, G. D. (2009). Endophenotypes in schizophrenia: A selective review. *Schizophrenia Research, 109*(1−3), 24−37. https://doi.org/10.1016/j.schres.2009.01.016

Aman, L. C. S., Manning, K. E., Whittington, J. E., & Holland, A. J. (2018). Mechanistic insights into the genetics of affective psychosis from Prader-Willi syndrome. *The Lancet Psychiatry, 5*(4), 370−378. https://doi.org/10.1016/S2215-0366(18)30009-9

Ambalavanan, A., Girard, S. L., Ahn, K., Zhou, S., Dionne-Laporte, A., Spiegelman, D., Bourassa, C. V., Gauthier, J., Hamdan, F. F., Xiong, L., Dion, P. A., Joober, R., Rapoport, J., & Rouleau, G. A. (2016). De novo variants in sporadic cases of childhood onset schizophrenia. *European Journal of Human Genetics, 24*(6), 944−948. https://doi.org/10.1038/ejhg.2015.218

Asarnow, R. F., & Forsyth, J. K. (2013). Genetics of childhood-onset schizophrenia. *Child and Adolescent Psychiatric Clinics of North America, 22*(4), 675−687. https://doi.org/10.1016/j.chc.2013.06.004

Asarnow, R. F., Nuechterlein, K. H., Fogelson, D., Subotnik, K. L., Payne, D. A., Russell, A. T., Asamen, J., Kuppinger, H., & Kendler, K. S. (2001). Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: The UCLA Family Study. *Archives of General Psychiatry, 58*(6), 581−588. https://doi.org/10.1001/archpsyc.58.6.581

Auton, A., Abecasis, G. R., Altshuler, D. M., Durbin, R. M., Bentley, D. R., Chakravarti, A., Clark, A. G., Donnelly, P., Eichler, E. E., Flicek, P., Gabriel, S. B., Gibbs, R. A., Green, E. D., Hurles, M. E., Knoppers, B. M., Korbel, J. O., Lander, E. S., Lee, C., Lehrach, H., … Schloss, J. A. (2015). A global reference for human genetic variation. *Nature, 526*(7571), 68−74. https://doi.org/10.1038/nature15393

Barnett, J. H., & Smoller, J. W. (2009). The genetics of bipolar disorder. *Neuroscience, 164*(1), 331−343. https://doi.org/10.1016/j.neuroscience.2009.03.080

Benard, V., Pignon, B., Geoffroy, P. A., Benradia, I., Roelandt, J. L., Rolland, B., Fovet, T., D'Hondt, F., Thomas, P., Vaiva, G., & Amad, A. (2020). Depression with and without a history of psychotic symptoms in the general population: Sociodemographic and clinical characteristics. *Journal of Affective Disorders, 273*, 247−251. https://doi.org/10.1016/j.jad.2020.04.048

Bennett, V., & Healy, J. (2009). Membrane domains based on ankyrin and spectrin associated with cell-cell interactions. *Cold Spring Harbor Perspectives in Biology, 1*(6), a003012. https://doi.org/10.1101/cshperspect.a003012

Boer, H., Holland, A., Whittington, J., Butler, J., Webb, T., & Clarke, D. (2002). Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet, 359*(9301), 135−136. https://doi.org/10.1016/S0140-6736(02)07340-3

Brandt, T., Sack, L. M., Arjona, D., Tan, D., Mei, H., Cui, H., Gao, H., Bean, L. J. H., Ankala, A., Del Gaudio, D., Knight Johnson, A., Vincent, L. M., Reavey, C., Lai, A., Richard, G., & Meck, J. M. (2020). Adapting ACMG/AMP sequence variant classification guidelines for single-gene copy number variants. *Genetics in Medicine, 22*(2), 336−344. https://doi.org/10.1038/s41436-019-0655-2

Bulik-Sullivan, B., Loh, P. R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., Daly, M. J., Price, A. L., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., … O'Donovan, M. C. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics, 47*(3), 291−295. https://doi.org/10.1038/ng.3211

Burd, L., & Kerbeshian, J. (1987). A north Dakota prevalence study of schizophrenia presenting in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 26*(3), 347−350. https://doi.org/10.1097/00004583-198705000-00012

de Carvalho Aguiar, P., Sweadner, K. J., Penniston, J. T., Zaremba, J., Liu, L., Caton, M., Linazasoro, G., Borg, M., Tijssen, M. A. J., Bressman, S. B., Dobyns, W. B., Brashear, A., & Ozelius, L. J. (2004). Mutations in the Na+/K+-ATPase α3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. *Neuron, 43*(2), 169−175. https://doi.org/10.1016/j.neuron.2004.06.028

Cassidy, S. B., & Schwartz, S. (1998). Prader-Willi and Angelman syndromes: Disorders of genomic imprinting. *Medicine, 77*(2), 140−151. https://doi.org/10.1097/00005792-199803000-00005

Caudle, K. E., Sangkuhl, K., Whirl-Carrillo, M., Swen, J. J., Haidar, C. E., Klein, T. E., Gammal, R. S., Relling, M. V., Scott, S. A., Hertz, D. L., Guchelaar, H. J., & Gaedigk, A.

(2020). Standardizing CYP2D6 genotype to phenotype translation: Consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clinical and Translational Science, 13*(1), 116–124. https://doi.org/10.1111/cts.12692

Cavalli, G., & Heard, E. (2019). Advances in epigenetics link genetics to the environment and disease. *Nature, 571*(7766), 489–499. https://doi.org/10.1038/s41586-019-1411-0

Charney, A. W., Stahl, E. A., Green, E. K., Chen, C. Y., Moran, J. L., Chambert, K., Belliveau, R. A., Forty, L., Gordon-Smith, K., Lee, P. H., Bromet, E. J., Buckley, P. F., Escamilla, M. A., Fanous, A. H., Fochtmann, L. J., Lehrer, D. S., Malaspina, D., Marder, S. R., Morley, C. P., … Sklar, P. (2019). Contribution of rare copy number variants to bipolar disorder risk is limited to schizoaffective cases. *Biological Psychiatry, 86*(2), 110–119. https://doi.org/10.1016/j.biopsych.2018.12.009

Chendo, I., Silva, C., Duarte, G. S., Prada, L., Voon, V., & Ferreira, J. J. (2022). Frequency and characteristics of psychosis in Parkinson's disease: A systematic review and meta-analysis. *Journal of Parkinson's Disease, 12*(1), 85–94. https://doi.org/10.3233/JPD-212930

Collins, F. S., Morgan, M., & Patrinos, A. (2003). The human genome project: Lessons from large-scale biology. *Science, 300*(5617), 286–290. https://doi.org/10.1126/science.1084564

Cosemans, N., Vandenhove, L., Vogels, A., Devriendt, K., Van Esch, H., Van Buggenhout, G., Olivié, H., De Ravel, T., Ortibus, E., Legius, E., Aerssens, P., Breckpot, J., Vermeesch, J. R., Shen, S., Fitzgerald, J., Gallagher, L., & Peeters, H. (2020). The clinical relevance of intragenic NRXN1 deletions. *Journal of Medical Genetics, 57*(5), 347–355. https://doi.org/10.1136/jmedgenet-2019-106448

Couvy-Duchesne, B., O'Callaghan, V., Parker, R., Mills, N., Kirk, K. M., Scott, J., Vinkhuyzen, A., Hermens, D. F., Lind, P. A., Davenport, T. A., Burns, J. M., Connell, M., Zietsch, B. P., Scott, J., Wright, M. J., Medland, S. E., McGrath, J., Martin, N. G., Hickie, I. B., & Gillespie, N. A. (2018). Nineteen and up study (19Up): Understanding pathways to mental health disorders in young Australian twins. *BMJ Open, 8*(3), e018959. https://doi.org/10.1136/bmjopen-2017-018959

Demos, M. K., Van Karnebeek, C. D. M., Ross, C. J. D., Adam, S., Shen, Y., Zhan, S. H., Shyr, C., Horvath, G., Suri, M., Fryer, A., Jones, S. J. M., & Friedman, J. M. (2014). A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. *Orphanet Journal of Rare Diseases, 9*(1). https://doi.org/10.1186/1750-1172-9-15

Devor, A., Andreassen, O. A., Wang, Y., Mäki-Marttunen, T., Smeland, O. B., Fan, C. C., Schork, A. J., Holland, D., Thompson, W. K., Witoelar, A., Chen, C. H., Desikan, R. S., McEvoy, L. K., Djurovic, S., Greengard, P., Svenningsson, P., Einevoll, G. T., & Dale, A. M. (2017). Genetic evidence for role of integration of fast and slow neurotransmission in schizophrenia. *Molecular Psychiatry, 22*(6), 792–801. https://doi.org/10.1038/mp.2017.33

Díaz-Caneja, C. M., Pina-Camacho, L., Rodríguez-Quiroga, A., Fraguas, D., Parellada, M., & Arango, C. (2015). Predictors of outcome in early-onset psychosis: A systematic review. *NPJ Schizophrenia, 1*(1). https://doi.org/10.1038/npjschz.2014.5

Dimick, M. K., Cazes, J., Fiksenbaum, L. M., Zai, C. C., Tampakeras, M., Freeman, N., Youngstrom, E. A., Kennedy, J. L., & Goldstein, B. I. (2020). Proof-of-concept study of a multi-gene risk score in adolescent bipolar disorder. *Journal of Affective Disorders, 262*, 211–222. https://doi.org/10.1016/j.jad.2019.11.009

Edvardsen, J., Torgersen, S., Røysamb, E., Lygren, S., Skre, I., Onstad, S., & Øien, P. A. (2008). Heritability of bipolar spectrum disorders. Unity or heterogeneity? *Journal of Affective Disorders, 106*(3), 229–240. https://doi.org/10.1016/j.jad.2007.07.001

Eggermann, T., Perez de Nanclares, G., Maher, E. R., Temple, I. K., Tümer, Z., Monk, D., Mackay, D. J. G., Grønskov, K., Riccio, A., Linglart, A., & Netchine, I. (2015). Imprinting

disorders: A group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci. *Clinical Epigenetics, 7*(1). https://doi.org/10.1186/s13148-015-0143-8

Fernandez, A., Drozd, M. M., Thümmler, S., Dor, E., Capovilla, M., Askenazy, F., & Bardoni, B. (2019). Childhood-onset schizophrenia: A systematic overview of its genetic heterogeneity from classical studies to the genomic era. *Frontiers in Genetics, 10*. https://doi.org/10.3389/fgene.2019.01137

Ferreira, M. A. R., O'Donovan, M. C., Meng, Y. A., Jones, I. R., Ruderfer, D. M., Jones, L., Fan, J., Kirov, G., Perlis, R. H., Green, E. K., Smoller, J. W., Grozeva, D., Stone, J., Nikolov, I., Chambert, K., Hamshere, M. L., Nimgaonkar, V. L., Moskvina, V., Thase, M. E., … Craddock, N. (2008). Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nature Genetics, 40*(9), 1056−1058. https://doi.org/10.1038/ng.209

Finucane, H. K., Reshef, Y. A., Anttila, V., Slowikowski, K., Gusev, A., Byrnes, A., Gazal, S., Loh, P. R., Lareau, C., Shoresh, N., Genovese, G., Saunders, A., Macosko, E., Pollack, S., Perry, J. R. B., Buenrostro, J. D., Bernstein, B. E., Raychaudhuri, S., McCarroll, S., … Price, A. L. (2018). Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nature Genetics, 50*(4), 621−629. https://doi.org/10.1038/s41588-018-0081-4

Fiorentini, A., Cantù, F., Crisanti, C., Cereda, G., Oldani, L., & Brambilla, P. (2021). Substance-induced psychoses: An updated literature review. *Frontiers in Psychiatry, 12*. https://doi.org/10.3389/fpsyt.2021.694863

Forsyth, J. K., & Asarnow, R. F. (2020). Genetics of childhood-onset schizophrenia 2019 update. *Child and Adolescent Psychiatric Clinics of North America, 29*(1), 157−170. https://doi.org/10.1016/j.chc.2019.08.007

Franklin, G. C., Adam, G. I. R., & Ohlsson, R. (1996). Genomic imprinting and mammalian development. *Placenta, 17*(1), 3−14. https://doi.org/10.1016/S0143-4004(05)80638-1

Frei, O., Holland, D., Smeland, O. B., Shadrin, A. A., Fan, C. C., Maeland, S., O'Connell, K. S., Wang, Y., Djurovic, S., Thompson, W. K., Andreassen, O. A., & Dale, A. M. (2019). Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nature Communications, 10*(1). https://doi.org/10.1038/s41467-019-10310-0

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., Stieglitz, R. D., Vita, A., McGuire, P., & Borgwardt, S. (2012). Cognitive functioning in prodromal psychosis: A meta-analysis. *Archives of General Psychiatry, 69*(6), 562−571. https://doi.org/10.1001/archgenpsychiatry.2011.1592

Gadelha, A., Ota, V. K., Cano, J. P., Melaragno, M. I., Smith, M. A. C., de Jesus Mari, J., Bressan, R. A., Belangero, S. I., Breen, G., & Potash, J. B. (2012). Linkage replication for chromosomal region 13q32 in schizophrenia: Evidence from a Brazilian pilot study on early onset schizophrenia families. *PLoS ONE, 7*(12), e52262. https://doi.org/10.1371/journal.pone.0052262

Gatt, J. M., Burton, K. L. O., Williams, L. M., & Schofield, P. R. (2015). Specific and common genes implicated across major mental disorders: A review of meta-analysis studies. *Journal of Psychiatric Research, 60*, 1−13. https://doi.org/10.1016/j.jpsychires.2014.09.014

Gayon, J. (2016). From Mendel to epigenetics: History of genetics. *Comptes Rendus Biologies, 339*(7−8), 225−230. https://doi.org/10.1016/j.crvi.2016.05.009

Genovese, G., Fromer, M., Stahl, E. A., Ruderfer, D. M., Chambert, K., Landén, M., Moran, J. L., Purcell, S. M., Sklar, P., Sullivan, P. F., Hultman, C. M., & McCarroll, S. A. (2016). Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. *Nature Neuroscience, 19*(11), 1433−1441. https://doi.org/10.1038/nn.4402

Giannitelli, M., Consoli, A., Raffin, M., Jardri, R., Levinson, D. F., Cohen, D., & Laurent-Levinson, C. (2018). An overview of medical risk factors for childhood psychosis:

Implications for research and treatment. *Schizophrenia Research, 192*, 39–49. https://doi.org/10.1016/j.schres.2017.05.011

Goldmuntz, E. (2020). 22q11.2 deletion syndrome and congenital heart disease. *American Journal of Medical Genetics, Part C: Seminars in Medical Genetics, 184*(1), 64–72. https://doi.org/10.1002/ajmg.c.31774

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160*(4), 636–645. https://doi.org/10.1176/appi.ajp.160.4.636

Gottesman, I. I., & Shields, J. (1973). Genetic theorizing and schizophrenia. *The British Journal of Psychiatry : The Journal of Mental Science, 122*(566), 15–30. https://doi.org/10.1192/bjp.122.1.15

Green, E. K., Rees, E., Walters, J. T. R., Smith, K. G., Forty, L., Grozeva, D., Moran, J. L., Sklar, P., Ripke, S., Chambert, K. D., Genovese, G., McCarroll, S. A., Jones, I., Jones, L., Owen, M. J., O'Donovan, M. C., Craddock, N., & Kirov, G. (2016). Copy number variation in bipolar disorder. *Molecular Psychiatry, 21*(1), 89–93. https://doi.org/10.1038/mp.2014.174

Hall, J. M., Lee, M. K., Newman, B., Morrow, J. E., Anderson, L. A., Huey, B., & King, M. C. (1990). Linkage of early-onset familial breast cancer to chromosome 17q21. *Science, 250*(4988), 1684–1689. https://doi.org/10.1126/science.2270482

Halvorsen, M., Huh, R., Oskolkov, N., Wen, J., Netotea, S., Giusti-Rodriguez, P., Karlsson, R., Bryois, J., Nystedt, B., Ameur, A., Kähler, A. K., Ancalade, N. E., Farrell, M., Crowley, J. J., Li, Y., Magnusson, P. K. E., Gyllensten, U., Hultman, C. M., Sullivan, P. F., & Szatkiewicz, J. P. (2020). Increased burden of ultra-rare structural variants localizing to boundaries of topologically associated domains in schizophrenia. *Nature Communications, 11*(1). https://doi.org/10.1038/s41467-020-15707-w

Heinzen, E. L., Swoboda, K. J., Hitomi, Y., Gurrieri, F., De Vries, B., Tiziano, F. D., Fontaine, B., Walley, N. M., Heavin, S., Panagiotakaki, E., Fiori, S., Abiusi, E., Di Pietro, L., Sweney, M. T., Newcomb, T. M., Viollet, L., Huff, C., Jorde, L. B., Reyna, S. P., … Poncelin, D. (2012). De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. *Nature Genetics, 44*(9), 1030–1034. https://doi.org/10.1038/ng.2358

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2017). Is an early age at illness onset in schizophrenia associated with increased genetic susceptibility? Analysis of data from the Nationwide Danish Twin Register. *EBioMedicine, 18*, 320–326. https://doi.org/10.1016/j.ebiom.2017.04.002

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T. M., Nordentoft, M., & Glenthøj, B. (2018). Heritability of schizophrenia and schizophrenia spectrum based on the Nationwide Danish Twin Register. *Biological Psychiatry, 83*(6), 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017

Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics, 6*(2), 95–108. https://doi.org/10.1038/nrg1521

Hofmann, F., Flockerzi, V., Kahl, S., & Wegener, J. W. (2014). L-type CaV1.2 calcium channels: From in vitro findings to in vivo function. *Physiological Reviews, 94*(1), 303–326. https://doi.org/10.1152/physrev.00016.2013

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III - the final common pathway. *Schizophrenia Bulletin, 35*(3), 549–562. https://doi.org/10.1093/schbul/sbp006

Iqbal, Z., Vandeweyer, G., Van der voet, M., Waryah, A. M., Zahoor, M. Y., Besseling, J. A., Roca, L. T., Vulto-van silfhout, A. T., Nijhof, B., Kramer, J. M., Van der Aa, N., Ansar, M., Peeters, H., Helsmoortel, C., Gilissen, C., Vissers, L. E. L. M., Veltman, J. A., De brouwer, A. P. M., Frank kooy, R., … Rooms, L. (2013). Homozygous and heterozygous disruptions of ANK3: At the crossroads of neurodevelopmental and psychiatric disorders. *Human Molecular Genetics, 22*(10), 1960−1970. https://doi.org/10.1093/hmg/ddt043

Jensen, K. V., & Abba-Aji, A. (2020). Isotretinoin-induced delusional disorder, somatic subtype. *Case Reports in Dermatological Medicine, 2020*. https://doi.org/10.1155/2020/8853167

Johansson, V., Kuja-Halkola, R., Cannon, T. D., Hultman, C. M., & Hedman, A. M. (2019). A population-based heritability estimate of bipolar disorder − in a Swedish twin sample. *Psychiatry Research, 278*, 180−187. https://doi.org/10.1016/j.psychres.2019.06.010

Jónsson, H., Sulem, P., Kehr, B., Kristmundsdottir, S., Zink, F., Hjartarson, E., Hardarson, M. T., Hjorleifsson, K. E., Eggertsson, H. P., Gudjonsson, S. A., Ward, L. D., Arnadottir, G. A., Helgason, E. A., Helgason, H., Gylfason, A., Jonasdottir, A., Jonasdottir, A., Rafnar, T., Frigge, M., … Stefansson, K. (2017). Parental influence on human germline de novo mutations in 1,548 trios from Iceland. *Nature, 549*(7673), 519−522. https://doi.org/10.1038/nature24018

Kallmann, F. J., & Roth, B. (1956). Genetic aspects of preadolescent schizophrenia. *The American Journal of Psychiatry, 112*(8), 599−606. https://doi.org/10.1176/ajp.112.8.599

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature, 581*(7809), 434−443. https://doi.org/10.1038/s41586-020-2308-7

Kendler, K. S., & Diehl, S. R. (1993). The genetics of schizophrenia: A current, genetic-epidemiologic perspective. *Schizophrenia Bulletin, 19*(2), 261−285. https://doi.org/10.1093/schbul/19.2.261

Kendler, K. S., McGuire, M., Gruenberg, A. M., O'Hare, A., Spellman, M., & Walsh, D. (1993a). The roscommon family study: I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Archives of General Psychiatry, 50*(7), 527−540. https://doi.org/10.1001/archpsyc.1993.01820190029004

Kendler, K. S., McGuire, M., Gruenberg, A. M., O'Hare, A., Spellman, M., & Walsh, D. (1993b). The roscommon family study: III. Schizophrenia-related personality disorders in relatives. *Archives of General Psychiatry, 50*(10), 781−788. https://doi.org/10.1001/archpsyc.1993.01820220033004

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2020). An extended Swedish national adoption study of bipolar disorder illness and cross-generational familial association with schizophrenia and major depression. *JAMA Psychiatry, 77*(8), 814−822. https://doi.org/10.1001/jamapsychiatry.2020.0223

Khachadourian, V., Zaks, N., Lin, E., Reichenberg, A., & Janecka, M. (2021). Advanced paternal age and risk of schizophrenia in offspring − review of epidemiological findings and potential mechanisms. *Schizophrenia Research, 233*, 72−79. https://doi.org/10.1016/j.schres.2021.06.016

Khavari, B., & Cairns, M. J. (2020). Epigenomic dysregulation in schizophrenia: In search of disease etiology and biomarkers. *Cells, 9*(8). https://doi.org/10.3390/cells9081837

Kirchheiner, J., Nickchen, K., Bauer, M., Wong, M. L., Licinio, J., Roots, I., & Brockmöller, J. (2004). Pharmacogenetics of antidepressants and antipsychotics: The contribution of allelic variations to the phenotype of drug response. *Molecular Psychiatry, 9*(5), 442−473. https://doi.org/10.1038/sj.mp.4001494

Kong, C., Dunn, M., & Parker, M. (2017). Psychiatric genomics and mental health treatment: Setting the ethical agenda. *American Journal of Bioethics, 17*(4), 3–12. https://doi.org/10.1080/15265161.2017.1284915

Kong, A., Masson, G., Frigge, M. L., Gylfason, A., Zusmanovich, P., Thorleifsson, G., Olason, P. I., Ingason, A., Steinberg, S., Rafnar, T., Sulem, P., Mouy, M., Jonsson, F., Thorsteinsdottir, U., Gudbjartsson, D. F., Stefansson, H., & Stefansson, K. (2008). Detection of sharing by descent, long-range phasing and haplotype imputation. *Nature Genetics, 40*(9), 1068–1075. https://doi.org/10.1038/ng.216

Koopmans, A. B., Braakman, M. H., Vinkers, D. J., Hoek, H. W., & van Harten, P. N. (2021). Meta-analysis of probability estimates of worldwide variation of CYP2D6 and CYP2C19. *Translational Psychiatry, 11*(141). https://doi.org/10.1038/s41398-020-01129-1

Kraepelin, E. (1919). *Dementia praecox and paraphrenia*. Livingstone.

Kushima, I., Aleksic, B., Nakatochi, M., Shimamura, T., Okada, T., Uno, Y., Morikawa, M., Ishizuka, K., Shiino, T., Kimura, H., Arioka, Y., Yoshimi, A., Takasaki, Y., Yu, Y., Nakamura, Y., Yamamoto, M., Iidaka, T., Iritani, S., Inada, T., … Ozaki, N. (2018). Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights. *Cell Reports, 24*(11), 2838–2856. https://doi.org/10.1016/j.celrep.2018.08.022

Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., Fitzhugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., Levine, R., McEwan, P., … Morgan, M. J. (2001). Initial sequencing and analysis of the human genome. *Nature, 409*(6822), 860–921. https://doi.org/10.1038/35057062

Lázaro-Muñoz, G., Sabatello, M., Huckins, L., Peay, H., Degenhardt, F., Meiser, B., Lencz, T., Soda, T., Docherty, A., Crepaz-Keay, D., Austin, J., Peterson, R. E., & Davis, L. K. (2019). International society of psychiatric genetics ethics committee: Issues facing us. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics, 180*(8), 543–554. https://doi.org/10.1002/ajmg.b.32736

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H., Mowry, B. J., Thapar, A., Goddard, M. E., Witte, J. S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O. A., Anjorin, A., Anney, R., Anttila, V., Arking, D. E., … Wray, N. R. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics, 45*(9), 984–994. https://doi.org/10.1038/ng.2711

Lichtenstein, P., Yip, B. H., Björk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *The Lancet, 373*(9659), 234–239. https://doi.org/10.1016/S0140-6736(09)60072-6

Lieberman, J. A., & First, M. B. (2018). Psychotic disorders. *New England Journal of Medicine, 379*(3), 270–280. https://doi.org/10.1056/NEJMra1801490

Liu, P., Carvalho, C. M. B., Hastings, P. J., & Lupski, J. R. (2012). Mechanisms for recurrent and complex human genomic rearrangements. *Current Opinion in Genetics and Development, 22*(3), 211–220. https://doi.org/10.1016/j.gde.2012.02.012

Lowther, C., Costain, G., Baribeau, D., & Bassett, A. S. (2017). Genomic disorders in psychiatry—what does the clinician need to know? *Current Psychiatry Reports, 19*(11), 1–10. https://doi.org/10.1007/s11920-017-0831-5

Marshall, C. R., Howrigan, D. P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D. S., Antaki, D., Shetty, A., Holmans, P. A., Pinto, D., Gujral, M., Brandler, W. M., Malhotra, D., Wang, Z., Fajarado, K. V. F., Maile, M. S., Ripke, S., Agartz, I., Albus, M., … Sebat, J. (2017).

Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nature Genetics, 49*(1), 27−35. https://doi.org/10.1038/ng.3725

Moghaddam, B., & Javitt, D. (2012). From revolution to evolution: The glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology, 37*(1), 4−15. https://doi.org/10.1038/npp.2011.181

Möller, H. J. (2003). Bipolar disorder and schizophrenia: Distinct illnesses or a continuum? *Journal of Clinical Psychiatry, 64*(6), 23−27.

Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., Als, T. D., Bigdeli, T. B., Børte, S., Bryois, J., Charney, A. W., Drange, O. K., Gandal, M. J., Hagenaars, S. P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., … Andreassen, O. A. (2020). Genome-wide association study of over 40,000 bipolar disorder cases provides new insights into the underlying biology. *medRxiv*. https://doi.org/10.1101/2020.09.17.20187054

Murray, G. K., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., & Wray, N. R. (2021). Could polygenic risk scores Be useful in psychiatry?: A review. *JAMA Psychiatry, 78*(2), 210−219. https://doi.org/10.1001/jamapsychiatry.2020.3042

Nakazawa, K., Zsiros, V., Jiang, Z., Nakao, K., Kolata, S., Zhang, S., & Belforte, J. E. (2012). GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology, 62*(3), 1574−1583. https://doi.org/10.1016/j.neuropharm.2011.01.022

Neuman, R. J., Geller, B., Rice, J. P., & Todd, R. D. (1997). Increased prevalence and earlier onset of mood disorders among relatives of prepubertal versus adult probands. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(4), 466−473. https://doi.org/10.1097/00004583-199704000-00008

Ng, M. Y. M., Levinson, D. F., Faraone, S. V., Suarez, B. K., Delisi, L. E., Arinami, T., Riley, B., Paunio, T., Pulver, A. E., Irmansyah, Holmans, P. A., Escamilla, M., Wildenauer, D. B., Williams, N. M., Laurent, C., Mowry, B. J., Brzustowicz, L. M., Maziade, M., Sklar, P., … Lewis, C. M. (2009). Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Molecular Psychiatry, 14*(8), 774−785. https://doi.org/10.1038/mp.2008.135

Ng, S. B., Turner, E. H., Robertson, P. D., Flygare, S. D., Bigham, A. W., Lee, C., Shaffer, T., Wong, M., Bhattacharjee, A., Eichler, E. E., Bamshad, M., Nickerson, D. A., & Shendure, J. (2009). Targeted capture and massively parallel sequencing of 12 human exomes. *Nature, 461*(7261), 272−276. https://doi.org/10.1038/nature08250

Ott, J., Wang, J., & Leal, S. M. (2015). Genetic linkage analysis in the age of whole-genome sequencing. *Nature Reviews Genetics, 16*(5), 275−284. https://doi.org/10.1038/nrg3908

Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. *The Lancet, 388*(10039), 86−97. https://doi.org/10.1016/S0140-6736(15)01121-6

Owens, E. M., Bachman, P., Glahn, D. C., & Bearden, C. E. (2016). Electrophysiological endophenotypes for schizophrenia. *Harvard Review of Psychiatry, 24*(2), 129−147. https://doi.org/10.1097/HRP.0000000000000110

Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S. E., Bishop, S., Cameron, D., Hamshere, M. L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J. H., McCarroll, S. A., Baune, B. T., Breen, G., … Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics, 50*(3), 381−389. https://doi.org/10.1038/s41588-018-0059-2

Pedersen, C. B., Mors, O., Bertelsen, A., LindumWaltoft, B., Agerbo, E., McGrath, J. J., Mortensen, P. B., & Eaton, W. (2014). A comprehensive nationwide study of the incidence rate

and lifetime risk for treated mental disorders. *JAMA Psychiatry, 71*(5), 573–581. https://doi.org/10.1001/jamapsychiatry.2014.16

Pourhamzeh, M., Moravej, F. G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., Ahadi, R., & Joghataei, M. T. (2021). The roles of serotonin in neuropsychiatric disorders. *Cellular and Molecular Neurobiology.* https://doi.org/10.1007/s10571-021-01064-9

Purcell, S. M., Moran, J. L., Fromer, M., Ruderfer, D., Solovieff, N., Roussos, P., O'Dushlaine, C., Chambert, K., Bergen, S. E., Kähler, A., Duncan, L., Stahl, E., Genovese, G., Fernández, E., Collins, M. O., Komiyama, N. H., Choudhary, J. S., Magnusson, P. K. E., Banks, E., … Sklar, P. (2014). A polygenic burden of rare disruptive mutations in schizophrenia. *Nature, 506*(7487), 185–190. https://doi.org/10.1038/nature12975

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., Ruderfer, D. M., McQuillin, A., Morris, D. W., Ogdushlaine, C. T., Corvin, A., Holmans, P. A., Ogdonovan, M. C., MacGregor, S., Gurling, H., Blackwood, D. H. R., Craddock, N. J., Gill, M., Hultman, C. M., … Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*(7256), 748–752. https://doi.org/10.1038/nature08185

Qiu, Y., Xu, M., & Huang, S. (2021). Long noncoding RNAs: Emerging regulators of normal and malignant hematopoiesis. *Blood, 138*(23), 2327–2336. https://doi.org/10.1182/blood.2021011992

Rapoport, J., Chavez, A., Greenstein, D., Addington, A., & Gogtay, N. (2009). Autism spectrum disorders and childhood-onset schizophrenia: Clinical and biological contributions to a relation revisited. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(1), 10–18. https://doi.org/10.1097/chi.0b013e31818b1c63

Rees, E., Kendall, K., Pardiñas, A. F., Legge, S. E., Pocklington, A., Escott-Price, V., MacCabe, J. H., Collier, D. A., Holmans, P., O'Donovan, M. C., Owen, M. J., Walters, J. T. R., & Kirov, G. (2016). Analysis of intellectual disability copy number variants for association with schizophrenia. *JAMA Psychiatry, 73*(9), 963–969. https://doi.org/10.1001/jamapsychiatry.2016.1831

Rees, E., Walters, J. T. R., Georgieva, L., Isles, A. R., Chambert, K. D., Richards, A. L., Mahoney-Davies, G., Legge, S. E., Moran, J. L., McCarroll, S. A., O'Donovan, M. C., Owen, M. J., & Kirov, G. (2014). Analysis of copy number variations at 15 schizophrenia-associated loci. *British Journal of Psychiatry, 204*(2), 108–114. https://doi.org/10.1192/bjp.bp.113.131052

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine, 17*(5), 405–424. https://doi.org/10.1038/gim.2015.30

Riglin, L., Collishaw, S., Richards, A., Thapar, A. K., Maughan, B., O'Donovan, M. C., & Thapar, A. (2017). Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: A population-based cohort study. *The Lancet Psychiatry, 4*(1), 57–62. https://doi.org/10.1016/S2215-0366(16)30406-0

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Belliveau, R. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421–427. https://doi.org/10.1038/nature13595

Ripke, S., Walters, J. T. R., & O'Donovan, M. C. (2020). Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *medRxiv*. https://doi.org/10.1101/2020.09.12.20192922

Risch, N. J. (2000). Searching for genetic determinants in the new millennium. *Nature, 405*(6788), 847−856. https://doi.org/10.1038/35015718

Rosenfeld, J., & Patel, A. (2017). Chromosomal microarrays: Understanding genetics of neurodevelopmental disorders and congenital anomalies. *Journal of Pediatric Genetics, 06*(01), 042−050. https://doi.org/10.1055/s-0036-1584306

Rosewich, H., Thiele, H., Ohlenbusch, A., Maschke, U., Altmüller, J., Frommolt, P., Zirn, B., Ebinger, F., Siemes, H., Nürnberg, P., Brockmann, K., & Gärtner, J. (2012). Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: A whole-exome sequencing gene-identification study. *The Lancet Neurology, 11*(9), 764−773. https://doi.org/10.1016/S1474-4422(12)70182-5

Schneider, M., Debbané, M., Bassett, A. S., Chow, E. W. C., Fung, W. L. A., Van Den Bree, M. B. M., Owen, M., Murphy, K. C., Niarchou, M., Kates, W. R., Antshel, K. M., Fremont, W., McDonald-McGinn, D. M., Gur, R. E., Zackai, E. H., Vorstman, J., Duijff, S. N., Klaassen, P. W. J., Swillen, A., … Eliez, S. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. *American Journal of Psychiatry, 171*(6), 627−639. https://doi.org/10.1176/appi.ajp.2013.13070864

Sekar, A., Bialas, A. R., De Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S. A., Handsaker, R. E., Daly, M. J., Carroll, M. C., Stevens, B., & McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature, 530*(7589), 177−183. https://doi.org/10.1038/nature16549

Singh, T., Poterba, T., Curtis, D., Akil, H., Eissa, M. A., Barchas, J. D., Bass, N., Bigdeli, T. B., Breen, G., Bromet, E. J., Buckley, P. F., Bunney, W. E., Bybjerg-Grauholm, J., Byerley, W. F., Chapman, S. B., Chen, W. J., Churchhouse, C., Craddock, N., Curtis, C., … Daly, M. J. (2020). Exome sequencing identifies rare coding variants in 10 genes which confer substantial risk for schizophrenia. *medRxiv*. https://doi.org/10.1101/2020.09.18.20192815

Singh, T., Walters, J. T. R., Johnstone, M., Curtis, D., Suvisaari, J., Torniainen, M., Rees, E., Iyegbe, C., Blackwood, D., McIntosh, A. M., Kirov, G., Geschwind, D., Murray, R. M., Di Forti, M., Bramon, E., Gandal, M., Hultman, C. M., Sklar, P., Palotie, A., … Barrett, J. C. (2017). The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. *Nature Genetics, 49*(8), 1167−1173. https://doi.org/10.1038/ng.3903

Smeland, O. B., & Andreassen, O. A. (2021). Polygenic risk scores in psychiatry − large potential but still limited clinical utility. *European Neuropsychopharmacology, 51*, 68−70. https://doi.org/10.1016/j.euroneuro.2021.05.007

Smeland, O. B., Bahrami, S., Frei, O., Shadrin, A., O'Connell, K., Savage, J., Watanabe, K., Krull, F., Bettella, F., Steen, N. E., Ueland, T., Posthuma, D., Djurovic, S., Dale, A. M., & Andreassen, O. A. (2020). Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Molecular Psychiatry, 25*(4), 844−853. https://doi.org/10.1038/s41380-018-0332-x

Smeland, O. B., Frei, O., Dale, A. M., & Andreassen, O. A. (2020). The polygenic architecture of schizophrenia — rethinking pathogenesis and nosology. *Nature Reviews Neurology, 16*(7), 366−379. https://doi.org/10.1038/s41582-020-0364-0

Smeland, O. B., Wang, Y., Frei, O., Li, W., Hibar, D. P., Franke, B., Bettella, F., Witoelar, A., Djurovic, S., Chen, C. H., Thompson, P. M., Dale, A. M., & Andreassen, O. A. (2018). Genetic overlap between schizophrenia and volumes of hippocampus, putamen, and intracranial volume indicates shared molecular genetic mechanisms. *Schizophrenia Bulletin, 44*(4), 854−864. https://doi.org/10.1093/schbul/sbx148

Song, J., Bergen, S. E., Kuja-Halkola, R., Larsson, H., Landén, M., & Lichtenstein, P. (2015). Bipolar disorder and its relation to major psychiatric disorders: A family-based study in the Swedish population. *Bipolar Disorders, 17*(2), 184−193. https://doi.org/10.1111/bdi.12242

Stahl, E. A., Breen, G., Forstner, A. J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J. R. I., Gaspar, H. A., de Leeuw, C. A., Steinberg, S., Pavlides, J. M. W., Trzaskowski, M., Byrne, E. M., Pers, T. H., Holmans, P. A., Richards, A. L., Abbott, L., … Sklar, P. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature Genetics, 51*(5), 793−803. https://doi.org/10.1038/s41588-019-0397-8

Stevens, B., Allen, N. J., Vazquez, L. E., Howell, G. R., Christopherson, K. S., Nouri, N., Micheva, K. D., Mehalow, A. K., Huberman, A. D., Stafford, B., Sher, A., Litke, A. M., Lambris, J. D., Smith, S. J., John, S. W. M., & Barres, B. A. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell, 131*(6), 1164−1178. https://doi.org/10.1016/j.cell.2007.10.036

Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Paulovich, A., Pomeroy, S. L., Golub, T. R., Lander, E. S., & Mesirov, J. P. (2005). Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences of the United States of America, 102*(43), 15545−15550. https://doi.org/10.1073/pnas.0506580102

Sullivan, P. F., Daly, M. J., & O'Donovan, M. (2012). Genetic architectures of psychiatric disorders: The emerging picture and its implications. *Nature Reviews Genetics, 13*(8), 537−551. https://doi.org/10.1038/nrg3240

Sullivan, P. F., & Geschwind, D. H. (2019). Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. *Cell, 177*(1), 162−183. https://doi.org/10.1016/j.cell.2019.01.015

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry, 60*(12), 1187−1192. https://doi.org/10.1001/archpsyc.60.12.1187

Szatkiewicz, J. P., Fromer, M., Nonneman, R. J., Ancalade, N. E., Johnson, J. S., Stahl, E. A., Rees, E., Bergen, S. E., Hultman, C. M., Kirov, G., O'Donovan, M., Owen, M., Holmans, P., Sklar, P., Sullivan, P. F., Purcell, S. M., Crowley, J. J., & Ruderfer, D. M. (2020). Characterization of single gene copy number variants in schizophrenia. *Biological Psychiatry, 87*(8), 736−744. https://doi.org/10.1016/j.biopsych.2019.09.023

Tam, V., Patel, N., Turcotte, M., Bossé, Y., Paré, G., & Meyre, D. (2019). Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics, 20*(8), 467−484. https://doi.org/10.1038/s41576-019-0127-1

Toma, C., Shaw, A. D., Heath, A., Pierce, K. D., Mitchell, P. B., Schofield, P. R., & Fullerton, J. M. (2021). A linkage and exome study of multiplex families with bipolar disorder implicates rare coding variants of ANK3 and additional rare alleles at 10q11-q21. *Journal of Psychiatry and Neuroscience, 46*(2), E247−E257. https://doi.org/10.1503/jpn.200083

Ursini, G., Punzi, G., Chen, Q., Marenco, S., Robinson, J. F., Porcelli, A., Hamilton, E. G., Mitjans, M., Maddalena, G., Begemann, M., Seidel, J., Yanamori, H., Jaffe, A. E., Berman, K. F., Egan, M. F., Straub, R. E., Colantuoni, C., Blasi, G., Hashimoto, R., …

Weinberger, D. R. (2018). Convergence of placenta biology and genetic risk for schizophrenia article. *Nature Medicine, 24*(6), 792−801. https://doi.org/10.1038/s41591-018-0021-y

Ursini, G., Punzi, G., Langworthy, B. W., Chen, Q., Xia, K., Cornea, E. A., Goldman, B. D., Styner, M. A., Knickmeyer, R. C., Gilmore, J. H., & Weinberger, D. R. (2021). Placental genomic risk scores and early neurodevelopmental outcomes. *Proceedings of the National Academy of Sciences of the United States of America, 118*(7). https://doi.org/10.1073/pnas.2019789118

Ursini, G., & Weinberger, D. R. (2022). Replicating G × E: The devil and the details. *Schizophrenia Bulletin, 48*(1), 4. https://doi.org/10.1093/schbul/sbab109

Vassos, E., & Murray, R. M. (2022). The jury is still out on placental genes and obstetric complications. *Schizophrenia Bulletin, 48*(1), 5. https://doi.org/10.1093/schbul/sbab117

Visscher, P. M., Wray, N. R., Zhang, Q., Sklar, P., McCarthy, M. I., Brown, M. A., & Yang, J. (2017). 10 Years of GWAS Discovery: Biology, function, and translation. *American Journal of Human Genetics, 101*(1), 5−22. https://doi.org/10.1016/j.ajhg.2017.06.005

Wagh, V. V., Vyas, P., Agrawal, S., Pachpor, T. A., Paralikar, V., & Khare, S. P. (2021). Peripheral blood-based gene expression studies in schizophrenia: A systematic review. *Frontiers in Genetics, 12*. https://doi.org/10.3389/fgene.2021.736483

Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., Nord, A. S., Kusenda, M., Malhotra, D., Bhandari, A., Stray, S. M., Rippey, C. F., Roccanova, P., Makarov, V., Lakshmi, B., Findling, R. L., Sikich, L., Stromberg, T., Merriman, B., … Sebat, J. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science, 320*(5875), 539−543. https://doi.org/10.1126/science.1155174

Webb, T., Clarke, A., Hanefeld, F., Pereira, J. L., Rosenbloom, L., & Woods, C. G. (1998). Linkage analysis in Rett syndrome families suggests that there may be a critical region at Xq28. *Journal of Medical Genetics, 35*(12), 997−1003. https://doi.org/10.1136/jmg.35.12.997

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44*(7), 660−669. https://doi.org/10.1001/archpsyc.1987.01800190080012

Willyard, C. (2018). New human gene tally reignites debate. *Nature, 558*(7710), 354−355. https://doi.org/10.1038/d41586-018-05462-w

Woolston, A. L., Hsiao, P. C., Kuo, P. H., Wang, S. H., Lien, Y. J., Liu, C. M., Hwu, H. G., Lu, T. P., Chuang, E. Y., Chang, L. C., Chen, C. H., Wu, J. Y., Tsuang, M. T., & Chen, W. J. (2017). Genetic loci associated with an earlier age at onset in multiplex schizophrenia. *Scientific Reports, 7*(1). https://doi.org/10.1038/s41598-017-06795-8

Wray, N. R., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., Murray, G. K., & Visscher, P. M. (2021). From basic science to clinical application of polygenic risk scores: A primer. *JAMA Psychiatry, 78*(1), 101−109. https://doi.org/10.1001/jamapsychiatry.2020.3049

Chapter 4

Early risk factors in early-onset psychosis

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Biological risk factors

Pre- and perinatal factors

There is a long history of research on how very early risk factors, occurring during the pre- and perinatal periods may impact psychosis onset. Such factors include obstetric complications, particularly fetal hypoxia (deprivation of oxygen), low birth weight, disturbances during pregnancy, such as maternal infection, stress, diabetes, and alterations in vitamin and nutrient levels. These complications can have acute effects, but they may also interfere with neurodevelopmental processes in a way that leaves the individual more vulnerable to insults later on in development. As such, they have the potential to impart changes present from birth and may in part explain the presence of early neurocognitive and social deficits in many the children who later develop schizophrenia spectrum disorders (Bearden et al., 2000; Rosso et al., 2000). Moreover, these risk factors may interact with underlying genetic liability for schizophrenia (Ursini et al., 2021; Van Erp et al., 2002), having more pronounced effects on those at risk. Here, as exemplars, I will focus on three factors: hypoxia, infection, and nutritional deprivation.

Hypoxia

Fetal hypoxia may occur due to many factors, including maternal health complications, preeclampsia, compression of the umbilical cord, or interruption of blood supply to the uterus (Wood & Keller-Wood, 2019). The rates of hypoxia in the general population have proven difficult to estimate and have not been the subject of epidemiological studies. This is largely due to the variety of mechanisms and types of hypoxias as well as different approaches to measurement. However, when broadly defined, rates in healthy individuals have been estimated to be 1%−15% (Giannopoulou et al., 2018; Mittal et al.,

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00003-2

2008). In individuals with schizophrenia, the estimated rate is much higher, at 20%−30% (Buka et al., 1993; Cannon et al., 2000). Hypoxia has been significantly associated with an increased risk of schizophrenia, showing the strongest association of all the obstetric complications (Cannon, 1997; Cannon et al., 2000). Important for our consideration of early-onset psychosis (EOP; i.e., the onset of illness before age 18 years), this association may be either specific to or stronger in earlier onset psychosis compared to adult-onset psychosis (Rosso et al., 2000; Verdoux et al., 1997). Moreover, in youth at clinical high risk (CHR) for psychosis, a history of obstetric complications, including hypoxia, has been associated with more pronounced symptom expression and an increased risk of conversion to a psychotic disorder (Mittal et al., 2009). In support of the notion that these very early risk factors may contribute to alterations in cognition and motor function in childhood, hypoxia was associated with unusual movements among children who later developed schizophrenia (Bearden et al., 2000). Finally, fetal hypoxia in patients with schizophrenia has been associated with more severe neural changes in adulthood, such as decreased hippocampal volume (Van Erp et al., 2002), decreased gray matter (Cannon et al., 2002), smaller intracranial volume (Wortinger et al., 2020, 2021) and decreased brain volume (Wortinger et al., 2020). Notably, these neural changes show an interaction with genetic liability (Van Erp et al., 2002), indicating greater severity of neural effects in those with underlying genetic risk. Moreover, 55% of schizophrenia candidate genes are regulated by hypoxia or expressed in the vascular system (Schmidt-Kastner et al., 2012), which supports the hypothesis that many of these risk factors may not act in isolation but interactively with other risk factors.

Infections

There is also a longstanding body of work investigating the role of prenatal infection in risk for schizophrenia (Buka et al., 2008). Early evidence for this hypothesis came from mixed observations about differences in schizophrenia risk based on the season of birth (Suvisaari et al., 2001, 2004) as well as patterns of schizophrenia prevalence in relation to influenza epidemics (Zimmer et al., 2021). These were followed by substantial research in longitudinally followed birth cohorts, which have demonstrated that maternal infection may be associated with an increased risk of schizophrenia in adulthood for the offspring (Fineberg & Ellman, 2013). Animal models have also supported the role of infection or immune activation as a risk factor for psychosis, including work related to specific infections such as influenza (Fatemi et al., 2002) as well as more generic inflammatory processes (Meyer, 2013). These findings have led to the idea that inflammation could be a common pathway for a diverse array of early risk factors (Fineberg & Ellman, 2013). Further, as with hypoxia, it is likely that this risk factor does not act in isolation but may interact with other factors such as genetic risk (Clarke et al., 2006). In addition to prenatal infection, there is growing evidence that

childhood infection is also a concern. In a meta-analysis, Khandaker and colleagues focused on childhood infections of the central nervous system such as meningitis or mumps and noted a twofold increase in risk for nonaffective psychosis in adulthood among the exposed individuals (Khandaker et al., 2012). Understanding the role of infection in the onset of mental illnesses such as schizophrenia has gained new urgency with the widespread infections associated with the COVID-19 global pandemic (Hoffman et al., 2021). COVID-19 has infected over 200 million people worldwide, including pregnant women and children. There is no doubt that the mental health ramifications of this devastating event will be studied for decades.

Nutrients

There is some evidence showing that deficiencies in vitamins and nutrients prenatally or in early life might serve as risk factors for the later development of psychosis. Early data supporting this idea came from longitudinal studies examining pregnant women who experienced extreme starvation events, such as the Dutch Hunger Winter and the Chinese Famine, which were associated with increases in schizophrenia in offspring (Brown & Susser, 2008). More recently an interest in specific nutrients has emerged. In particular, choline, folic acid, and vitamin D might have specific importance, and while data have been mixed, in many studies they have been associated with either increased risk for psychosis or related phenotypes (Freedman et al., 2021). It is likely that these micronutrients impart risk on their own but also interact with other risk factors such as genetic liability.

In general, many of the earliest risk factors have been hypothesized to contribute to increased schizophrenia risk through a "two-hit" model (Mednick et al., 1998), in which an early vulnerability (e.g., genetic liability) interacts with a later environmental factor (as will be discussed in the remainder of the chapter). Initially, the two-hit risk model was conceived of as genetic liability in combination with another relatively early event, such as an obstetric complication (Van Erp et al., 2002) or infection (Clarke et al., 2006). However, it is now considered that events during adolescence, such as environmental stressors or altered neurodevelopment, may also serve as second hits. This highlights the importance of understanding the risk factors that occur during adolescence. Furthermore, it also encourages us to remember that risk factors we examine later in life exist in the context of a history of other early events.

Cannabis use

As described previously, one complication in understanding risk for psychosis is the potential for interactions between different risk factors. However, another complication is that different risk factors may have greater importance at different time points in the lifespan. For example, epidemiological work has implicated cannabis use with an increased risk for psychosis, and it may be

that the developing adolescent brain has a heightened vulnerability to the effects of cannabis. It also is possible that females are more vulnerable to these effects than males (Wainberg et al., 2021). Cannabis use during adolescence in vulnerable individuals has been associated with an increased risk for psychiatric disorders, for example, increased risk for psychosis spectrum disorders in those with genetic risk factors (Wahbeh & Avramopoulos, 2021). These more severe consequences may be due to the potential of cannabis to interfere with the ongoing neurodevelopmental changes during the neuroplastic period of adolescence. In turn, this may have long-term ramifications in terms of both neural structure and function, and behavior.

Cannabis is a psychoactive drug that acts on the brain's endocannabinoid system. Tetrahydrocannabinol (THC) is the primary psychoactive component of cannabis and has been associated with cannabinoid receptor type 1 (CB1) and type 2 (CB2). The endocannabinoid system has a number of roles important for development, including mediating synaptic plasticity, regulating axonal guidance and migration, and modulating the balance of inhibition and excitation (Long et al., 2012). The potential effects of THC on neurodevelopment may explain findings that those who initiate use during adolescence have more severe cognitive impairment (Brook et al., 2008). One normally occurring developmental change in the endocannabinoid system is that the density of prefrontal CB1 receptors, and their distribution among the cortical layers, changes across the lifetime (Batalla et al., 2013). THC exposure has been found to disrupt the normal patterns of prefrontal cortex maturation and the synaptic pruning process that naturally occurs during this period (Rubino et al., 2015). Accordingly, adolescent cannabis use is associated with structural alterations in the prefrontal cortex (Albaugh et al., 2021; Batalla et al., 2013), as well as functional disruptions, for instance, during working memory tasks (Padula et al., 2007). Therefore, it is critical to gain a full understanding of not only the immediate impact of cannabis exposure on the adolescent brain but also the impact it may have on the neurodevelopmental trajectory. Adolescence may represent a sensitive period for adverse effects of cannabis use on the brain, particularly considering the differential effects of use on the brain and behavior in adults versus adolescents (Wahbeh & Avramopoulos, 2021).

There is evidence that cannabis use is associated with increased rates of depression, anxiety, and psychosis (Chadwick et al., 2013). In part, this evidence comes from bidirectional findings that rates of cannabis use in patients from these populations are higher than expected (Koskinen et al., 2010), and that risk for psychosis is heightened in individuals with high levels of use (Moore et al., 2007). Many psychiatric disorders, including psychosis, have their onset during late adolescence or early adulthood. Therefore, a neural insult such as cannabis has the potential to impact the developing brain in a way that makes disorders more likely to develop. Many of the structures with heavy densities of CB1 receptors are also regions

implicated in mood and psychotic spectrum disorders, such as the hippocampus, dorsolateral prefrontal cortex (DLPFC), and amygdala. Accordingly, it appears that earlier use is particularly risky (Arseneault et al., 2002; McGrath et al., 2010), as is the use of high potency (high THC) cannabis (Di Forti et al., 2014). However, the degree to which cannabis use may serve as a causal factor for psychosis is currently under debate, as findings have been mixed (Auther et al., 2015).

Although there is increasing evidence for a relationship between THC and psychosis and although cannabis interacts with neurodevelopmental processes, the relationship between adolescent cannabis use and psychosis risk is not straightforward. This is in part because there are over 700 strains of cannabis, each containing different cannabinoid profiles with unique effects (Klumpers & Thacker, 2019). For instance, THC has different effects than cannabidiol (CBD), another common cannabinoid. While THC is an agonist at CB1 and CB2 receptors, CBD may act as a dopamine antagonist, in a way that is analogous to antipsychotics, and thus may potentially dampen or even prevent psychotic symptoms from emerging (Seeman, 2016). This is likely why CBD appears to not have the same psychosis-inducing or risk-heightening effects as THC (Bhattacharyya et al., 2010; Leweke et al., 2012), although more research is needed. However, at the same time as we gain more information about different cannabinoid effects and strains, particularly in regions where cannabis is sold legally, individuals have access to more options about the relative proportions of cannabinoids in the cannabis they consume. This can further serve to complicate research in this area. Furthermore, many studies have focused on the development of full-blown psychiatric illnesses. However, there is evidence that in addition to the risk of psychotic disorders, cannabis use might put individuals at risk of experiencing disturbing and disruptive subclinical psychotic experiences that are below the threshold for diagnosis. This may in turn set the stage for a further decline in illness (Kuepper et al., 2011). Thus, understanding the relationship of cannabis to all components of the psychosis spectrum would be useful.

Finally, there is some evidence that, as with other risk factors and consistent with a two or multi-hit conceptualization, adolescent cannabis use may also interact with underlying genetic risk for psychosis (Estrada et al., 2011). This evidence initially came from candidate genes that appeared to impart vulnerability to the effects of cannabis, although more recent data on this question is mixed (Vaessen et al., 2018). There is emerging evidence indicating that the relationship is even more complicated and that there may be an overlap in the genetic liability for cannabis use disorder and schizophrenia (Johnson et al., 2021).

In general, the relationship between adolescent cannabis use and psychosis risk is complex, and the variability of differential risk for different cannabis strains, along with the potential interaction of cannabis use with environmental, genetic, and other behavioral factors requires further research.

Hormonal changes

One of the reasons why the understanding of risk factors associated with psychosis during adolescence is so complex is that everything we measure takes place against the background of profound physiological change, including hormonal changes. Whether hormones play a role in the onset of psychosis spectrum disorders, including schizophrenia, has long been an interest due to the difference in incidence and timing of onset of schizophrenia spectrum disorders in males and females (Dalsgaard et al., 2020; Trotman et al., 2013). The onset of adolescence is often defined as beginning with puberty, although what precisely defines pubertal onset is complex (Shirtcliff et al., 2009). The earliest phase of the initiation of puberty is the secretion of androgens from the adrenal gland, or adrenarche, which starts in childhood (Vijayakumar, Op de Macks et al., 2018). Androgen levels continue to increase across development and reach adult levels in the late teens or early 20s (Havelock et al., 2004). This increase is associated with the development of secondary sex characteristics (Vijayakumar, Op de Macks et al., 2018). Gonadarche, which starts a few years later, is by some considered the true beginning of puberty. Gonadarche is the activation of the hypothalamic-pituitary-gonadal (HPG) axis (Vijayakumar, Op de Macks et al., 2018), which stimulate ovaries and testes to produce estrogen and testosterone, ultimately leading to sexual maturity. The exact time period for the beginning of "adolescence" is not entirely clear, with different groups believing it begins relatively earlier or later. This discrepancy in part reflects the complexity of the social, emotional, cognitive, and biological changes occurring, as well as differences in societal expectations. At first glance, hormones may seem appealing as a more "biologically based" measure of the timing of adolescence. However, the issue is multifaceted as hormonal changes related to, but do not perfectly mirror, physical development (Shirtcliff et al., 2009), and may be quite different from social development. Moreover, hormonal measures vary widely between individuals, and within and between pubertal stages (Dorn, 2006). Thus, multimodal assessments, for example, combinations of examination of physical changes with measurement of hormonal changes, appear critical for an accurate measure of the timing of adolescence. However, multimodal assessment is not common and thus the interpretation of existing data on pubertal change both in healthy youth and those with psychosis can be complicated.

In addition to impacting the body, hormonal changes during puberty and across adolescence profoundly impact the brain (Vijayakumar, Op de Macks et al., 2018). Effects of hormones can include both organizational effects, which are structural changes, and activational effects, which are changes in neural activity levels (Arnold, 2009). During typical adolescent neurodevelopment, increases in sex hormones (Vijayakumar, Mills, & Flournoy, 2018), such as testosterone and estradiol (Peper & Dahl, 2013), contribute to a

period of structural reorganization involving gray matter volume decrease, consistent with cortical pruning, and increases in white matter volume and integrity (Peper & Dahl, 2013; Peper et al., 2009; Vijayakumar, Mills, & Flournoy, 2018), consistent with myelination. In addition, these hormonal changes have been associated with improved cognitive functioning during adolescence, and other factors relevant to psychosis, such as affective reactivity and reward processing (Peper & Dahl, 2013; Vijayakumar et al., 2019). Gonadal and stress hormones are closely intertwined, and in many cases fluctuate together (Marceau et al., 2015). Accordingly, in addition to gonadal hormones, stress hormones such as cortisol also increase basal levels during puberty (Elmlinger et al., 2002), as does cortisol release in response to stress (Gunnar et al., 2009). This is a domain in which the adolescent brain may be especially vulnerable, as the neurological effects of stress and cortisol exposure in adolescence seem to be more pervasive compared to adulthood (Romeo, 2010). Furthermore, the susceptibility to stress hormones during adolescence also has relevance to the importance of trauma as a risk factor (discussed later in this Chapter).

There have also been findings of altered hormone levels in adult patients with schizophrenia (Misiak et al., 2018; Trotman et al., 2013). One hypothesis is that estrogen moderates the pruning of excitatory synapses and thus serves as a neuroprotective factor (Gogos et al., 2015). Estrogen also has effects on dendritic spine density (Gould et al., 1990), which may counter the decreased spine density observed in patients with schizophrenia. In addition to potential estrogenergic effects, there have been findings of reduced testosterone in adults with schizophrenia (Owens et al., 2018). Given the overlap in timing between the postpubertal period and the peak time of psychosis onset (age 15−25 years (Sham et al., 1994) it is also important to consider the potential for age-specific impacts of hormonal changes in adolescence, both in terms of risk and protective factors. For example, the activational effects of sex hormones may render neural circuits more sensitive to environmental input (Vijayakumar, Op de Macks et al., 2018). In addition, elevated dopaminergic signaling during adolescence may be moderated by testosterone (Sato et al., 2008), and potentially contributes to risk during this period. Accordingly, there has been recent work investigating the potential for hormonally-based interventions, but these have not yet been tested in adolescent patients (Owens et al., 2018).

In addition to gonadal hormones, the observed relationships between psychosis onset and relapse to stress have prompted investigations into the function and development of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates numerous physiological processes, including stress (Holtzman et al., 2013). For example, increased basal cortisol and blunted cortisol reactivity have been found in individuals with psychotic disorders (Shah et al., 2015). However, while the existing observations have prompted theoretical links to be drawn between neuromaturation, hormonal changes, and psychosis

onset (Galdos et al., 1993; Saugstad, 1989), there is little empirical data, particularly as related to pubertal hormones. Further research across these domains is therefore needed (Trotman et al., 2013).

Psychological risk factors

Clinical high-risk

In addition to the biological factors that can contribute to the risk for psychotic disorders, there are early psychological factors that can be predictive of illness onset (Mennigen & Bearden, 2020). Schizophrenia is known to have an insidious onset, often showing a slow progression of change in affected individuals. In the beginning, generic changes may be observed, such as sleep changes, anxiety, social withdrawal, or a decline in social and role functioning. Later come more psychosis-like changes, that are more specific and resemble psychotic symptoms, but at a milder level. This phase is often referred to as the clinical high-risk state (CHR), and studies in this population started in earnest in the early 1990s (Yung & McGorry, 1996). Alternatively, it has also been referred to as ultrahigh risk (UHR) and at-risk mental state (ARMS). CHR individuals are typically within the typical age range for onset of psychosis and are classified based on a combination of symptoms and other factors. The most common presentation in this group is subclinical (attenuated) levels of psychotic symptoms. There can also be psychotic symptoms above clinical threshold, but these are brief and occur too infrequently to qualify for a psychotic disorder diagnosis. The least common presentation is individuals with genetic risk accompanied by a gradual decline in functioning (Addington et al., 2019). However, while the insidious onset of "prodromal" symptoms is predictive of later onset of psychotic spectrum disorders, only approximately 25%−35% of individuals at CHR go on to develop a psychotic disorder (Salazar De Pablo et al., 2021), with others either improving, remaining in a subclinical state, or developing other mental disorders (Addington et al., 2019). Therefore, it is of great interest to identify which factors might be most predictive in those individuals who convert to a psychotic disorder. Knowing this would enable earlier identification and treatment, which has been associated with improved outcomes (McGorry et al., 2008). Given the variability in clinical presentation, as well as differences in functional and clinical outcomes, studying the CHR state with rigor requires large samples. To achieve sufficient sample sizes, studies are frequently conducted by large-scale consortiums, such as the North American Longitudinal Prodromal Study (NAPLS) (Addington et al., 2007), the Psychosis Risk Outcomes Network (ProNET), and the European Prediction of Psychosis Study (EPOS) (Klosterkötter et al., 2005). Of these large studies in high-risk samples, there have been multiple attempts to generate predictive risk models, or "risk calculators". The first model was generated based on data from NAPLS, finding that the most important predictive factors were unusual thought content, suspiciousness/

paranoia, the decline in social functioning, and verbal learning and memory deficits, with the additional inclusion of exposure to stressful life events, family history of psychosis, younger age at baseline, impaired processing speed, and history of trauma (Cannon et al., 2016). This risk model was externally validated in two separate samples: the Early Detection, Intervention, and Prevention of Psychosis Program (EDIPPP) (Carrión et al., 2016) and the Shanghai At Risk for Psychosis (SHARP) sample (Zhang et al., 2019), which is very promising. One complexity regarding the CHR state is that it typically occurs during the time of ongoing adolescent neurodevelopment. Thus, it is important to work toward finding ways to dissociate typical developmental change from change related to the onset of psychotic illness.

Early childhood adversity

Early childhood adversity, such as abuse, neglect, bullying, and related experiences has been shown to significantly increase the risk for a number of different poor health outcomes in both the short-term (McLaughlin et al., 2012) and the long-term (McLaughlin et al., 2010). Recent findings have shown that childhood adversity is associated with a substantially increased risk for psychosis, with a population attributable risk of 33% (Varese et al., 2012). One important aspect of this is childhood maltreatment, in which the severity and frequency of childhood maltreatment are positively related to hallucinations and delusions (Schenkel et al., 2005), consistent with a dose-response relationship (Kelleher et al., 2013). DeRosse and colleagues found positive correlations between childhood maltreatment and psychotic symptoms in adult patients with schizophrenia and unaffected controls experiencing psychotic-like experiences (Pamela DeRosse et al., 2014). The patients scored higher than the controls on both childhood maltreatment and symptoms, but the strength of the relationship between the factors was not significantly different between groups. It is thus possible that childhood adversity may impart a biological or psychological vulnerability to the development of psychotic symptoms (Janssen et al., 2004). However, it is not known why some individuals develop full-blown psychosis and others psychotic-like experiences. It may be a consequence of the severity of the maltreatment, an additive effect of multiple traumas (Anglin et al., 2021), or, it may be related to the presence of other risk factors, for instance, prenatal environmental factors or underlying genetic vulnerability. Several possibilities have been investigated and childhood adversity may impact some or multiple of them in an interactive fashion. It is also important to consider that, in addition to maltreatment, other aspects of childhood adversity, such as social disadvantage, trauma, and stress have been associated with the emergence of psychotic symptoms and disorders. Specifically implicated factors include immigrant status (discussed later in this Chapter) (Kirkbride et al., 2017), low socioeconomic status (Hur et al., 2015), and other traumatic events such as experiences of child abuse (Read et al., 2005).

Emotion regulation

Emotion regulation has been a focus in the developmental neuroscience literature on childhood adversity. Prolonged childhood adversity has been associated with premature onset of adult-like emotion regulation in preclinical studies, with evidence still emerging in humans (Teicher et al., 2016). Neuroimaging studies of emotion regulation have focused primarily on the relationship between the amygdala, which plays a role in emotional responsivity, and prefrontal cortical regions (ventromedial prefrontal cortex (VMPFC)), DLPFC, and ventrolateral prefrontal cortex (VLPFC), which are believed to regulate amygdalar responses. In typical development, fMRI studies have shown that the amygdala-VMPFC connectivity changes with increasing age, with the VMPFC showing increased activity during the emotional challenge and the amygdala showing decreased activity and lower anxiety (Gee et al., 2013; Silvers et al., 2017). Thus, it appears that the VMPFC putatively is taking on a sort of "braking" or modulatory emotional response function and that this change supports successful emotion regulation in adulthood (Teicher et al., 2016). In young (preadolescent) children, the child's brain is able to show this effect, but only in the presence of their caregiver (Tottenham, 2015), indicating that in this early stage, emotion regulation ability is intertwined with caregiver relationships. In comparison, during the emotional challenge, in children who have experienced trauma and neglect, particularly in the form of chronic maternal deprivation, the brain shows more adult-like connectivity, with increased VMPFC and decreased amygdala activity (Gee et al., 2013). The degree to which changes in emotion regulation during the CHR phase correlate with childhood adversity is not yet known. However, youth at CHR also show a disruption in the VLPFC-amygdala circuit (Gee et al., 2012). These individuals showed increased amygdala and decreased VLPFC activation with age, which is the opposite of the pattern found in controls. Further, connectivity strength between these regions was weaker than in controls. These findings show that while the disruptions in individuals with psychosis may not be exactly the same as those seen in individuals who have only experienced trauma, similar circuits may show vulnerability, and raises the possibility that this may be a general rather than a specific risk factor.

Hypothalamic-pituitary-adrenal (HPA) axis

Another hypothesis regarding potential mechanisms of childhood adversity and psychosis risk is based on the idea that childhood adversity is associated with the heightened activity of the HPA axis, exposing the developing brain to high levels of corticosteroids (Essex et al., 2011), and impacting circuitry associated with emotion processing. Quite a bit of work has been done in this area and collectively demonstrates that there are long-term effects on the brain and the HPA axis from these early childhood experiences. For instance, even in adulthood, patients with schizophrenia who had a history of childhood

adversity showed increased hair cortisol concentrations (Xu et al., 2019) and alterations of HPA responsivity to social stress (Lange et al., 2017), compared to patients without a history of childhood adversity. Furthermore, in healthy adults as well as those with schizophrenia, there have been findings that a history of childhood adversity moderates the relationship between cortisol reactivity and amygdala-DLPFC connectivity (Quidé et al., 2021). Additionally, diathesis-stress models propose that underlying genetic liability along with early life insults increase adolescent vulnerability to stress (Walker et al., 2001). This highlights the importance of investigations of interactions between diathesis factors and adolescent stressors on neurodevelopment or emergence and progression of psychosis.

Dopamine

Finally, exposure to childhood and adolescent trauma has also been associated with altered striatal dopamine function in healthy adults (Oswald et al., 2014). This line of work is critical given the key role of dopamine in central hypotheses about the neural basis of psychosis. One proposal regarding how stress, including childhood adversity, might impact the dopaminergic circuitry, is that it might serve to sensitize the mesostriatal dopamine system (Howes & Murray, 2014). Accordingly, positron-emission tomography (PET) studies have shown that there is an interaction between dopamine release and childhood trauma in predicting positive symptoms of psychosis as induced by dexamphetamine (Dahoun et al., 2019). Childhood adversity has been associated with increased dopamine function in the striatum in adulthood in both individuals at CHR and healthy subgroups (Howes & Murray, 2014). This supports the notion of a risk factor that may increase risk but also interact with other factors.

Social risk factors

Social stress

In addition to investigations of childhood adversity, or maltreatment, there is a growing interest in the effects of social stress on psychosis severity and risk. This is particularly important for adolescent risk, as adolescence may be a period of particular sensitivity to social factors (Blakemore & Mills, 2014). Peer relationships are deeply influential during this period, gradually taking a more central role relative to family relationships (Furman, 2002). One reason for the growing interest in social factors as risk factors is that many individuals with psychotic disorders, or in the CHR state, experience social exclusion, social isolation, bullying, and other negative social events. Given how pervasive these experiences can be, and given that there is some potential for intervention, for instance at the school level, there is an interest in understanding how they may moderate or exacerbate risk levels.

One contributing factor may be that individuals who develop psychosis also demonstrate poorer premorbid social functioning (Tarbox et al., 2013). This decrease in social functioning can have substantial impacts on individuals' abilities to develop social support networks. Social networks have been demonstrated to be buffering factors for mental illness and improve outcomes (Degnan et al., 2018). Furthermore, during adolescence, peer networks become more complex and complicated to navigate (Steinberg & Morris, 2001), something that could be difficult for someone already experiencing social and cognitive difficulties. The resulting loneliness from this combination of factors may itself be a stressor. For example, in youth at CHR, impaired social functioning and, relatedly, decreased size and quality of social networks have been associated with lower functioning and increased risk of conversion to psychosis (Cornblatt et al., 2012; Robustelli et al., 2017). The relationship of social factors to functional outcome is not limited to individuals with a psychosis diagnosis or those in the CHR state. The presence of psychotic-like experiences has also been shown to predict poor social functioning and social competence in children and adolescents (P. DeRosse et al., 2017) and has been associated with loneliness in adults (Leathem et al., 2021). While some social risk factors such as decreased overall social support and friendship networks may be insidious and long-term stressors, there are also acute social stressors, such as bullying or peer victimization. Exposure to these factors during the vulnerable adolescent period has been associated with an increase in psychotic-like experiences in adulthood (Liu et al., 2021). Furthermore, youth at CHR have reported elevated levels of both physical and psychological bullying (in addition to emotional neglect, and physical, psychological, and sexual abuse, as addressed above), which were associated with worsening symptoms of depression and anxiety (Addington et al., 2013). Social functioning may thus be an important area for intervention, and it may be particularly critical during the adolescent period.

Immigrant, racial and ethnic minority status

Immigrant status has been long implicated as a risk factor for psychosis in the epidemiological literature, going back to the early 1900s (Odegaard, 1932). It was initially not clear what perpetrated the risk increase, for instance, whether there was a difference in risk already prior to immigration, or a selection bias in those who decided to immigrate. However, evidence has shown that the risk for psychotic disorders is increased not only for first-generation immigrants but also for their second-generation offspring (Bourque et al., 2011). Notably, this effect is buffered by "ethnic density", by living in a region more densely populated with people from your home region (Van Der Ven & Selten, 2018) or of your same ethnic group (Anglin et al., 2021).

Experiences of perceived discrimination have been associated with increases in reported psychotic experiences (Pearce et al., 2019). Discrimination

is a topic of growing importance in our society. There is a new appreciation for racial and ethnic disparities in medical care, and accordingly, the American Medical Association has recently acknowledged systemic racism and discrimination as risk factors for public health. This is in part due to treatment disparities that make minority patients less likely to get adequate health care, including mental health treatment (van der Ven et al., 2020). It is likely also due to the substantial stress associated with discrimination, which has been associated with the risk for psychosis (Walker et al., 2001).

Immigrant status and perceived discrimination may have a special risk for adolescents. This could be, in part, because of the sensitivity of adolescents to social factors, or the sensitivity of the developing HPA stress system. In support of this idea are findings that minority immigrants who immigrated during childhood demonstrated a higher risk of developing psychosis compared to adult immigrants, perhaps because of the presence of this substantial stressor (Harrell, 2000; Kirkbride et al., 2017) early in life as well as due to the initiation of discriminatory experiences and resulting trauma during this vulnerable period (Kirkbride et al., 2017). There may also be different rates of other traumas or adversities in different neighborhoods or environments (Anglin et al., 2021), which can have an important impact on risk, as discussed above.

In general, these findings support the hypothesis that the increased risk for psychosis is due to factors that occur postmigration, such as increased stress, lack of social support, and potentially discrimination experienced by those immigrants who are in a minority group in their new country. It is important to assess how the risk factors of immigration and discrimination interact with others, in an additive or interactive pattern. This is something that we have a responsibility to understand more deeply, and which is the subject of important ongoing work.

Conclusions

In conclusion, the risk for psychosis is complex, fluctuates during multiple time periods across the lifespan, and is still a topic of keen investigation. One theme that has emerged repeatedly, even with risk factors initially thought to have substantial independent effects such as genetics, is that almost all known risk factors interact with, build on, or are accentuated by the presence of other risk factors. Among patients with psychosis, having an earlier age of onset, as is the case in adolescent-onset psychosis, has been associated with a number of less optimal outcomes, including more hospitalizations (Immonen et al., 2017), lower level of premorbid function (Stentebjerg-Olesen et al., 2016), poorer cognitive function (Rajji et al., 2009), and poorer overall prognosis (Lay et al., 2000). Thus, having psychosis in adolescence may carry special risks. In addition to this, there are risk factors, such as cannabis use, hormones, stress, and migration, which adolescents may be particularly vulnerable to, and

which may impart special risk during this developmental period. Taken together, this highlights the importance of fully understanding risk factors, developmental trajectories, and onset patterns during this critical and unique time period. As we learn more about the broader spectrum of risk factors it would also be valuable to gain an understanding of the relative severity of risk factors, and which might be more important to target. However, it is equally important to consider that in addition to conferring heightened vulnerability and risk, the dynamic neurodevelopmental, social, and cognitive changes occurring during adolescence may have the potential to confer unique avenues to resilience and special opportunities for developmental stage-specific interventions.

Clinical implications

As described in this Chapter, adolescence is a period in which humans may have special vulnerabilities that can increase the risk for psychotic disorders. However, while the considerable physiological, neural, and environmental changes experienced in adolescence may be associated with risk, they may also offer opportunities for resilience. The importance of early intervention is already well-established (Kane et al., 2016; Perkins et al., 2005). However, this is often discussed in terms of disease course. Less often discussed is the fact that those early in the illness are also likely to be younger, and the treatments may potentially be leveraging some of the neuroplasticity presents during this time. It is possible that, in many ways, adolescence is an optimal time for intervention as it potentially provides the unique opportunity to alter the developmental illness trajectory and substantially impact the outcome (Marín, 2016). In addition, it is important to consider that some risk factors discussed in this review are more moveable than others. For example, education about substance use in those at genetic risk, increasing support for those who immigrate during childhood, promoting antibullying campaigns, developing programs to help with social skills, and continuing to increase provider and educator knowledge about the CHR state are all things that could broadly improve outcomes.

Future directions

There has been a growing interest in schizophrenia as a developmental disorder, including psychosis during adolescence, which is reflected in a rapidly growing literature. However, our understanding of risk and resilience during adolescent psychosis faces a number of hurdles. First, there is the challenge of dissociating disease process from developmental processes and disease-related confounds such as medication, all of which require careful study design and interpretation. Second, as we continue to gain a greater understanding of risk factors, and treatments, it will be important to explore the potential for age-

targeted neurodevelopmentally appropriate treatments. This work has begun in preclinical models (Cabungcal et al., 2014; Du & Grace, 2013) but has not been broadly extended to humans. Finally, I have discussed many factors, which are either directly affected by genetics or act interactively with genetic risk. As we continue to learn more about the genetics of mental illness, and as individuals get access to more information about their own genetics, it will be important to continue to think about how genetic risk factors intersect with other risk and resilience factors. In sum, the field of adolescent psychosis is rapidly growing, as is our understanding of how risk may change across the lifespan, which hopefully will continue to help us learn how to mitigate the effects of early psychosis.

Acknowledgment

This work was funded by NIMH Grant MH116433. The author reports no conflicts of interest.

References

Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M., Walker, E. F., Woods, S. W., & Heinssen, R. (2007). North American prodrome longitudinal study: A collaborative multisite approach to prodromal schizophrenia research. *Schizophrenia Bulletin, 33*(3), 665–672. https://doi.org/10.1093/schbul/sbl075

Addington, J., Stowkowy, J., Cadenhead, K. S., Cornblatt, B. A., Mcglashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cannon, T. D. (2013). Early traumatic experiences in those at clinical high risk for psychosis. *Early Intervention in Psychiatry, 7*(3), 300–305. https://doi.org/10.1111/eip.12020

Addington, J., Stowkowy, J., Liu, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Bearden, C. E., Mathalon, D. H., Santesteban-Echarri, O., & Woods, S. W. (2019). Clinical and functional characteristics of youth at clinical high-risk for psychosis who do not transition to psychosis. *Psychological Medicine, 49*(10), 1670–1677. https://doi.org/10.1017/S0033291718002258

Albaugh, M. D., Ottino-Gonzalez, J., Sidwell, A., Lepage, C., Juliano, A., Owens, M. M., Chaarani, B., Spechler, P., Fontaine, N., Rioux, P., Lewis, L., Jeon, S., Evans, A., D'Souza, D., Radhakrishnan, R., Banaschewski, T., Bokde, A. L. W., Quinlan, E. B., Conrod, P., … Garavan, H. (2021). Association of cannabis use during adolescence with neurodevelopment. *JAMA Psychiatry, 78*(9), 1031–1040. https://doi.org/10.1001/jamapsychiatry.2021.1258

Anglin, D. M., Ereshefsky, S., Klaunig, M. J., Bridgwater, M. A., Niendam, T. A., Ellman, L. M., DeVylder, J., Thayer, G., Bolden, K., Musket, C. W., Grattan, R. E., Lincoln, S. H., Schiffman, J., Lipner, E., Bachman, P., Corcoran, C. M., Mota, N. B., & van der Ven, E. (2021). From womb to neighborhood: A racial analysis of social determinants of psychosis in the United States. *The American Journal of Psychiatry, 178*(7), 599–610. https://doi.org/10.1176/appi.ajp.2020.20071091

Arnold, A. P. (2009). The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. *Hormones and Behavior, 55*(5), 570–578. https://doi.org/10.1016/j.yhbeh.2009.03.011

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal, 325*(7374), 1212−1213. https://doi.org/10.1136/bmj.325.7374.1212

Auther, A. M., Cadenhead, K. S., Carrión, R. E., Addington, J., Bearden, C. E., Cannon, T. D., Mcglashan, T. H., Perkins, D. O., Seidman, L., Tsuang, M., Walker, E. F., Woods, S. W., & Cornblatt, B. A. (2015). Alcohol confounds relationship between cannabis misuse and psychosis conversion in a high-risk sample. *Acta Psychiatrica Scandinavica, 132*(1), 60−68. https://doi.org/10.1111/acps.12382

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J. A., Nogué, S., Torrens, M., Pujol, J., Farré, M., Martin-Santos, R., & Lu, L. (2013). Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLoS One, 8*(2), e55821. https://doi.org/10.1371/journal.pone.0055821

Bearden, C. E., Rosso, I. M., Hollister, J. M., Sanchez, L. E., Hadley, T., & Cannon, T. D. (2000). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophrenia Bulletin, 26*(2), 395−410. https://doi.org/10.1093/oxfordjournals.schbul.a033461

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C. M., Seal, M., Allen, P., Mehta, M. A., Stone, J. M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R. M., Zuardi, A. W., Crippa, J. A., Atakan, Z., & McGuire, P. K. (2010). Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35*(3), 764−774. https://doi.org/10.1038/npp.2009.184

Blakemore, S. J., & Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annual Review of Psychology, 65*, 187−207. https://doi.org/10.1146/annurev-psych-010213-115202

Bourque, F., Van Der Ven, E., & Malla, A. (2011). A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychological Medicine, 41*(5), 897−910. https://doi.org/10.1017/S0033291710001406

Brook, J. S., Stimmel, M. A., Zhang, C., & Brook, D. W. (2008). The association between earlier marijuana use and subsequent academic achievement and health problems: A longitudinal study. *American Journal on Addictions, 17*(2), 155−160. https://doi.org/10.1080/10550490701860930

Brown, A. S., & Susser, E. S. (2008). Prenatal nutritional deficiency and risk of adult schizophrenia. *Schizophrenia Bulletin, 34*(6), 1054−1063. https://doi.org/10.1093/schbul/sbn096

Buka, S. L., Cannon, T. D., Torrey, E. F., & Yolken, R. H. (2008). Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. *Biological Psychiatry, 63*(8), 809−815. https://doi.org/10.1016/j.biopsych.2007.09.022

Buka, S. L., Tsuang, M. T., & Lipsitt, L. P. (1993). Pregnancy/delivery complications and psychiatric diagnosis: A prospective study. *Archives of General Psychiatry, 50*(2), 151−156. https://doi.org/10.1001/archpsyc.1993.01820140077009

Cabungcal, J. H., Counotte, D. S., Lewis, E. M., Tejeda, H. A., Piantadosi, P., Pollock, C., Calhoon, G. G., Sullivan, E. M., Presgraves, E., Kil, J., Hong, L. E., Cuenod, M., Do, K. Q., & O'Donnell, P. (2014). Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. *Neuron, 83*(5), 1073−1084. https://doi.org/10.1016/j.neuron.2014.07.028

Cannon, T. D. (1997). On the nature and mechanisms of obstetric influences in schizophrenia: A review and synthesis of epidemiologic studies. *International Review of Psychiatry, 9*(4), 387−398. https://doi.org/10.1080/09540269775259

Cannon, T. D., Rosso, I. M., Hollister, J. M., Bearden, C. E., Sanchez, L. E., & Hadley, T. (2000). A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophrenia Bulletin, 26*(2), 351−366. https://doi.org/10.1093/oxfordjournals.schbul.a033458

Cannon, T. D., Van Erp, T. G. M., Rosso, I. M., Huttunen, M., Lönnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V. P., & Standertskjöld-Nordenstam, C. G. (2002). Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Archives of General Psychiatry, 59*(1), 35–41. https://doi.org/10.1001/archpsyc.59.1.35

Cannon, T. D., Yu, C., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Heinssen, R., Jeffries, C. D., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Kattan, M. W. (2016). An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry, 173*(10), 980–988. https://doi.org/10.1176/appi.ajp.2016.15070890

Carrión, R. E., Demmin, D., Auther, A. M., McLaughlin, D., Olsen, R., Lencz, T., Correll, C. U., & Cornblatt, B. A. (2016). Duration of attenuated positive and negative symptoms in individuals at clinical high risk: Associations with risk of conversion to psychosis and functional outcome. *Journal of Psychiatric Research, 81*, 95–101. https://doi.org/10.1016/j.jpsychires.2016.06.021

Chadwick, B., Miller, M. L., & Hurd, Y. L. (2013). Cannabis use during adolescent development: Susceptibility to psychiatric illness. *Frontiers in Psychiatry, 4*. https://doi.org/10.3389/fpsyt.2013.00129

Clarke, M. C., Harley, M., & Cannon, M. (2006). The role of obstetric events in schizophrenia. *Schizophrenia Bulletin, 32*(1), 3–8. https://doi.org/10.1093/schbul/sbj028

Cornblatt, B. A., Carrion, R. E., Addington, J., Seidman, L., Walker, E. F., Cannon, T. D., Cadenhead, K. S., McGlashan, T. H., Perkins, D. O., Tsuang, M. T., Woods, S. W., Heinssen, R., & Lencz, T. (2012). Risk factors for psychosis: Impaired social and role functioning. *Schizophrenia Bulletin, 38*(6), 1247–1257. https://doi.org/10.1093/schbul/sbr136

Dahoun, T., Nour, M. M., McCutcheon, R. A., Adams, R. A., Bloomfield, M. A. P., & Howes, O. D. (2019). The relationship between childhood trauma, dopamine release and dexamphetamine-induced positive psychotic symptoms: A [11C]-(+)-PHNO PET study. *Translational Psychiatry, 9*(1). https://doi.org/10.1038/s41398-019-0627-y

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B. B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K. B., Timmerman, A., Schendel, D., McGrath, J. J., Mortensen, P. B., & Pedersen, C. B. (2020). Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. *JAMA Psychiatry, 77*(2), 155–164. https://doi.org/10.1001/jamapsychiatry.2019.3523

Degnan, A., Berry, K., Sweet, D., Abel, K., Crossley, N., & Edge, D. (2018). Social networks and symptomatic and functional outcomes in schizophrenia: A systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology, 53*(9), 873–888. https://doi.org/10.1007/s00127-018-1552-8

DeRosse, P., Ikuta, T., Karlsgodt, K. H., Peters, B. D., Gopin, C. B., Szeszko, P. R., & Malhotra, A. K. (2017). White matter abnormalities associated with subsyndromal psychotic-like symptoms predict later social competence in children and adolescents. *Schizophrenia Bulletin, 43*(1), 152–159. https://doi.org/10.1093/schbul/sbw062

DeRosse, Pamela, Nitzburg, G. C., Kompancaril, B., & Malhotra, A. K. (2014). The relation between childhood maltreatment and psychosis in patients with schizophrenia and non-psychiatric controls. *Schizophrenia Research, 155*(1–3), 66–71. https://doi.org/10.1016/j.schres.2014.03.009

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., Marconi, A., La Cascia, C., Marques, T. R., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A. S., Morgan, C., Stahl, D., … Murray, R. M. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin, 40*(6), 1509–1517. https://doi.org/10.1093/schbul/sbt181

Dorn, L. D. (2006). Measuring puberty. *Journal of Adolescent Health, 39*(5), 625−626. https://doi.org/10.1016/j.jadohealth.2006.05.014

Du, Y., & Grace, A. A. (2013). Peripubertal diazepam administration prevents the emergence of dopamine system hyperresponsivity in the MAM developmental disruption model of schizophrenia. *Neuropsychopharmacology, 38*(10), 1881−1888. https://doi.org/10.1038/npp.2013.101

Elmlinger, M. W., Kühnel, W., & Ranke, M. B. (2002). Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. *Clinical Chemistry and Laboratory Medicine, 40*(11), 1151−1160. https://doi.org/10.1515/CCLM.2002.202

Essex, M. J., Shirtcliff, E. A., Burk, L. R., Ruttle, P. L., Klein, M. H., Slattery, M. J., Kalin, N. H., & Armstrong, J. M. (2011). Influence of early life stress on later hypothalamic - pituitary - adrenal axis functioning and its covariation with mental health symptoms: A study of the allostatic process from childhood into adolescence. *Development and Psychopathology, 23*(4), 1039−1058. https://doi.org/10.1017/S0954579411000484

Estrada, G., Fatjó-Vilas, M., Muñoz, M. J., Pulido, G., Miñano, M. J., Toledo, E., Illa, J. M., Martín, M., Miralles, M. L., Miret, S., Campanera, S., Bernabeu, C., Navarro, M. E., & Fañanás, L. (2011). Cannabis use and age at onset of psychosis: Further evidence of interaction with COMT Val158Met polymorphism. *Acta Psychiatrica Scandinavica, 123*(6), 485−492. https://doi.org/10.1111/j.1600-0447.2010.01665.x

Fatemi, S. H., Earle, J., Kanodia, R., Kist, D., Emamian, E. S., Patterson, P. H., Shi, L., & Sidwell, R. (2002). Prenatal viral infection leads to pyramidal cell atrophy and macrocephaly in adulthood: Implications for genesis of autism and schizophrenia. *Cellular and Molecular Neurobiology, 22*(1), 25−33. https://doi.org/10.1023/A:1015337611258

Fineberg, A. M., & Ellman, L. M. (2013). Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. *Biological Psychiatry, 73*(10), 951−966. https://doi.org/10.1016/j.biopsych.2013.01.001

Freedman, R., Hunter, S. K., Law, A. J., Clark, A. M., Roberts, A., & Hoffman, M. C. (2021). Choline, folic acid, Vitamin D, and fetal brain development in the psychosis spectrum. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2021.03.008

Furman, W. (2002). The emerging field of adolescent romantic relationships. *Current Directions in Psychological Science, 11*(5), 177−180. https://doi.org/10.1111/1467-8721.00195

Galdos, P. M., van Os, J. J., & Murray, R. M. (1993). Puberty and the onset of psychosis. *Schizophrenia Research, 10*(1), 7−14. https://doi.org/10.1016/0920-9964(93)90071-P

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., Hare, T. A., Bookheimer, S. Y., & Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *Journal of Neuroscience, 33*(10), 4584−4593. https://doi.org/10.1523/jneurosci.3446-12.2013

Gee, D. G., Karlsgodt, K. H., van Erp, T. G. M., Bearden, C. E., Lieberman, M. D., Belger, A., Perkins, D. O., Olvet, D. M., Cornblatt, B. A., Constable, T., Woods, S. W., Addington, J., Cadenhead, K. S., McGlashan, T. H., Seidman, L. J., Tsuang, M. T., Walker, E. F., & Cannon, T. D. (2012). Altered age-related trajectories of amygdala-prefrontal circuitry in adolescents at clinical high risk for psychosis: A preliminary study. *Schizophrenia Research, 134*(1), 1−9. https://doi.org/10.1016/j.schres.2011.10.005

Giannopoulou, I., Pagida, M. A., Briana, D. D., & Panayotacopoulou, M. T. (2018). Perinatal hypoxia as a risk factor for psychopathology later in life: The role of dopamine and neurotrophins. *Hormones, 17*(1), 25−32. https://doi.org/10.1007/s42000-018-0007-7

Gogos, A., Sbisa, A. M., Sun, J., Gibbons, A., Udawela, M., & Dean, B. (2015). A role for estrogen in schizophrenia: Clinical and preclinical findings. *International Journal of Endocrinology.* https://doi.org/10.1155/2015/615356, 2015.

Gould, E., Woolley, C., Frankfurt, M., & McEwen, B. (1990). Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *The Journal of Neuroscience, 10*(4), 1286−1291. https://doi.org/10.1523/jneurosci.10-04-01286.1990

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology, 21*(1), 69−85. https://doi.org/10.1017/S0954579409000054

Harrell, S. P. (2000). A multidimensional conceptualization of racism-related stress: Implications for the well-being of people of color. *American Journal of Orthopsychiatry, 70*(1), 42−57. https://doi.org/10.1037/h0087722

Havelock, J. C., Auchus, R. J., & Rainey, W. E. (2004). The rise in adrenal androgen biosynthesis: Adrenarche. *Seminars in Reproductive Medicine, 22*(4), 337−347. https://doi.org/10.1055/s-2004-861550

Hoffman, M. C., Freedman, R., Law, A. J., Clark, A. M., & Hunter, S. K. (2021). Maternal nutrients and effects of gestational COVID-19 infection on fetal brain development. *Clinical Nutrition ESPEN, 43*, 1−8. https://doi.org/10.1016/j.clnesp.2021.04.019

Holtzman, C. W., Trotman, H. D., Goulding, S. M., Ryan, A. T., MacDonald, A. N., Shapiro, D. I., Brasfield, J. L., & Walker, E. F. (2013). Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience, 249*, 172−191. https://doi.org/10.1016/j.neuroscience.2012.12.017

Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. *The Lancet, 383*(9929), 1677−1687. https://doi.org/10.1016/S0140-6736(13)62036-X

Hur, J. W., Choi, S. H., Yun, J. Y., Chon, M. W., & Kwon, J. S. (2015). Parental socioeconomic status and prognosis in individuals with ultra-high risk for psychosis: A 2-year follow-up study. *Schizophrenia Research, 168*(1−2), 56−61. https://doi.org/10.1016/j.schres.2015.07.020

Immonen, J., Jääskeläinen, E., Korpela, H., & Miettunen, J. (2017). Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Intervention in Psychiatry, 11*(6), 453−460. https://doi.org/10.1111/eip.12412

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., De Graaf, R., & Van Os, J. (2004). Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandinavica, 109*(1), 38−45. https://doi.org/10.1046/j.0001-690X.2003.00217.x

Johnson, E. C., Hatoum, A. S., Deak, J. D., Polimanti, R., Murray, R. M., Edenberg, H. J., Gelernter, J., Di Forti, M., & Agrawal, A. (2021). The relationship between cannabis and schizophrenia: A genetically informed perspective. *Addiction, 116*(11), 3227−3234. https://doi.org/10.1111/add.15534

Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., Addington, J., Brunette, M. F., Correll, C. U., Estroff, S. E., Marcy, P., Robinson, J., Meyer-Kalos, P. S., Gottlieb, J. D., Glynn, S. M., Lynde, D. W., Pipes, R., Kurian, B. T., Miller, A. L., … Heinssen, R. K. (2016). Comprehensive versus usual community care for first-episode psychosis: 2-Year outcomes from the NIMH RAISE early treatment program. *American Journal of Psychiatry, 173*(4), 362−372. https://doi.org/10.1176/appi.ajp.2015.15050632

Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2013). Childhood trauma and psychosis in a prospective cohort study: Cause, effect, and directionality. *American Journal of Psychiatry, 170*(7), 734−741. https://doi.org/10.1176/appi.ajp.2012.12091169

Khandaker, G. M., Zimbron, J., Dalman, C., Lewis, G., & Jones, P. B. (2012). Childhood infection and adult schizophrenia: A meta-analysis of population-based studies. *Schizophrenia Research, 139*(1−3), 161−168. https://doi.org/10.1016/j.schres.2012.05.023

Kirkbride, J. B., Hameed, Y., Ioannidis, K., Ankireddypalli, G., Crane, C. M., Nasir, M., Kabacs, N., Metastasio, A., Jenkins, O., Espandian, A., Spyridi, S., Ralevic, D., Siddabattuni, S., Walden, B., Adeoye, A., Perez, J., & Jones, P. B. (2017). Ethnic minority status, age-at-immigration and psychosis risk in rural environments: Evidence from the SEPEA study. *Schizophrenia Bulletin, 43*(6), 1251−1261. https://doi.org/10.1093/schbul/sbx010

Klosterkötter, J., Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Linszen, D., Birchwood, M., Juckel, G., Morrison, A., Vázquèz-Barquero, J. L., Hambrecht, M., & Reventlow. (2005). The European prediction of psychosis study (EPOS): Integrating early recognition and intervention in. *Europe. World Psychiatry : Official Journal of the World Psychiatric Association (WPA), 4*(3), 161−167.

Klumpers, L. E., & Thacker, D. L. (2019). A brief background on cannabis: From plant to medical indications. *Journal of AOAC International, 102*(2), 412−420. https://doi.org/10.5740/jaoacint.18-0208

Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., & Miettunen, J. (2010). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: A meta-analysis. *Schizophrenia Bulletin, 36*(6), 1115−1130. https://doi.org/10.1093/schbul/sbp031

Kuepper, R., van Os, J., Lieb, R., Wittchen, H.-U., Hofler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ, 342*(mar01 1). https://doi.org/10.1136/bmj.d738. d738−d738.

Lange, C., Deutschenbaur, L., Borgwardt, S., Lang, U. E., Walter, M., & Huber, C. G. (2017). Experimentally induced psychosocial stress in schizophrenia spectrum disorders: A systematic review. *Schizophrenia Research, 182*, 4−12. https://doi.org/10.1016/j.schres.2016.10.008

Lay, B., Blanz, B., Hartmann, M., & Schmidt, M. H. (2000). The psychosocial outcome of adolescent-onset schizopherenia: A 12-year followup. *Schizophrenia Bulletin, 26*(4), 801−816. https://doi.org/10.1093/oxfordjournals.schbul.a033495

Leathem, L. D., Currin, D. L., Montoya, A. K., & Karlsgodt, K. H. (2021). Socioemotional mechanisms of loneliness in subclinical psychosis. *Schizophrenia Research, 238*, 145−151. https://doi.org/10.1016/j.schres.2021.10.002

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., Klosterkötter, J., Hellmich, M., & Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry, 2*(3). https://doi.org/10.1038/tp.2012.15. e94−e94.

Liu, Y., Mendonça, M., Johnson, S., O'Reilly, H., Bartmann, P., Marlow, N., & Wolke, D. (2021). Testing the neurodevelopmental, trauma and developmental risk factor models of psychosis using a naturalistic experiment. *Psychological Medicine, 51*(3), 460−469. https://doi.org/10.1017/S0033291719003349

Long, L. E., Lind, J., Webster, M., & Weickert, C. S. (2012). Developmental trajectory of the endocannabinoid system in human dorsolateral prefrontal cortex. *BMC Neuroscience, 13*(1). https://doi.org/10.1186/1471-2202-13-87

Marceau, K., Ruttle, P. L., Shirtcliff, E. A., Hastings, P. D., Klimes-Dougan, B., & Zahn-Waxler, C. (2015). Within-person coupling of changes in cortisol, testosterone, and DHEA across the day in adolescents. *Developmental Psychobiology, 57*(6), 654−669. https://doi.org/10.1002/dev.21173

Marín, O. (2016). Developmental timing and critical windows for the treatment of psychiatric disorders. *Nature Medicine, 22*(11), 1229−1238. https://doi.org/10.1038/nm.4225

McGorry, P. D., Killackey, E., & Yung, A. (2008). Early intervention in psychosis: Concepts, evidence and future directions. *World Psychiatry, 7*(3), 148–156. https://doi.org/10.1002/j.2051-5545.2008.tb00182.x

McGrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R., Alati, R., Williams, G. M., Bor, W., & Najman, J. M. (2010). Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Archives of General Psychiatry, 67*(5), 440–447. https://doi.org/10.1001/archgenpsychiatry.2010.6

McLaughlin, K. A., Conron, K. J., Koenen, K. C., & Gilman, S. E. (2010). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: A test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine, 40*(10), 1647–1658. https://doi.org/10.1017/S0033291709992121

McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2012). Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry, 69*(11), 1151–1160. https://doi.org/10.1001/archgenpsychiatry.2011.2277

Mednick, S. A., Watson, J. B., Huttunen, M., Cannon, T. D., Katila, H., Machon, R., Mednick, B., Hollister, M., Parnas, J., Schulsinger, F., Sajaniemi, N., Voldsgaard, P., Pyhala, R., Gutkind, D., & Wang, X. (1998). In M. F. Lenzenweger, & R. H. Dworkin (Eds.), *27–66A two-hit working model of the etiology of schizophrenia*. American Psychological Association. https://doi.org/10.1037/10305-002

Mennigen, E., & Bearden, C. E. (2020). Psychosis risk and development: What do we know from population-based studies? *Biological Psychiatry, 88*(4), 315–325. https://doi.org/10.1016/j.biopsych.2019.12.014

Meyer, U. (2013). Developmental neuroinflammation and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 42*, 20–34. https://doi.org/10.1016/j.pnpbp.2011.11.003

Misiak, B., Frydecka, D., Loska, O., Moustafa, A. A., Samochowiec, J., Kasznia, J., & Stańczykiewicz, B. (2018). Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis. *Psychoneuroendocrinology, 89*, 92–102. https://doi.org/10.1016/j.psyneuen.2018.01.007

Mittal, V. A., Ellman, L. M., & Cannon, T. D. (2008). Gene-environment interaction and covariation in schizophrenia: The role of obstetric complications. *Schizophrenia Bulletin, 34*(6), 1083–1094. https://doi.org/10.1093/schbul/sbn080

Mittal, V. A., Willhite, R., Daley, M., Bearden, C. E., Niendam, T., Ellman, L. M., & Cannon, T. D. (2009). Obstetric complications and risk for conversion to psychosis among individuals at high clinical risk. *Early Intervention in Psychiatry, 3*(3), 226–230. https://doi.org/10.1111/j.1751-7893.2009.00137.x

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet, 370*(9584), 319–328. https://doi.org/10.1016/S0140-6736(07)61162-3

Odegaard, O. (1932). Emigration and insanity. *Acta Psychiatrica et Neurologica, 4*, 1–206.

Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. *Psychopharmacology, 231*(12), 2417–2433. https://doi.org/10.1007/s00213-013-3407-z

Owens, S. J., Murphy, C. E., Purves-Tyson, T. D., Weickert, T. W., & Shannon Weickert, C. (2018). Considering the role of adolescent sex steroids in schizophrenia. *Journal of Neuroendocrinology, 30*(2). https://doi.org/10.1111/jne.12538

Padula, C. B., Schweinsburg, A. D., & Tapert, S. F. (2007). Spatial working memory Performance and fMRI activation interactions in abstinent adolescent marijuana users. *Psychology of Addictive Behaviors, 21*(4), 478−487. https://doi.org/10.1037/0893-164X.21.4.478

Pearce, J., Rafiq, S., Simpson, J., & Varese, F. (2019). Perceived discrimination and psychosis: A systematic review of the literature. *Social Psychiatry and Psychiatric Epidemiology, 54*(9), 1023−1044. https://doi.org/10.1007/s00127-019-01729-3

Peper, J. S., Brouwer, R. M., Schnack, H. G., van Baal, G. C., van Leeuwen, M., van den Berg, S. M., Delemarre-Van de Waal, H. A., Boomsma, D. I., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Sex steroids and brain structure in pubertal boys and girls. *Psychoneuroendocrinology, 34*(3), 332−342. https://doi.org/10.1016/j.psyneuen.2008.09.012

Peper, J. S., & Dahl, R. E. (2013). The teenage brain: Surging hormones-brain-behavior interactions during puberty. *Current Directions in Psychological Science, 22*(2), 134−139. https://doi.org/10.1177/0963721412473755

Perkins, D. O., Gu, H., Boteva, K., & Lieberman, J. A. (2005). Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. *American Journal of Psychiatry, 162*(10), 1785−1804. https://doi.org/10.1176/appi.ajp.162.10.1785

Quidé, Y., Girshkin, L., Watkeys, O. J., Carr, V. J., & Green, M. J. (2021). The relationship between cortisol reactivity and emotional brain function is differently moderated by childhood trauma, in bipolar disorder, schizophrenia and healthy individuals. *European Archives of Psychiatry and Clinical Neuroscience, 271*(6), 1089−1109. https://doi.org/10.1007/s00406-020-01190-3

Rajji, T. K., Ismail, Z., & Mulsant, B. H. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *British Journal of Psychiatry, 195*(4), 286−293. https://doi.org/10.1192/bjp.bp.108.060723

Read, J., Van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica, 112*(5), 330−350. https://doi.org/10.1111/j.1600-0447.2005.00634.x

Robustelli, B. L., Newberry, R. E., Whisman, M. A., & Mittal, V. A. (2017). Social relationships in young adults at ultra high risk for psychosis. *Psychiatry Research, 247*, 345−351. https://doi.org/10.1016/j.psychres.2016.12.008

Romeo, R. D. (2010). Adolescence: A central event in shaping stress reactivity. *Developmental Psychobiology, 52*(3), 244−253. https://doi.org/10.1002/dev.20437

Rosso, I. M., Cannon, T. D., Huttunen, T., Huttunen, M. O., Lönnqvist, J., & Gasperoni, T. L. (2000). Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. *American Journal of Psychiatry, 157*(5), 801−807. https://doi.org/10.1176/appi.ajp.157.5.801

Rubino, T., Prini, P., Piscitelli, F., Zamberletti, E., Trusel, M., Melis, M., Sagheddu, C., Ligresti, A., Tonini, R., Di Marzo, V., & Parolaro, D. (2015). Adolescent exposure to THC in female rats disrupts developmental changes in the prefrontal cortex. *Neurobiology of Disease, 73*, 60−69. https://doi.org/10.1016/j.nbd.2014.09.015

Salazar De Pablo, G., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., Soardo, L., Cabras, A., Fortea, L., Catalan, A., Vaquerizo-Serrano, J., Coronelli, F., Kaur, S., Da Silva, J., Shin, J. I., Solmi, M., Brondino, N., Politi, P., McGuire, P., & Fusar-Poli, P. (2021). Probability of transition to psychosis in individuals at clinical high risk: An updated meta-analysis. *JAMA Psychiatry, 78*(9), 970−978. https://doi.org/10.1001/jamapsychiatry.2021.0830

Sato, S. M., Schulz, K. M., Sisk, C. L., & Wood, R. I. (2008). Adolescents and androgens, receptors and rewards. *Hormones and Behavior, 53*(5), 647−658. https://doi.org/10.1016/j.yhbeh.2008.01.010

Saugstad, L. F. (1989). Mental illness and cognition in relation to age at puberty: A hypothesis. *Clinical Genetics, 36*(3), 156–167. https://doi.org/10.1111/j.1399-0004.1989.tb03182.x

Schenkel, L. S., Spaulding, W. D., DiLillo, D., & Silverstein, S. M. (2005). Histories of childhood maltreatment in schizophrenia: Relationships with premorbid functioning, symptomatology, and cognitive deficits. *Schizophrenia Research, 76*(2–3), 273–286. https://doi.org/10.1016/j.schres.2005.03.003

Schmidt-Kastner, R., Van Os, J., Esquivel, G., Steinbusch, H. W. M., & Rutten, B. P. F. (2012). An environmental analysis of genes associated with schizophrenia: Hypoxia and vascular factors as interacting elements in the neurodevelopmental model. *Molecular Psychiatry, 17*(12), 1194–1205. https://doi.org/10.1038/mp.2011.183

Seeman, P. (2016). Cannabidiol is a partial agonist at dopamine D2High receptors, predicting its antipsychotic clinical dose. *Translational Psychiatry, 6*(10), e920. https://doi.org/10.1038/tp.2016.195

Shah, J. L., Tandon, N., Howard, E. R., Mermon, D., Miewald, J. M., Montrose, D. M., & Keshavan, M. S. (2015). Pituitary volume and clinical trajectory in young relatives at risk for schizophrenia. *Psychological Medicine, 45*(13), 2813–2824. https://doi.org/10.1017/S003329171500077X

Sham, P. C., Jones, P., Russell, A., Gilvarry, K., Bebbington, P., Lewis, S., Toone, B., & Murray, R. (1994). Age at onset, sex, and familial psychiatric morbidity in schizophrenia. Camberwell collaborative psychosis study. *British Journal of Psychiatry, 165*, 466–473. https://doi.org/10.1192/bjp.165.4.466

Shirtcliff, E. A., Dahl, R. E., & Pollak, S. D. (2009). Pubertal development: Correspondence between hormonal and physical development. *Child Development, 80*(2), 327–337. https://doi.org/10.1111/j.1467-8624.2009.01263.x

Silvers, J. A., Insel, C., Powers, A., Franz, P., Helion, C., Martin, R., Weber, J., Mischel, W., Casey, B. J., & Ochsner, K. N. (2017). The transition from childhood to adolescence is marked by a general decrease in amygdala reactivity and an affect-specific ventral-to-dorsal shift in medial prefrontal recruitment. *Developmental Cognitive Neuroscience, 25*, 128–137. https://doi.org/10.1016/j.dcn.2016.06.005

Steinberg, L., & Morris, A. S. (2001). Adolescent development. *Annual Review of Psychology, 52*, 83–110. https://doi.org/10.1146/annurev.psych.52.1.83

Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, P. (2016). Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: A systematic review. *Journal of Child and Adolescent Psychopharmacology, 26*(5), 410–427. https://doi.org/10.1089/cap.2015.0097

Suvisaari, J. M., Haukka, J. K., & Lönnqvist, J. K. (2001). Season of birth among patients with schizophrenia and their siblings: Evidence for the procreational habits hypothesis. *American Journal of Psychiatry, 158*(5), 754–757. https://doi.org/10.1176/appi.ajp.158.5.754

Suvisaari, J. M., Haukka, J. K., & Lönnqvist, J. K. (2004). No association between season of birth of patients with schizophrenia and risk of schizophrenia among their siblings. *Schizophrenia Research, 66*(1), 1–6. https://doi.org/10.1016/S0920-9964(02)00506-6

Tarbox, S. I., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Heinssen, R., McGlashan, T. H., & Woods, S. W. (2013). Premorbid functional development and conversion to psychosis in clinical high-risk youths. *Development and Psychopathology, 25*(4), 1171–1186. https://doi.org/10.1017/S0954579413000448

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews Neuroscience, 17*(10), 652–666. https://doi.org/10.1038/nrn.2016.111

Tottenham, N. (2015). Social scaffolding of human amygdala-mPFCcircuit development. *Social Neuroscience, 10*(5), 489−499. https://doi.org/10.1080/17470919.2015.1087424

Trotman, H. D., Holtzman, C. W., Ryan, A. T., Shapiro, D. I., MacDonald, A. N., Goulding, S. M., Brasfield, J. L., & Walker, E. F. (2013). The development of psychotic disorders in adolescence: A potential role for hormones. *Hormones and Behavior, 64*(2), 411−419. https://doi.org/10.1016/j.yhbeh.2013.02.018

Ursini, G., Punzi, G., Langworthy, B. W., Chen, Q., Xia, K., Cornea, E. A., Goldman, B. D., Styner, M. A., Knickmeyer, R. C., Gilmore, J. H., & Weinberger, D. R. (2021). Placental genomic risk scores and early neurodevelopmental outcomes. *Proceedings of the National Academy of Sciences of the United States of America, 118*(7). https://doi.org/10.1073/pnas.2019789118

Vaessen, T. S. J., de Jong, L., Schäfer, A. T., Damen, T., Uittenboogaard, A., Krolinski, P., Nwosu, C. V., Pinckaers, F. M. E., Rotee, I. L. M., Smeets, A. P. W., Ermiş, A., Kennedy, J. L., Nieman, D. H., Tiwari, A., van Os, J., Drukker, M., & YUE, W. (2018). The interaction between cannabis use and the Val158Met polymorphism of the COMT gene in psychosis: A transdiagnostic meta − analysis. *PLoS One, 13*(2), e0192658. https://doi.org/10.1371/journal.pone.0192658

Van Der Ven, E., & Selten, J. P. (2018). Migrant and ethnic minority status as risk indicators for schizophrenia: New findings. *Current Opinion in Psychiatry, 31*(3), 231−236. https://doi.org/10.1097/YCO.0000000000000405

Van Erp, T. G. M., Saleh, P. A., Rosso, I. M., Huttunen, M., Lönnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V. P., Standertskjöld-Nordenstam, C. G., & Cannon, T. D. (2002). Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. *American Journal of Psychiatry, 159*(9), 1514−1520. https://doi.org/10.1176/appi.ajp.159.9.1514

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., Van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin, 38*(4), 661−671. https://doi.org/10.1093/schbul/sbs050

van der Ven, E., Susser, E., Dixon, L. B., Olfson, M., & Gilmer, T. P. (2020). Racial-ethnic differences in service use patterns among young, commercially insured individuals with recent-onset psychosis. *Psychiatric Services, 71*(5), 433−439. https://doi.org/10.1176/appi.ps.201900301

Verdoux, H., Geddes, J. R., Takei, N., Lawrie, S. M., Bovet, P., Eagles, J. M., Heun, R., McCreadie, R. G., McNeil, T. F., O'Callaghan, E., Stöber, G., Willinger, U., Wright, P., & Murray, R. M. (1997). Obstetric complications and age at onset in schizophrenia: An international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry, 154*(9), 1220−1227. https://doi.org/10.1176/ajp.154.9.1220

Vijayakumar, Mills, K., & Flournoy, J. (2018). *Methodological considerations for the association between pubertal development and brain structure. Presented at: Society for Research on. Adolescence Biennial Meeting*.

Vijayakumar, N., Op de Macks, Z., Shirtcliff, E. A., & Pfeifer, J. H. (2018). Puberty and the human brain: Insights into adolescent development. *Neuroscience and Biobehavioral Reviews, 92*, 417−436. https://doi.org/10.1016/j.neubiorev.2018.06.004

Vijayakumar, N., Pfeifer, J. H., Flournoy, J. C., Hernandez, L. M., & Dapretto, M. (2019). *Affective reactivity during adolescence: Associations with age, puberty and testosterone*. https://doi.org/10.1101/524033. bioRxiv.

Wahbeh, M. H., & Avramopoulos, D. (2021). Gene-environment interactions in schizophrenia: A literature review. *Genes, 12*(12). https://doi.org/10.3390/genes12121850

Wainberg, M., Jacobs, G. R., di Forti, M., & Tripathy, S. J. (2021). Cannabis, schizophrenia genetic risk, and psychotic experiences: A cross-sectional study of 109,308 participants from the UK Biobank. *Translational Psychiatry, 11*(1). https://doi.org/10.1038/s41398-021-01330-w

Walker, E. F., Walder, D. J., & Reynolds, F. (2001). Developmental changes in cortisol secretion in normal and at-risk youth. *Development and Psychopathology, 13*(3), 721−732. https://doi.org/10.1017/S0954579401003169

Wood, C. E., & Keller-Wood, M. (2019). Current paradigms and new perspectives on fetal hypoxia: Implications for fetal brain development in late gestation. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology, 317*(1), R1−R13. https://doi.org/10.1152/ajpregu.00008.2019

Wortinger, L. A., Engen, K., Barth, C., Andreassen, O. A., Nordbø Jørgensen, K., & Agartz, I. (2020). Asphyxia at birth affects brain structure in patients on the schizophrenia-bipolar disorder spectrum and healthy participants. *Psychological Medicine*. https://doi.org/10.1017/S0033291720002779

Wortinger, L. A., Jørgensen, K. N., Barth, C., Nerland, S., Smelror, R. E., Vaskinn, A., Ueland, T., Andreassen, O. A., & Agartz, I. (2021). Significant association between intracranial volume and verbal intellectual abilities in patients with schizophrenia and a history of birth asphyxia. *Psychological Medicine*, 1−10. https://doi.org/10.1017/s0033291721000489

Xu, P., Klaasen, N. G., Opmeer, E. M., Pijnenborg, G. H. M., van Tol, M. J., Liemburg, E. J., & Aleman, A. (2019). Intrinsic mesocorticolimbic connectivity is negatively associated with social amotivation in people with schizophrenia. *Schizophrenia Research, 208*, 353−359. https://doi.org/10.1016/j.schres.2019.01.023

Yung, A. R., & McGorry, P. O. (1996). The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin, 22*(2), 353−370. https://doi.org/10.1093/schbul/22.2.353

Zhang, J. P., Robinson, D., Yu, J., Gallego, J., Fleischhacker, W. W., Kahn, R. S., Crespo-Facorro, B., Vazquez-Bourgon, J., Kane, J. M., Malhotra, A. K., & Lencz, T. (2019). Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis. *American Journal of Psychiatry, 176*(1), 21−28. https://doi.org/10.1176/appi.ajp.2018.17121363

Zimmer, A., Youngblood, A., Adnane, A., Miller, B. J., & Goldsmith, D. R. (2021). Prenatal exposure to viral infection and neuropsychiatric disorders in offspring: A review of the literature and recommendations for the COVID-19 pandemic. *Brain, Behavior, and Immunity, 91*, 756−770. https://doi.org/10.1016/j.bbi.2020.10.024

Chapter 5

Adolescent psychosis and transdiagnostic delimitations to other clinical syndromes

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Introduction

Most instances of early-onset psychotic disorders (EOP; illness onset before 18 years of age (Werry et al., 1991) occur during adolescence after age 13 years (Dalsgaard et al., 2020). The majority of cases have some kind of precursors/pre-psychosis "signals" that have either been overlooked or diagnosed under different other categories in early childhood. These range from motor delay/late walker, developmental delay, speech-language disorder, and learning disorder through autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and tic syndromes. Underlying these types of problems are often aberrant/variant genes or a combination of genes and pre-, peri-, and postnatal risk factors, such as infections in utero, birth asphyxia, and/or extremes of prematurity. In other instances, "premorbid" depression and anxiety disorders may have been considered before emergence of psychotic symptoms lead to assessment and diagnoses of schizophrenia or other adolescent-onset psychotic disorders. In such cases of depression and anxiety also, there is often a history of neurodevelopmental problems of various kinds, deficits, and disorders that may or may not have been recognized before the emergence of psychotic symptoms.

This chapter looks at the whole area of *Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations* (ESSENCE) and suggests implications for future directions in terms of early diagnosis, follow-up and prevention measures.

Prenatal and young life predictors of early-onset psychosis

That genetic factors, complex and interactive, are of major importance when it comes to accounting for the variance in adolescent-onset psychosis, is

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00001-9

indisputable, but will not be further dealt with in any depth in this chapter. For more information about the genetics of adolescent psychosis, please see Chapter 3 in this book.

Mednick and Schulzinger (Mednick et al., 1987) from the Copenhagen cohort and the Gothenburg studies in the 1980s, reported on the population-based studies of the antecedents of adolescent-onset psychosis (Gillberg et al., 1986, 1993). Ever since their seminal publications it has been well established that pre- and perinatal risk factors are associated with adolescent psychosis of various kinds (Coleman & Gillberg, 1996; Hultman et al., 1999; Schlosser et al., 2012). However, there has been no agreement as to which individual risk factors might be salient. Studies of school health records and early life developmental milestones had also shown that in many cases of adolescent-onset psychosis or schizophrenia there had been minor neuro-developmental disorders or problems preceding the onset of the psychotic symptoms in adolescence (Hellgren et al., 1987; Sørensen et al., 2010).

ESSENCE

Not only pre- and perinatal risk factors are important in the pathogenetic chain of events in adolescent psychosis. Certain behavioral and developmental syndromes that are symptomatic already in early childhood carry a relatively high risk of later onset of psychosis (Gillberg, 2010, 1992; Huttunen & Mednick, 2018; Mednick et al., 1987).

It has been known for centuries that intellectual disability or intellectual developmental disorder tends to bring about major long-term adjustment problems. In the more recent past, childhood autism or autism spectrum disorder has also come to be viewed as a, often severe, functional impairment with effects lasting through adolescence into adulthood. However, it is still not generally recognized that early-onset concentration difficulties, planning issues, attention deficits, impulsiveness, and restlessness (nowadays often diagnosed as ADHD) can lead to or predict social exclusion, academic failure, and major additional psychiatric problems, including psychosis (Nourredine et al., 2021). Other developmental difficulties among children, including (1) language disorder, (2) developmental coordination disorder, (3) perception disorders, (4) mild learning difficulties (which in our day and age should not be taken lightly), (5) conduct disorders, (6) various tic- and obsessive-compulsive related conditions, and (7) early-onset mood swings/dysregulation (which may sometimes precede bipolar disorder), also greatly increase the risk of significant mental health deterioration, including teenage emergence of psychotic symptoms (Gillberg, 2010, 1995).

These neuropsychiatric or developmental problems virtually always occur in groups of two or more. Nowadays, in many countries, they lead to early consultations with nurses, pediatricians, psychologists, and speech and language therapists (Hatakenaka et al., 2017; Sim et al., 2013). Usually, attention

is directed at only one specific aspect of the full set of problems (e.g., language disorder or autism).

ESSENCE as a concept

The problem with the umbrella terms typically used within the field, primarily in the areas of "neuropsychiatry" and "neurodevelopment" is that they assume ADHD, autism, Tourette syndrome, or intellectual developmental disorder, for example, to be the primary diagnosis and that comorbidity is not the rule. Also, it is not logical to label only certain psychiatric problems as neuropsychiatric; all psychiatric problems originate in the brain and should therefore be considered "neuro." The term "neurodevelopmental" is also misleading in that it implies that the problems only exist during development. The concept of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) instead assumes that comorbidity might *usually* be present. That symptoms of specific disorders might well be identical at the beginning of the child's life, and that it is not always possible to *permanently* decide which diagnosis should apply (even though it is necessary to address the issues as a real problem requiring an actual name). Furthermore, the concept of ESSENCE assumes that one or the other (e.g., ADHD or autism) could be more salient at different times during development (Gillberg, 2010, 2014, 2021). For example, it is not unusual for a child to initially, at the age of 2−3 years, having seemed to *primarily* suffer from autism, only to eventually fit the criteria for ADHD much better at the age of 10 years (even if the autistic symptoms linger, they are no longer as much of an impediment as the symptoms that warrant an ADHD diagnosis), and then to present to adult psychiatry after the age of 16 years with adolescent-onset psychosis (Hellgren et al., 1994).

Underlying the various ESSENCE-disorders, there is a variety of factors, including risk genes, pre- and perinatal risk factors, and, occasionally, syndromes subsumed under the BPS acronym (BPS for Behavioral Phenotype Syndromes), such as Down syndrome, fragile-X syndrome, 22q11 deletion syndrome, neurofibromatosis, tuberous sclerosis, etc.

Prevalence of ESSENCE

The total rate of early, which is to say upon entering school or earlier, diagnosable ESSENCE (sometimes also referred to as child neuropsychiatric or neurodevelopmental disorders/impairments/variations) is about 10% of the population (probably around 13% of all boys and 7% of all girls) (see Table 5.1). In many countries, about half of these children (probably 8% of all boys but only 2% of all girls (Gillberg, 2021)) have already shown up before age 10 years at some kind of healthcare clinic and been examined by a doctor, psychologist, or speech and language therapist, often with a resulting diagnosis

TABLE 5.1 Early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE).

Syndrome	Prevalence (%)	References
Autism spectrum disorder (ASD)	1.0–1.5	Coleman and Gillberg (2012), Fombonne et al. (2021), Lundström et al. (2015)
Attention-deficit/hyperactivity disorder (ADHD)	3.7–5.0	Faraone et al. (2003), Kadesjö and Gillberg (2001)
Tourette's disorder	1.1	Kadesjö and Gillberg (2000)
Intellectual developmental disorder (IDD)	2.5	Gillberg and Soderstrom (2003)
Speech and language disorder	4.0	Miniscalco et al. (2006)
Developmental coordination disorder (DCD)	4.9	Kadesjö and Gillberg (1999)
Reactive attachment disorder (RAD) and disinhibited social engagement disorder (DSED)	0.5–1.5	Sadiq et al. (2012)
Selective mutism	0.2–2.0	Kopp and Gillberg (1997)
Severe early-onset affective disorders	?	Biederman et al. (2003)
Pediatric acute-onset neuropsychiatric syndrome (PANS); pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)	?	Johnson et al. (2019)
Behavioral phenotype syndromes (BPS)	2.0	Gillberg and O'Brien (2000)
Epilepsy with other ESSENCE	0.5	Aicardi (2009)
Total prevalence (overlap accounted for)	~10.0	Gillberg (2010, 2021)

of language disorder, developmental delay, or autism. Quite often, the conclusion at an early age is that there is some unspecified abnormality in the child's development, but there is no diagnosis given for it. In other cases, parents might get some reassuring news e.g., at the autism clinic where they are told "it's not autism, so there isn't anything for us to deal with" or be told to "wait and see." The remaining half will be detected as "problematic cases"

before reaching teenage and then often given diagnoses such as ADHD, depression, anxiety, or family relationship problems. Rarely if ever is the family made aware from the outset that the child has a complex set of problems which, at least partially, meet criteria for several of the neurodevelopmental diagnoses indicated in the diagnostic manuals used in healthcare services, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) or the International Classification of Diseases (ICD-11) (World Health Organization, 2018). Then, when psychotic symptoms emerge at ages 13 years or above, they can be perceived or construed as arising "out of the blue" without any prior warning having been present. In many cases of adolescent psychosis this is the typical background.

Attention-deficit/hyperactivity disorder

ADHD is the most common of all ESSENCE, affecting at least 5% of school-age children worldwide (Gillberg, 2021). ADHD, sometimes, particularly in boys, presents very early in life (in the first year) either with extremes of hyperactivity (and usually, and often unexpectedly to parents and professionals, with early-onset walking unsupported) or, the opposite, namely, passivity and inattention (often combined with relatively late-onset of walking). However, usually, ADHD is not suspected until later in the preschool or early school years, and sometimes, especially in girls, not at all until other mental health/psychiatric issues have emerged in middle school age or adolescence.

In the children with early extremes of hyperactive and impulsive behaviors, there is often a variety of other ESSENCE-suspected "signals" present, such as mild autistic features, compulsive behaviors, tics, emotional dysregulation, and oppositional-defiant attitudes. These children may be referred to a health professional under age 3 years because of parental or child health visitor concern. The autistic features, even when quite mild compared to the extremes, in terms of activity and emotional dysregulation, sometimes lead clinicians to first assess and work-up the case for an autism spectrum disorder.

In the children where passivity and inattention dominate the picture in early life (later often diagnosed as ADHD mainly inattentive subtype), there is often early concern about hearing ("does not seem to listen"), motor milestone delay, language problems and marked autistic features, leading to referral to speech and language pathologists, child psychiatrists, or specialized clinics for assessing autism.

It is not uncommon for children with ADHD under the age of 5 years to meet criteria for at least one more ESSENCE syndrome. In early studies by Kadesjö and colleagues (Kadesjö & Gillberg, 1998, 1999, 2000), 3-year-olds with ADHD met criteria for oppositional defiant disorder in 60% of the cases. Moreover, 7-year-olds in the general population with ADHD met criteria for at

least one other ESSENCE disorder, usually speech-language disorder, developmental coordination disorder or oppositional defiant disorder, in 87% of the cases. Recently published studies have found the combination of ADHD and autism to be quite common also (Påhlman et al., 2021).

Autism spectrum disorder

While 50 years ago considered an extremely rare disorder affecting fewer than 0.05% of all individuals, autism is now known to affect at least 1% of the general population of children starting school (Fombonne et al., 2021). In recent years, the rate of registered diagnoses of autism has increased dramatically, even to the extent that "over-diagnosis" has been discussed. However, it seems clear that "typical" autism is no more common now than 20 years ago and that many children with problems under the ESSENCE umbrella (not least those with the combination of ADHD and developmental coordination disorder) get autism diagnoses even when they only have a few autistic symptoms (Arvidsson et al., 2018). There used to be clear distinctions between different kinds of autism: autistic syndrome, Asperger's syndrome, disintegrative disorder, Rett syndrome, and other autistic-like conditions. However, in current diagnostic manuals, all of these conditions fall under the same umbrella of "autism spectrum disorder." This term is problematic in that autism, like other clinical syndromes, is not one spectrum with one shared cause, and it also cannot be considered a disorder of something that was once "normal" (on the contrary, the condition is present from birth, or even earlier, and onward in more than three-quarters of all cases). Today, the defining features of autism are generally agreed to be early-onset severe abnormalities, in terms of mutual social/communicative interaction and concurrent behavioral-perceptual disorders, marked by stereotypical movements and speech, over- or underreaction to sensory stimuli, along with general mental rigidity.

Most cases of classic autism can today be identified and diagnosed before the age of 3 years, but what is (still) described (although not separately coded in the diagnostic manuals) as Asperger's syndrome, with formally good to excellent expressive language skills, often goes (partially) unrecognized until the first years of school, or in the case of females, well into adolescence or later. In practice, typical autism symptoms are still often diagnosed as autism when combined with some degree of general intellectual disability (below the normal variation range of IQ) and Asperger's syndrome when combined with normal or high intelligence. Many argue for the utility of Asperger's syndrome, constituting about half of all cases of autism (Gillberg, 2021), as a separate diagnosis, due to its perception as less severe than autism and its frequent association with relatively high general intellectual ability.

There are many possible first symptoms of autism: motor abnormalities, abnormal perception (unexpected/strange reactions to sound, light, smell, taste, touch, pain, cold, heat), inattention, low interest in initiating social

interaction (including the absence of pointing), rigid demands for rituals and strong opposition to changes, tantrums in response to any adversity, stereotypical movements (such as hand-waving or head-bobbing, finger-flickering), delayed speech, sleep disorders, unstable mood, impulsiveness/hyperactivity and a poor sense of what constitutes real danger. Many of these symptoms are also typical of ADHD, which makes differential diagnosis difficult or even impossible at an early age. Childhood autism is an almost perfect predictor of adult autism (almost 100% of individuals diagnosed with classic autism before the age of 10 also meet criteria after the age of 20), while more than two-thirds of those with a diagnosis of Asperger's syndrome meet diagnostic criteria for autism spectrum disorder 10–20 years later (Helles et al., 2017). The remainder have autistic symptoms without reaching thresholds for diagnosis. Autism is almost always associated with other problems: intellectual developmental disorder, motor disorders (developmental coordination disorder, tics), language disorder, ADHD, epilepsy, psychosis, and a range of other neurological and medical conditions, including behavioral phenotype syndromes. Autism is considerably more common in males, but the diagnosis also tends to go undetected in females throughout pre-school (girls are generally more "social" than boys, so the possibility of autism is rarely even raised), creating the impression of an exceedingly skewed gender distribution. Girls diagnosed with autism before entering school are often just as severely impaired as boys with the same diagnosis, but the vast majority of girls with typical autism are not detected and diagnosed until later in life.

The core symptoms of autism rarely change dramatically over time. Most adults who met diagnostic criteria as children continue to struggle with social interaction and rapid communication with other people. They tend to grow obsessive and compulsive, particularly in stressful situations.

The results of prospective long-term follow-up studies of children with autism (i.e., individuals that have been recognized and diagnosed before age 10 years) suggest that the development of psychosis in adolescence is rare (only a few percent affected) (Billstedt et al., 2007; Gillberg et al., 2016; Helles et al., 2017). However, the combined results of retrospective community-based studies of adolescent psychosis and schizophrenia (Hallerbäck et al., 2012; Hellgren et al., 1987) suggest that if autism remains undiagnosed in childhood there may well be a high rate of "psychotic breakdown" after the childhood period.

Speech and language disorder

Most children who have delayed language development (i.e., who have no more than a small number of expressive words, major language comprehension problems or severe dysarticulation) at age 2.5 years actually have some kind of language disorder or another condition meeting criteria for an ESSENCE-diagnosis (Miniscalco et al., 2018; Nygren et al., 2012). Screening

for language delay at 2.5–3 years will identify about 4%–6% of the population as having a language problem that requires diagnostic assessment and intervention (Schachinger-Lorentzon et al., 2018).

Prospective longitudinal studies of children with early language delay (recognized before age 3 years) have a very high rate of persistent ESSENCE-problems in the early school years (ADHD, autism, intellectual disability, dyslexia, and language problems) (Miniscalco et al., 2006) and it has been well established in other studies that such early school-age problems are important red flags for adolescent-onset psychosis (Hellgren et al., 1987; Petruzzelli et al., 2018).

Developmental coordination disorder

Developmental coordination disorder is one of the most common syndromes under the ESSENCE-umbrella, affecting at least one in 20 children at school-age. However, of all the ESSENCE, it is still the least commonly recognized and diagnosed syndrome. This is unfortunate because there are effective interventions available that may well prevent the development of a lot of secondary problems, including social exclusion, depression, anxiety, and maybe even psychosis (Doering et al., 2019; Smits-Engelsman et al., 2018). One of the early "warning signals" (albeit not in itself diagnostic) in developmental coordination disorder is a delay in early motor development, such as walking unsupported. It has been known for decades that motor milestone development has often been significantly delayed in adolescent-onset schizophrenia (Filatova et al., 2017).

Intellectual developmental disorder and borderline intellectual functioning

At least 2% of all young people will test under IQ 70 on a standardized IQ-test after the age of 6 years, and, if there are associated adaptive functioning deficits, a diagnosis of intellectual developmental disorder, is appropriate. Another 10% have borderline intellectual functioning or learning disorder. Borderline intellectual functioning is mentioned in the ICD-11 diagnostic guidelines draft in individuals who fall one to two standard deviations (SD) below the mean on standardized tests. It is not recognized as a diagnosable disorder but as a condition requiring early intervention. Cognitive problems severe enough to warrant a diagnosis of intellectual developmental disorder or to fall under the category of borderline intellectual functioning should always be acknowledged in individuals with any kind of mental health problem and considered when laying out treatment, intervention, or education plans. This, of course, also holds true for individuals with adolescent-onset psychosis, but in clinical practice, this basic prerequisite for appropriately tailored personalized medicine is often overlooked. People with moderate to severe cognitive problems have much higher rates of mental health problems than those with mild or no such problems (Gillberg & Soderstrom, 2003).

Tourette's disorder and other tic syndromes

The combination of several motor tics and one or more vocal tics is the symptomatic requirement for a diagnosis of Tourette's disorder. Individuals who present at clinics constitute about 1% of the general population and usually have "comorbid" ADHD and/or obsessive-compulsive disorder. When it comes to clinical severity of Tourette's and other "simple" motor or vocal tic disorders, the associated ADHD and/or obsessive-compulsive disorder is usually what drives the level of overall impairment, not the tics themselves. However, in rare cases, the tics themselves can be very severe and complex and mimic catatonia, psychotic posturing, and psychotic intrusion of thoughts. This, together with the added effect of severe ADHD and full-blown obsessive-compulsive disorder, the clinical presentation can be acute psychosis. For that reason, it is important to always consider whether there are some clear motor or vocal tics and/or a family history of Tourette's in individuals with adolescent-onset psychosis. The tics themselves should only rarely be treated with pharmacological agents, and if so, both typical and atypical neuroleptics are often effective. In this context, it is important to consider the side effects of neuroleptics as a differential diagnostic condition in individuals presenting with "psychosis and odd motor movement disorders (including tics)."

Reactive attachment disorder and disinhibited social engagement disorder

Some children who have been abused or neglected in early life develop symptoms consistent with diagnoses of reactive attachment disorder ("frozen watchfulness") or disinhibited social engagement disorder ("overly friendly or lacking in reticence"). The majority of these children also have other ESSENCE (Minnis et al., 2013). Some of these children later develop psychosis or are diagnosed with schizophrenia in adolescence (Picken et al., 2010). Recent studies suggest that most of the symptomatology of "ESSENCE" in young people with a background in maltreatment is accounted for by genes (Dinkler et al., 2017), and that it is unlikely that the abuse and neglect "in themselves" have caused the neurodevelopmental or psychiatric symptoms.

Pediatric acute-onset neuropsychiatric disorder (PANS/PANDAS)

Pediatric acute-onset neuropsychiatric disorder is a diagnostic condition listed at the US National Institute of Mental Health that should only be applied in children with acute-onset (days-weeks) severe neuropsychiatric problems, including obsessive-compulsive disorder/tic symptoms and/or acute-onset severe feeding disorder. The disorder may be associated with streptococcal infection or infections caused by other microorganisms, and it probably often (albeit yet to be determined how often) is associated with autoimmune risk

factors of various kinds, including a family history of moderate to severe autoimmune disorders (Johnson et al., 2019). The disorder can be very difficult to separate from adolescent-onset psychosis or catatonia and should still be considered the remit of highly specialized clinics when it comes to definitive diagnosis and treatment. It is usually associated with an autoimmune family history and/or premorbid ESSENCE that may or may not have been diagnosed long before the emergence of the "new" acute and severe symptoms.

Behavioral phenotype syndromes and neurological disorders

There are hundreds of documented genetic or otherwise prenatally caused conditions affecting early brain development that bring about typical or relatively uniform psychiatric problems or disorders. Usually, but not always, these conditions also manifest with typical physical changes, such as minor abnormalities in facial anatomy, heart defects, brain structure abnormalities (Sønderby et al., 2021) and abnormalities in the skeletal structure of hands or feet. Examples of such behavioral phenotype syndromes include Down syndrome, fragile X syndrome, muscular dystrophy syndromes, neurofibromatosis tuberous sclerosis, 22q11 deletion syndrome, Noonan syndrome, XYY syndrome, XXX syndrome, and Turner and Klinefelter syndrome. Other syndromes included in this group are fetal alcohol syndrome, fetal alcohol effects, fetal alcohol spectrum disorder, fetal valproate syndrome (which may occur if the mother is on valproate medication during pregnancy), and thalidomide syndrome (Gillberg & O'Brien, 2000).

All behavioral phenotype syndromes share a number of features: (1) each is rare (except fetal alcohol syndrome and -effects, together affecting around 1%−2% of all children); (2) there is a known cause; (3) the affected families are likely to know next to nothing about the condition; and (4) the affected families will generally have a lot of valuable knowledge to share with other families dealing with the same syndrome. In many cases (e.g., with 22q11 deletion syndrome), the behavioral phenotype syndrome is only detected after one or multiple other ESSENCE or psychiatric diagnoses have already been given, including autism, ADHD, intellectual developmental disorder, psychosis, and schizophrenia. Health professionals should be aware that at least 1% of the population at large have some kind of behavioral phenotype syndrome (2%−3% or more if fetal alcohol syndrome and -effects are included), meaning that whenever ESSENCE or adolescent-onset psychoses diagnoses are considered, one must always consider whether a behavioral phenotype syndrome might be the underlying cause or at least an important associated factor. Many of these syndomes can now be addressed with specific treatment methods. Moreover, assessing the risk of repetition in pregnancy and likely long-term prognosis is much easier with knowledge of what exactly is causing ESSENCE or psychosis in each individual case.

Even though epilepsy, cerebral palsy, and muscular dystrophy disorders (including Duchenne's and dystrophia myotonica) are not to be seen as "typical" behavioral phenotype syndromes (i.e., one etiology for the whole syndrome), they are certainly neurological disorders that contribute to the panorama of ESSENCE (Jacobs et al., 2017; Påhlman et al., 2021; Reilly et al., 2015) and should also always be considered in the assessment and treatment of individuals with adolescent-onset psychosis.

Substance-induced psychosis

This chapter does not deal specifically with psychotic conditions triggered by drug or alcohol use or prescribed or nonprescribed medication use. However, it needs to be stated here, that in all cases of adolescent-onset psychosis, regardless of the need to assess for ESSENCE (which in itself is associated with increased prevalence rates of drug and alcohol abuse), one must assess a reasonable history regarding substance uses of various kinds. It is important in this context to be aware that some medications used routinely in pediatric and adolescent medicine practice, can be triggers of even severe psychotic symptoms. Overmedication for allergies and sleep problems (e.g., steroids for asthma, and a number of psychopharmacological medications, including the benzodiazepines) can contribute to, or themselves be the major cause of what appears at first to be "psychotic breakdown."

When should one suspect an ESSENCE disorder?

Children, adolescents, or adults for that matter, having shown signs or symptoms of unusual or atypical development, behavioral disorder, mood problems, or psychotic symptoms severe enough to have caused concern for parents or others in the child's environment, have ESSENCE-related problems in the majority of cases. The symptoms and concerns have in most cases been present for many months or years. However, symptoms can also appear suddenly, over the course of just a few days, in a child who initially showed completely "normal" development, such as in the case of pediatric acute-onset neuropsychiatric disorder. All children with long-term or extremely acute-onset problems of the kinds listed in Table 5.2 should be subjected to some kind of developmental evaluation/screen for all the possible ESSENCE syndromes (Gillberg, 2021). This could be done by using one or more of the validated screening instruments in the first clinical assessment regardless of which presenting major symptom has led to the clinical assessment, acute or otherwise. The best-validated instruments in the field are the ESSENCE-Q (Cederlund, 2022; Hatakenaka et al., 2020), the A-TAC (Hansson et al., 2005), and the Five-To-Fifteen (Kadesjö et al., 2004) which exist in different versions for different age groups and different informants.

TABLE 5.2 Problems of concern that might indicate ESSENCE.

Concern regarding the child's development	Example
General development	Late
Motor—movement	Poor coordination, delayed, low muscle tone, little mimicry
Communication—speech	Little babbling, delayed or no speech, monotone
Social interaction—contact	Little or no interaction, does not initiate contact
Activity—impulsivity	Extremely active or inactive, extremely impulsive
Attention—concentration	Flimsy, never there, in his/her own world, cannot concentrate
Behavior	Stereotypical movements, cannot tolerate routine change
Mood	Extreme mood instability
Sleep	Extreme sleep disturbance that has lasted many months
Feeding	Major feeding problems that have lasted many months
Sensory reaction	Over- or underreacting to sounds, smells, light, touch, pain, heat, cold, etc.

Outcome of ESSENCE

Long-term follow-up of children with any of the diagnoses of autism spectrum disorder, language disorder, intellectual developmental disorder, learning problems, or ADHD has demonstrated that in many cases the fundamental problems outlined under these diagnostic categories (social interaction difficulties, communication problems, learning difficulties, reading and writing difficulties (dyslexia), isolated hyperlexia, motor coordination problems, and attention disorders) remain through adolescence and into adulthood, even in cases for whom all diagnostic criteria necessary to make the individual diagnosis no longer apply. We also know that the mortality rate is elevated, even though the vast majority will live to old age (Gillberg, 2021).

Taken together, at least 6%−8% of the adolescent and adult population still have diagnosable ESSENCE problems long after childhood. The majority of adults with ESSENCE, particularly if undiagnosed and untreated during

childhood and the early teenage period, will sooner or later meet criteria for an additional diagnosis—including psychosis, depression, anxiety, pain disorder, personality disorder (antisocial, avoidant, borderline, etc.), and drug addiction (Biederman et al., 2003).

The results of some studies indirectly suggest that an early diagnosis of autism spectrum disorder, with adequate intervention measures put in place before adolescence, might reduce stress to such an extent that psychotic symptoms or disorders, including schizophrenia, might be prevented (Hallerbäck et al., 2012). If these results are borne out by other studies, then one of the most important public health interventions, or preventive measures, when it comes to lessening the burdens for individuals affected by adolescent-onset psychosis, would be early identification of autism (and perhaps other ESSENCE).

How to deal with ESSENCE specifically in the context of early-onset psychosis

Any individual presenting with psychotic symptoms during the teenage period must be screened for ESSENCE as part of the postacute psychiatric assessment.

In the acute phase of the disorder, parents, siblings or other people who have known the young person during early childhood will usually be the best sources of screening information. Questionnaires are often very helpful. Using validated screening instruments such as the ESSENCE-Q, A-TAC, and Five To 15, will help in honing in on the core syndromes of autism spectrum disorder, ADHD, intellectual developmental disorder and developmental coordination disorder, and in making decisions as to who should receive a more in-depth assessment of what type of problem. The majority of individuals with adolescent-onset psychosis will probably screen positive for one or more of the ESSENCE categories. Further in-depth assessment needed will have to be individualized and guided not only by scores on the questionnaires mentioned, but on early developmental history, academic results and neuromotor examination of the individual. This latter part should also include a screen for minor physical anomalies and a consideration of the need for further work-up regarding possible underlying behavioral phenotype syndromes, including fragile X-syndrome, chromosome 15q.11 deletion, and 22q11 deletion syndromes.

ESSENCE-D (Landberg et al., 2021) is a new semi-structured, investigator-based interview for providing sufficient information to make preliminary diagnoses of ADHD, autism spectrum disorder, developmental coordination disorder, and Tourette's syndrome. It is currently undergoing validation in several countries.

Individuals with adolescent-onset psychosis should be considered for neuropsychological assessment after the acute phase of psychotic symptoms

has been treated or overcome. This should usually include testing with one of the best-established cognitive batteries, such as the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 2014), the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008), or the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008). More information regarding the use of these cognitive batteries in adolescents with early-onset psychosis is described in Chapter 6.

Implications of further intervention/treatment approaches

For virtually all the disorders subsumed under the ESSENCE umbrella, there are helpful interventions/treatments. Some of these, such as stimulant medication for ADHD, and focused motor task training for developmental coordination disorder, have been shown to have short-, intermediate- and long-term positive effects that have led to significantly improved outcomes both in terms of symptom reduction, quality of life, decreased antisocial tendencies, lower rates of severe psychiatric disorders in adult life and increased survival rates (Gillberg, 2021). It is therefore not appropriate to see such interventions or treatments as "second-line" or "try-only-when-we-have-tried-everything-else."

Future directions

There is a need for all services involved in assessing and treating adolescent-onset psychosis to adopt the ESSENCE perspective from the start, to expect that such psychosis is usually not a circumscribed single disorder with a time-limited course or a one-treatment-for-all condition. Instead, it should be seen as an episodic or complex disorder that has usually been preceded by moderate to major early childhood problems, that will need a long-term approach to intervention and follow-up. Healthcare services, especially within psychiatry, need to organize themselves to be prepared for this situation, so that young people and their next-of-kin can expect to be approached in a holistic way, both as regards assessment and treatment, and long-term follow-up.

In terms of clinical research, there is an additional need to explore established treatment strategies for underlying ESSENCE in the overall design of new intervention studies aimed to treat psychotic symptoms.

References

Aicardi, J. (Ed.). (2009). *Diseases of the nervous system in childhood* (3rd ed.). Mac Keith Press.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Publishing.

Arvidsson, O., Gillberg, C., Lichtenstein, P., & Lundström, S. (2018). Secular changes in the symptom level of clinically diagnosed autism. *Journal of Child Psychology and Psychiatry, 59*(7), 744–751. https://doi.org/10.1111/jcpp.12864

Biederman, J., Mick, E., Wozniak, J., Monuteaux, M. C., Galdo, M., & Faraone, S. V. (2003). Can a subtype of conduct disorder linked to bipolar disorder be identified? Integration of findings from the Massachusetts general hospital pediatric psychopharmacology research program. *Biological Psychiatry, 53*(11), 952−960. https://doi.org/10.1016/S0006-3223(03)00009-X

Billstedt, E., Carina Gillberg, I., & Gillberg, C. (2007). Autism in adults: Symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. *Journal of Child Psychology and Psychiatry, 48*(11), 1102−1110. https://doi.org/10.1111/j.1469-7610.2007.01774.x

Cederlund, M. (2022). Parent questionnaires in the evaluation of pre-school children referred for neuropsychiatric assessment. *Journal of Autism and Developmental Disorders, 52*(4), 1742−1751. https://doi.org/10.1007/s10803-021-05080-y

Coleman, M., & Gillberg, C. (1996). *The Schizophrenias: A Biological Approach to the Schizophrenia Spectrum Disorders*. Springer Publishing Company.

Coleman, M., & Gillberg, C. (2012). *The Autisms* (4th. edn.). Oxford University Press.

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B. B., Schullehner, J., Plana-Ripoll, O., Brikell, I., Wimberley, T., Thygesen, M., Madsen, K. B., Timmerman, A., Schendel, D., McGrath, J. J., Mortensen, P. B., & Pedersen, C. B. (2020). Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. *JAMA Psychiatry, 77*(2), 155−164. https://doi.org/10.1001/jamapsychiatry.2019.3523

Dinkler, L., Lundström, S., Gajwani, R., Lichtenstein, P., Gillberg, C., & Minnis, H. (2017). Maltreatment-associated neurodevelopmental disorders: A co-twin control analysis. *Journal of Child Psychology and Psychiatry, 58*(6), 691−701. https://doi.org/10.1111/jcpp.12682

Doering, S., Lichtenstein, P., Gillberg, C., Boomsma, D. I., Van Beijsterveldt, T. C. E. M., Ligthart, L., Willemsen, G., De Geus, E., Middeldorp, C. M., Bartels, M., Kuja-Halkola, R., & Lundström, S. (2019). Anxiety at age 15 predicts psychiatric diagnoses and suicidal ideation in late adolescence and young adulthood: Results from two longitudinal studies. *BMC Psychiatry, 19*(1). https://doi.org/10.1186/s12888-019-2349-3

Faraone, S., Sergeant, J., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: Is it an American condition? *World Psychiatry, 2*(2), 104.

Filatova, S., Koivumaa-Honkanen, H., Hirvonen, N., Freeman, A., Ivandic, I., Hurtig, T., Khandaker, G. M., Jones, P. B., Moilanen, K., & Miettunen, J. (2017). Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research, 188*, 13−20. https://doi.org/10.1016/j.schres.2017.01.029

Fombonne, E., MacFarlane, H., & Salem, A. C. (2021). Epidemiological surveys of ASD: Advances and remaining challenges. *Journal of Autism and Developmental Disorders, 51*, 4271−4290. https://doi.org/10.1007/s10803-021-05005-9

Gillberg, C. (1992). The Emanuel Miller Memorial Lecture 1991. *Journal of Child Psychology and Psychiatry, 33*(5), 813−842. https://doi.org/10.1111/j.1469-7610.1992.tb01959.x

Gillberg, C. (1995). *Clinical Child Neuropsychiatry*. Cambridge University Press.

Gillberg, C. (2010). The ESSENCE in Child Psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. *Research in Developmental Disabilities, 31*(6), 1543−1551. https://doi.org/10.1016/j.ridd.2010.06.002

Gillberg, C. (2014). *ADHD and its Many Associated Problems*. Oxford University Press.

Gillberg, C. (2021). *The ESSENCE of Autism and Other Neurodevelopmental Conditions: Rethinking Co-morbidities, Assessment, and Intervention*. Jessica Kingsley Publishers.

Gillberg, I. C., Helles, A., Billstedt, E., & Gillberg, C. (2016). Boys with Asperger syndrome grow up: Psychiatric and neurodevelopmental disorders 20 Years after initial diagnosis. *Journal of*

Autism and Developmental Disorders, 46(1), 74−82. https://doi.org/10.1007/s10803-015-2544-0

Gillberg, I. C., Hellgren, L., & Gillberg, C. (1993). Psychotic disorders diagnosed in adolescence. Outcome at age 30 years. *Journal of Child Psychology and Psychiatry, 34*(7), 1173−1185. https://doi.org/10.1111/j.1469-7610.1993.tb01781.x

Gillberg, C., & O'Brien, G. (2000). *Developmental disability and behaviour.* Mac Keith Press.

Gillberg, C., & Soderstrom, H. (2003). Learning disability. *Lancet, 362*(9386), 811−821. https://doi.org/10.1016/S0140-6736(03)14275-4

Gillberg, C., Wahlström, J., Forsman, A., Hellgren, L., & Gillberg, I. C. (1986). Teenage psychosis - epidemiology, classification and reduced optimality in the pre-, peri- and neonatal periods. *Journal of Child Psychology and Psychiatry, 27*(1), 87−98. https://doi.org/10.1111/j.1469-7610.1986.tb00624.x

Hallerbäck, M. U., Lugnegård, T., & Gillberg, C. (2012). Is autism spectrum disorder common in schizophrenia? *Psychiatry Research, 198*(1), 12−17. https://doi.org/10.1016/j.psychres.2012.01.016

Hansson, S. L., Röjvall, A. S., Rastam, M., Gillberg, C., Gillberg, C., & Anckarsäter, H. (2005). Psychiatric telephone interview with parents for screening of childhood autism - tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): Preliminary reliability and validity. *British Journal of Psychiatry, 187*, 262−267. https://doi.org/10.1192/bjp.187.3.262

Hatakenaka, Y., Maeda, M., Ninomiya, H., Hachiya, K., Fernell, E., & Gillberg, C. (2020). ESSENCE-Q obtained in routine Japanese public child health check-ups may be a valuable tool in neurodevelopmental screening. *Acta Paediatrica, 109*(4), 764−773. https://doi.org/10.1111/apa.15029

Hatakenaka, Y., Ninomiya, H., Billstedt, E., Fernell, E., & Gillberg, C. (2017). ESSENCE-Q−used as a screening tool for neurodevelopmental problems in public health checkups for young children in south Japan. *Neuropsychiatric Disease and Treatment, 13*, 1271−1280. https://doi.org/10.2147/ndt.S132546

Helles, A., Gillberg, I. C., Gillberg, C., & Billstedt, E. (2017). Asperger syndrome in males over two decades: Quality of life in relation to diagnostic stability and psychiatric comorbidity. *Autism, 21*(4), 458−469. https://doi.org/10.1177/1362361316650090

Hellgren, L., Gillberg, C., & Enerskog, I. (1987). Antecedents of adolescent psychoses: A population-based study of school health problems in children who develop psychosis in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 26*(3), 351−355. https://doi.org/10.1097/00004583-198705000-00013

Hellgren, L., Gillberg, C., & Gillberg, I. C. (1994). Children with deficits in attention, motor control and perception (DAMP) almost grown up: The contribution of various background factors to outcome at age 16 years. *European Child & Adolescent Psychiatry, 3*(1), 1−15. https://doi.org/10.1007/BF01977607

Hultman, C. M., Sparén, P., Takei, N., Murray, R. M., Cnattingius, S., & Geddes, J. (1999). Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: Case-control study. *BMJ, 318*(7181), 421−426. https://doi.org/10.1136/bmj.318.7181.421

Huttunen, M. O., & Mednick, S. A. (2018). Polyvagal theory, neurodevelopment and psychiatric disorders. *Irish Journal of Psychological Medicine, 35*(1), 9−10. https://doi.org/10.1017/ipm.2017.66

Jacobs, D., Willekens, D., de Die-Smulders, C., Frijns, J. P., & Steyaert, J. (2017). Delusional and psychotic disorders in juvenile myotonic dystrophy type-1. *American Journal of Medical*

Genetics, Part B: Neuropsychiatric Genetics, 174(4), 359−366. https://doi.org/10.1002/ajmg.b.32524

Johnson, M., Fernell, E., Preda, I., Wallin, L., Fasth, A., Gillberg, C., & Gillberg, C. (2019). Paediatric acute-onset neuropsychiatric syndrome in children and adolescents: An observational cohort study. *Lancet Child and Adolescent Health, 3*(3), 175−180. https://doi.org/10.1016/S2352-4642(18)30404-8

Kadesjö, B., & Gillberg, C. (1998). Attention deficits and clumsiness in Swedish 7-year-old children. *Developmental Medicine and Child Neurology, 40*(12), 796−804. https://doi.org/10.1111/j.1469-8749.1998.tb12356.x

Kadesjö, B., & Gillberg, C. (1999). Developmental coordination disorder in Swedish 7-year-old children. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(7), 820−828. https://doi.org/10.1097/00004583-199907000-00011

Kadesjö, B., & Gillberg, C. (2000). Tourette's disorder: Epidemiology and comorbidity in primary school children. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(5), 548−555. https://doi.org/10.1097/00004583-200005000-00007

Kadesjö, B., & Gillberg, C. (2001). The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*(4), 487−492. https://doi.org/10.1017/S0021963001007090

Kadesjö, B., Janols, L.-O., Korkman, M., Mickelsson, K., Strand, G., Trillingsgaard, A., & Gillberg, C. (2004). The FTF (five to fifteen): The development of a parent questionnaire for the assessment of ADHD and comorbid conditions. *European Child & Adolescent Psychiatry, 13*(3), iii3−iii13. https://doi.org/10.1007/s00787-004-3002-2

Kopp, S., & Gillberg, C. (1997). Selective mutism: A population-based study: A research note. *Journal of Child Psychology and Psychiatry, 38*(2), 257−262. https://doi.org/10.1111/j.1469-7610.1997.tb01859.x

Landberg, S., Koepplinger, S., & Stevanovic, D. (2021). *ESSENCE-D − the development of a new instrument for aid in diagnosis of neurodevelopmental disorders*.

Lundström, S., Reichenberg, A., Melke, J., Råstam, M., Kerekes, N., Lichtenstein, P., Gillberg, C., & Anckarsäter, H. (2015). Autism spectrum disorders and coexisting disorders in a nationwide Swedish twin study. *Journal of Child Psychology and Psychiatry, 56*(6), 702−710. https://doi.org/10.1111/jcpp.12329

Mednick, S. A., Parnas, J., & Schulsinger, F. (1987). The copenhagen high-risk project, 1962-86. *Schizophrenia Bulletin, 13*(3), 485−495. https://doi.org/10.1093/schbul/13.3.485

Miniscalco, C., Fernell, E., Thompson, L., Sandberg, E., Kadesjö, B., & Gillberg, C. (2018). Development problems were common five years after positive screening for language disorders and, or, autism at 2.5 years of age. *Acta Paediatrica, 107*(10), 1739−1749. https://doi.org/10.1111/apa.14358

Miniscalco, C., Nygren, G., Hagberg, B., Kadesjö, B., & Gillberg, C. (2006). Neuropsychiatric and neurodevelopmental outcome of children at age 6 and 7 years who screened positive for language problems at 30 months. *Developmental Medicine and Child Neurology, 48*(5), 361−366. https://doi.org/10.1017/S0012162206000788

Minnis, H., Macmillan, S., Pritchett, R., Young, D., Wallace, B., Butcher, J., Sim, F., Baynham, K., Davidson, C., & Gillberg, C. (2013). Prevalence of reactive attachment disorder in a deprived population. *British Journal of Psychiatry, 202*(5), 342−346. https://doi.org/10.1192/bjp.bp.112.114074

Nourredine, M., Gering, A., Fourneret, P., Rolland, B., Falissard, B., Cucherat, M., Geoffray, M. M., & Jurek, L. (2021). Association of attention-deficit/hyperactivity disorder in childhood and adolescence with the risk of subsequent psychotic disorder: A systematic

review and meta-analysis. *JAMA Psychiatry, 78*(5), 519−529. https://doi.org/10.1001/jamapsychiatry.2020.4799

Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., Essock, S., Fenton, W. S., Frese, F. J., Gold, J. M., Goldberg, T., Heaton, R. K., Keefe, R. S. E., Kraemer, H., Mesholam-Gately, R., Seidman, L. J., Stover, E., Weinberger, D. R., Young, A. S., … Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *American Journal of Psychiatry, 165*(2), 203−213. https://doi.org/10.1176/appi.ajp.2007.07010042

Nygren, G., Sandberg, E., Gillstedt, F., Ekeroth, G., Arvidsson, T., & Gillberg, C. (2012). A new screening programme for autism in a general population of Swedish toddlers. *Research in Developmental Disabilities, 33*(4), 1200−1210. https://doi.org/10.1016/j.ridd.2012.02.018

Påhlman, M., Gillberg, C., & Himmelmann, K. (2021). Autism and attention-deficit/hyperactivity disorder in children with cerebral palsy: High prevalence rates in a population-based study. *Developmental Medicine and Child Neurology, 63*(3), 320−327. https://doi.org/10.1111/dmcn.14736

Petruzzelli, M. G., Margari, L., Bosco, A., Craig, F., Palumbi, R., & Margari, F. (2018). Early onset first episode psychosis: Dimensional structure of symptoms, clinical subtypes and related neurodevelopmental markers. *European Child & Adolescent Psychiatry, 27*(2), 171−179. https://doi.org/10.1007/s00787-017-1026-7

Picken, A. L., Berry, K., Tarrier, N., & Barrowclough, C. (2010). Traumatic events, posttraumatic stress disorder, attachment style, and working alliance in a sample of people with psychosis. *Journal of Nervous and Mental Disease, 198*(10), 775−778. https://doi.org/10.1097/NMD.0b013e3181f4b163

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F. M., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. R. (2015). Features of autism spectrum disorder (asd) in childhood epilepsy: A population-based study. *Epilepsy & Behavior, 42*, 86−92. https://doi.org/10.1016/j.yebeh.2014.11.014

Sadiq, F. A., Slator, L., Skuse, D., Law, J., Gillberg, C., & Minnis, H. (2012). Social use of language in children with reactive attachment disorder and autism spectrum disorders. *European Child & Adolescent Psychiatry, 21*(5), 267−276. https://doi.org/10.1007/s00787-012-0259-8

Schachinger-Lorentzon, U., Kadesjö, B., Gillberg, C., & Miniscalco, C. (2018). Children screening positive for language delay at 2.5 years: Language disorder and developmental profiles. *Neuropsychiatric Disease and Treatment, 14*, 3267−3277. https://doi.org/10.2147/NDT.S179055

Schlosser, D. A., Miklowitz, D. J., O'Brien, M. P., De Silva, S. D., Zinberg, J. L., & Cannon, T. D. (2012). A randomized trial of family focused treatment for adolescents and young adults at risk for psychosis: Study rationale, design and methods. *Early Intervention in Psychiatry, 6*(3), 283−291. https://doi.org/10.1111/j.1751-7893.2011.00317.x

Sim, F., O'Dowd, J., Thompson, L., Law, J., Macmillan, S., Affleck, M., Gillberg, C., & Wilson, P. (2013). Language and social/emotional problems identified at a universal developmental assessment at 30 months. *BMC Pediatrics, 13*(1). https://doi.org/10.1186/1471-2431-13-206

Smits-Engelsman, B., Vinçon, S., Blank, R., Quadrado, V. H., Polatajko, H., & Wilson, P. H. (2018). Evaluating the evidence for motor-based interventions in developmental coordination disorder: A systematic review and meta-analysis. *Research in Developmental Disabilities, 74*, 72−102. https://doi.org/10.1016/j.ridd.2018.01.002

Sønderby, I. E., Ching, C. R. K., Thomopoulos, S. I., van der Meer, D., Sun, D., Villalon-Reina, J. E., Agartz, I., Amunts, K., Arango, C., Armstrong, N. J., Ayesa-Arriola, R., Bakker, G., Bassett, A. S., Boomsma, D. I., Bülow, R., Butcher, N. J., Calhoun, V. D.,

Caspers, S., Chow, E. W. C., … Andreassen, O. A. (2021). Effects of copy number variations on brain structure and risk for psychiatric illness: Large-scale studies from the ENIGMA working groups on CNVs. *Human Brain Mapping, 43*, 300–328. https://doi.org/10.1002/hbm.25354

Sørensen, H. J., Mortensen, E. L., Schiffman, J., Ekstrøm, M., Denenney, D., & Mednick, S. A. (2010). Premorbid IQ and adult schizophrenia spectrum disorder: Verbal Performance subtests. *Psychiatry Research, 178*(1), 23–26. https://doi.org/10.1016/j.psychres.2010.03.016

Wechsler, D. (2008). *Wechsler adult intelligence scale–fourth edition (WAIS-IV)*.

Wechsler, D. (2014). *Wechsler intelligence scale for children–fifth edition (WISC-V)*.

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 457–465. https://doi.org/10.1097/00004583-199105000-00017

World Health Organization. (2018). *International classification of Diseases* (11th ed.). World Health Organization.

Chapter 6

Cognitive functioning in early-onset psychosis

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Introduction

Early-onset psychosis (EOP) is an umbrella term for psychotic disorders with a debut before 18 years of age (Werry et al., 1991). The clinical presentation of EOP in children and adolescents is similar to psychotic disorders in adults, in which cognitive impairment is considered a central feature (Kahn & Keefe, 2013). Diagnoses included in EOP comprise nonaffective disorders (e.g., schizophrenia and schizoaffective disorder) and affective disorders (e.g., bipolar and major depressive disorders with psychotic features). Cognitive research in children and adolescents with EOP has mainly included individuals with nonaffective disorders, and especially schizophrenia. Thus, the majority of EOP research reviewed in this chapter includes youth with nonaffective EOP. When presenting studies including people with affective EOP, such as bipolar disorder, we will specify this.

Cognition is the common term covering both neurocognition and social cognition. Neurocognition encompasses the mental processes involved in rational thinking and information processing, such as attention, memory, problem solving, and language processing. More recently, social cognition has also become a cognitive domain of increasing interest in psychotic disorders. Social cognition has been defined as "the mental operations that underlie social interactions, including perceiving, interpreting and generating responses to the intentions, dispositions and behaviors of others" (Green et al., 2008). Cognitive deficits are typically more frequent and severe in patients with schizophrenia-spectrum disorders, but they are also evident in patients with bipolar disorder (Bora & Pantelis, 2016; Demmo et al., 2016). Moreover, studies of adolescents with EOP have documented impairments that are comparable, or larger, in magnitude to what is found in adult-onset illness

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00007-X

(Nieto & Castellanos, 2011; Rajji et al., 2009; Smelror et al., 2021). Today, cognitive dysfunction is considered a core feature of psychotic disorders, and not secondary to clinical symptoms, medication effects, or other illness-related factors (Gold, 2004; Robinson et al., 2006; Seidman & Mirsky, 2017). Cognitive impairments are also consistently found to be associated with impaired daily functioning in children, adolescents, and adults with psychotic disorders (Bowie et al., 2006; Depp et al., 2012; Green, 1996; Rajji et al., 2014; Smelror et al., 2020), underlining the importance of focusing on this feature in clinical practice.

Relevant cognitive domains

In 2002, the US National Institute of Mental Health (NIMH) established an initiative to assist the development of psychopharmacological treatments that could improve cognitive functioning in individuals with schizophrenia (Marder & Fenton, 2004). To systematically test pharmacological effects in clinical trials, there was a need for a consensus-driven, reliable, and valid cognitive test battery that covered the most relevant cognitive domains for patients with schizophrenia (Kern et al., 2004). To this end, a panel of leading experts in the field of neuroscience and cognitive research agreed on seven cognitive domains: processing speed, working memory, verbal/visual learning and memory, attention/vigilance, reasoning and problem-solving (part of executive functions), and social cognition (Green et al., 2004). In the following section, we describe these domains in more detail and review findings for young people with EOP.

Processing speed

Processing speed is the ability to process mental information effectively in an appropriate tempo. Adequate processing speed (including reaction time and psychomotor speed) is essential in most cognitive operations, such as attention and working memory (Lezak et al., 2012). While other cognitive domains, to a larger degree, are more related to specific brain regions (e.g., executive tests and dorsolateral prefrontal cortex [DLPFC]), processing speed seems to involve the integration and coordination of distributed brain networks (Dickinson, 2008). Thus, it is not a unitary construct involving a single neural network but a result of a coordinated activity across multiple networks (Eckert et al., 2010).

Impaired processing speed is consistently found to be the most impaired cognitive domain in adolescents with EOP, including bipolar disorder (Nieto & Castellanos, 2011; Smelror et al., 2021; Victoria et al., 2019). Impairment in this domain is also found in community-based adolescents with psychotic symptoms (Kelleher et al., 2013), and in adults with schizophrenia, from premorbid to chronic phases (Sheffield et al., 2018). Adolescents with EOP

show the largest processing speed deficits when compared to other children and adolescents with disorders such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, obsessive compulsive disorder, major depressive disorder, and posttraumatic stress disorder (Braaten et al., 2020; East-Richard et al., 2020). As processing speed deficits are common in neurodevelopmental disorders, such as ADHD and autism spectrum disorder, and share underlying genetic liability with psychosis (Elia et al., 2010), impairment in this domain may be a transdiagnostic marker for the development of neurodevelopmental disorders.

Learning and memory

Learning entails the acquisition of information while memory involves the retention of information (Lieberman, 2021). Learning and memory includes a range of different components, which are associated with different brain regions (Squire, 2004). Encoding (learning) and consolidation (memory) of facts and events have consistently been associated with structures in the medial temporal lobe, particularly the hippocampus (Eldridge et al., 2000). However, the prefrontal cortex also plays a crucial role in this process (Barch, 2005), and it has been proposed that the medial prefrontal cortex functions as a filter to sort information relevant enough to be retained in the long-term memory system (Takehara-Nishiuchi, 2020).

Learning and memory (particularly verbal learning/memory) are of unique interest in adolescents and adults with psychotic disorders. Impairment in this domain has been associated with reduced functional outcome (Depp et al., 2012; Green, 1996; Smelror et al., 2020), earlier age of onset (Tuulio-Henriksson et al., 2004) and is one of the earliest predictors of conversion to full-blown psychosis in individuals at clinical high-risk (Carrión et al., 2018; Seidman et al., 2016).

Working memory

In 1974, Baddeley and Hitch introduced the term "working memory" as a replacement for "short-term memory," suggesting that working memory is a control system of both storage and mental processing (Baddeley & Hitch, 1974). Working memory can therefore be defined as the ability to temporarily store *and* manipulate information, hence involving executive functions and focused attention (Conway et al., 2003; Lezak et al., 2012). Functional magnetic resonance imaging (fMRI) studies have demonstrated that working memory deficits are associated with a dysregulation in the DLPFC (Glahn et al., 2005), and that impaired working memory performance occurs, for the most part, during the information encoding process (Bittner et al., 2015; Mayer & Park, 2012).

In a recent study including a large sample of adolescents with nonaffective EOP (N = 71), working memory was the second-most impaired domain after processing speed (Smelror et al., 2021). This finding is in accordance with a previous meta-analysis where young people with nonaffective EOP and bipolar disorder were included and compared. In this study, impaired working memory was the third largest deficit, after processing speed and attention (non-affective EOP), and verbal learning (bipolar disorder) (Nieto & Castellanos, 2011).

Attention

Attentional capacity is involved in most mental activities and is difficult to define as a single construct. As an example, the amount of information the attentional system can process (i.e., working memory) depends on how fast it operates (i.e., processing speed) (Lezak et al., 2012). As such, the human attentional system is very complex and involves a wide range of brain regions (for more information, see Petersen & Posner, 2012). However, when assessing cognition, attention is often referred to as the ability to sustain focused attention over time (concentration) while remaining vigilant to target stimuli (Lezak et al., 2012). A meta-analysis found that vigilance was associated with a right-lateralized extended cortico-subcortical network (Langner & Eickhoff, 2013), indicating that vigilant performance is specifically related to the right hemisphere.

In adolescents with nonaffective EOP, vigilance is often found to be one of the most impaired domains, while a more modest impairment is found for adolescents with bipolar disorder (Nieto & Castellanos, 2011; Smelror et al., 2021). However, results are mixed as some studies, only including patients with schizophrenia have not found an impairment in this domain relative to healthy controls (Kravariti et al., 2003; Ueland et al., 2004; Øie & Rund, 1999).

Executive functions

Executive functions are complex, higher-order cognitive abilities, meaning that they are voluntary and effortful multidimensional control processes (Paz-Alonso et al., 2014). They are crucial for monitoring, planning, problem-solving, decision-making, and performance of socially appropriate and purposive behavior (Lezak et al., 2012). As such, all activities, except for the most basic and routinized, involve some degree of executive functioning (Burgess, 2010, pp. 349–368). Executive functioning is closely related to the frontal cortex but as with most cognitive domains, these functions also depend on neural networks, particularly the cortico-striatal circuitry (Elliott, 2003). Due to their associations with the prefrontal cortex, a brain region strongly maturing during adolescence, executive functions are of particular interest in adolescents with EOP. Alterations in the maturational pattern of this brain

region during adolescence may be a contributing factor to the development of psychotic disorders (Gogtay et al., 2004). As executive functions are comprised of several components, different tests are used to assess this domain, which in turn may affect the results. Two executive subfunctions often measured in adolescents with EOP are planning/problem-solving and decision-making/mental flexibility.

In general, these executive components are consistently found to be impaired in adolescents with EOP (Smelror et al., 2021; Ueland et al., 2004; Victoria et al., 2019; Zabala et al., 2010; Øie & Rund, 1999). In a previous study, executive functions (i.e., mental flexibility and response inhibition) were compared between adolescents with EOP, adults with schizophrenia, and healthy adolescents and adults. The results showed that both adolescent and adult patients had significantly lower executive performance compared to their age-matched healthy controls (Holmén et al., 2012). However, when controlling for the performance level of their age-matched healthy controls, no differences were found between the clinical groups, indicating that the same level of executive dysfunction is present in adolescents and adults with psychotic disorders (Holmén et al., 2012).

Social cognition

Social cognition consists of several subdomains including: (1) emotion processing (the ability to perceive and use emotions); (2) social perception (the ability to identify social roles, rules and context); (3) theory of mind (the ability to infer intentions, dispositions and beliefs of other persons); and (4) attributional bias/style (how a person interprets causes of negative and positive events) (Green et al., 2008). Social cognition has become a major research focus in the study of cognitive function in people with psychotic disorders across age. Substantial impairments have been documented in the three first domains in adults with schizophrenia with less evidence of impairments in attributional style (Savla et al., 2013). Studies of adults with bipolar disorder have also documented social cognitive impairments with the largest effect size for emotion recognition and theory of mind (Gillissie et al., 2022). A meta-analysis comparing social cognition between adults with bipolar disorder and schizophrenia showed results that largely mirrored the findings in other cognitive domains, namely milder impairments in the group with bipolar disorder than with schizophrenia (Bora & Pantelis, 2016). Social cognition has also been investigated in individuals at clinical high-risk and first-episode psychosis (Friedman-Yakoobian et al., 2019; Glenthøj et al., 2020; Kurtz et al., 2016; Nijman et al., 2020), but to our knowledge very few studies have included adolescents with EOP. A meta-analysis of patients with early-onset and first-episode psychosis found impairments in facial emotion identification relative to healthy controls (Barkl et al., 2014). Unfortunately, norms for social cognitive tests primarily include adults and are not necessarily age

appropriate for adolescents. For instance, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing emotions (Mayer et al., 2002), which is the social cognitive test included in the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008), discussed later in this chapter, has been found less suitable for use in adolescents (Holmén et al., 2010).

Intelligence quotient (IQ)

Current knowledge of brain functioning and organization makes a unitary concept of intelligence less informative and partly irrelevant, as it is impossible to predict specific cognitive strengths and weaknesses based on an average composite score (Lezak et al., 2012). However, the concept of IQ has a long history (e.g., Binet & Simon, 1948; Spearman, 1904) and remains influential. Thus, IQ is still included as an outcome measure in many cognitive studies. When comparing IQ between patients with EOP and healthy controls, the patients most often demonstrate significant deficits of about one standard deviation below the healthy reference group (Fagerlund et al., 2006; Hollis, 2000). A typical discussion with regard to IQ/cognitive composite scores in people with psychotic disorders is whether the cognitive impairments are global across domains, or if they are domain specific. The studies to date indicate that both adolescents with EOP (particularly schizophrenia) and adults with schizophrenia suffer from a global cognitive impairment when compared to age-matched healthy controls, although results are mixed (Fagerlund et al., 2006).

The neurobiology of cognition

A single neuron in the brain might be connected with thousands of other neurons and thus be involved in the highly complex network of synapses underlying cognitive functioning and behavior (Lezak et al., 2012). If neurons misfire or misconnect, they can produce significant changes in brain connectivity and functioning (Izhikevich & Edelman, 2008). Thus, knowledge about brain connectivity is vital in the understanding of cognitive functioning in general, and for psychotic disorders in particular. This is especially relevant for EOP, as adolescence is a period of substantial brain development and maturation (Blakemore & Choudhury, 2006). Although we know that efficient cognitive functioning is depended on the integrity of dynamic brain networks (Heinrichs, 2005; Kelly et al., 2019), little is known about how psychotic disorders compromise the normal functioning of these networks (Harrison & Weinberger, 2005). Brain imaging (MRI) studies have shown associations between structural and white matter abnormalities, and cognitive performance in people with early- and adult-onset psychotic disorders (Antoniades et al., 2018; Epstein et al., 2014; Jirsaraie et al., 2018; Juuhl-Langseth et al., 2015), but predictable, consistent associations between brain abnormalities and

cognitive processes are yet to be determined (Heinrichs, 2005; Jirsaraie et al., 2018; Larsen & Luna, 2018). Furthermore, why individuals with psychotic disorders have deficits across cognitive domains and brain regions, also remains largely unknown. It has been suggested that a common underlying factor of cognitive deficits in these individuals is aberrant functioning in the cortical–subcortical–cerebellar circuitry (Andreasen et al., 1998). More specifically, the DLPFC and its connectivity to other brain regions and networks appears particularly relevant (Barch & Ceaser, 2012; Lesh et al., 2011). Further large-scale studies are needed before consistent conclusions can be drawn regarding the brain-behavior relationship of cognition (Jirsaraie et al., 2018).

Cognitive course

Atypical cognitive development can be observed from infancy throughout childhood and adolescence in premorbid individuals who later develop a psychotic disorder (Fuller et al., 2002; Mollon et al., 2018; Reichenberg et al., 2010; Trotta et al., 2015). It has been suggested that EOP may be a more severe form of illness associated with a poorer clinical outcome than adult-onset illness (Clemmensen et al., 2012; Werry et al., 1991). An important question pertaining to illness course is whether cognitive dysfunction over time is progressive in adolescents with EOP or has the same relatively stable course as in individuals with adult-onset schizophrenia and bipolar disorder (Bora & Özerdem, 2017; Bozikas & Andreou, 2011). As adolescents are still developing, it is important to use age-appropriate norms or age-matched healthy controls when investigating the cognitive course in this group. In general, cross-sectional studies of typical cognitive development have demonstrated increasing performance throughout childhood and adolescence (Gur et al., 2012; Nitzburg et al., 2014; Smelror et al., 2019; Stone et al., 2016; Waber et al., 2007). For most cognitive domains, the age effects in normative samples are quadratic, meaning that cognitive performance increases more rapidly among younger individuals and flattens out during middle/late adolescence.

A fair number of studies have investigated the longitudinal cognitive course in people with EOP. In general, studies find continuously impaired albeit relatively stable cognitive performance after the onset of illness (Cervellione et al., 2007; Frangou et al., 2008; Jepsen et al., 2010; Teigset et al., 2018; Øie et al., 2021). Most studies show slight increases in performance over time but less so than what is found in healthy adolescents in studies including control groups. Furthermore, some studies have shown deterioration in some functions, such as verbal learning and memory (Frangou et al., 2008; Øie et al., 2010). A study including adolescents with schizophrenia, bipolar disorder, schizoaffective disorder, and psychotic disorder not otherwise specified, found that all groups were equally impaired on measures of attention, working

memory, learning and memory, executive functions and a global composite score, compared to a healthy control group (Bombin et al., 2013). The clinical groups improved equally over the 2-year period in all cognitive domains except working memory, although they remained impaired across all domains relative to healthy controls.

In sum, these findings generally indicate a similar degree of stability in cognitive performance in adolescents with EOP, as is found in adult patients (Holmén et al., 2012). Furthermore, relative to healthy controls the cognitive performance in youth with EOP is impaired throughout adolescence, indicating a developmental lag in performance but not a deteriorating course. The fact that the cognitive performance is relatively stable and does not deteriorate over time in patients with EOP indicates a neurodevelopmental origin (Øie et al., 2021).

Sex differences in cognitive functioning

There is no clear consensus regarding sex differences in cognitive functioning among patients with psychotic disorders across age. The sex differences found in individuals with schizophrenia tend to reflect the differences found in typical cognitive functioning. Generally, when sex differences are found, females tend to perform better than males on tests measuring processing speed, verbal learning and memory, and social cognition, while males tend to perform better on visuospatial and perceptual tests (Gur et al., 2012; Kern et al., 2008; Pérez-Garza et al., 2016; Smelror et al., 2019, 2021; Waber et al., 2007). However, it is worth noting that several studies of adolescents with EOP have not found any significant sex differences in cognitive performance (Kravariti et al., 2003; Ruiz-Veguilla et al., 2017).

Cognition and symptoms

Although varying in correlational strength, cognitive deficits are consistently found to be associated with characteristic symptoms of psychotic disorders. Generally, the most consistent associations are found for negative and disorganized symptoms, and less for positive symptoms. In a systematic review including more than 5000 individuals (mean age 35 years) with nonaffective psychotic disorders, negative and disorganized symptoms were significantly associated with deficits in cognitive domains, such as processing speed, attention, learning and memory, and executive functions (de Gracia Dominguez et al., 2009). Performance on verbal fluency tests demonstrated the strongest associations with negative symptoms, while disorganized symptoms were strongest correlated with tests measuring executive functions and attention. In the same review, positive symptoms were only significantly correlated with processing speed (de Gracia Dominguez et al., 2009). Fewer studies have examined associations between cognition and symptoms solely in

individuals with EOP. However, in the studies investigating this, the same pattern of associations emerges for adolescents as for adults, with significant associations with negative and disorganized symptoms, and less for positive symptoms (Huang et al., 2016; Mørch-Johnsen et al., 2022; Puig et al., 2017; Rhinewine et al., 2005; Smelror et al., 2020). In a recent study including adolescents with nonaffective EOP, we investigated associations between cognitive functioning and two established negative symptom domains (apathy and diminished expression). In this study, we found significant associations between higher levels of apathy and diminished expression, and impaired verbal learning (Mørch-Johnsen et al., 2022). As discussed earlier in this chapter, verbal learning impairment in adolescents with EOP is of particular interest due to its association with an earlier age of onset, worse functional outcome, and its role as predictor of conversion to psychosis among individuals at clinical high-risk. Hence, adolescents presenting with both negative symptoms and verbal learning deficits may represent a more vulnerable subgroup with increased risk of functional impairment, and antipsychotic treatment failure (Downs et al., 2019). This group could benefit from treatments such as cognitive remediation, in addition to antipsychotic medication.

Cognition and functional outcome

Functional outcome is a broad term encompassing various aspects of daily living such as community, occupational, academic, and social functioning. Due to the age of onset in individuals with EOP, there is an increased risk of early disruption of psychosocial development which can negatively impact functional outcome. Functional outcome in individuals with EOP has indeed been reported to be poor in several studies (Clemmensen et al., 2012; Werry et al., 1991), although some have reported better outcomes which have been attributed to the implementation of early intervention strategies (Amminger et al., 2011). Nevertheless, identification of factors related to poor functional outcome in this group is particularly important. Cognitive functioning is consistently found to be associated with functional outcomes in adults with schizophrenia and bipolar disorder (Lepage et al., 2014; Martinez-Aran et al., 2007). Several studies have documented that these associations also pertain to adolescents with EOP. In a recent study, we found a significant association between verbal learning deficits and impaired global functioning in adolescents with EOP (Smelror et al., 2020). Øie and colleagues investigated the long-term relationship between cognitive functioning and functional outcome in a 13-year follow-up study of individuals with early-onset schizophrenia and ADHD. Baseline memory, attention, and executive functioning were positively correlated with social and community functioning in the group with schizophrenia at the 13-year follow-up (Øie et al., 2011). Similar correlations were also evident in the ADHD group, although to a lesser, nonsignificant degree. A

similar study of adolescents with early-onset schizophrenia found positive correlations between baseline attention, working memory, and verbal memory, and social/communication, personal living, and community living skills at follow-up (Cervellione et al., 2007). The relationships between these cognitive domains and functional outcome were stronger than with a global measure of intelligence (Cervellione et al., 2007).

Social cognition is also associated with functional outcome in adults with schizophrenia and bipolar disorder (Horan et al., 2012; Vlad et al., 2018), and even more so than neurocognition in some studies, at least in schizophrenia (Fett et al., 2011). The association between social cognition and functional outcome has to our knowledge not specifically been investigated in adolescents with EOP.

Cognitive assessment

Given the prevalence of cognitive impairment in adolescents with EOP and its documented impact on functional outcome, a neuropsychological evaluation should be included as part of the overall assessment of these persons. The information obtained can provide valuable input for treatment, rehabilitation, and academic planning. If a full neuropsychological assessment is not possible, a shorter cognitive screening covering the most relevant domains can be useful. Obtaining information about the individuals' subjective experience of cognitive functioning and information from family members, teachers and other relevant persons who know the adolescent, can also provide valuable information. Structured questionnaires such as the Behavior Rating Inventory of Executive Function (BRIEF) Second Edition (Gioia et al., 2015), can be useful to assess executive functioning in the home and academic environments.

In the next section, we will outline some common cognitive test batteries used in research on psychotic disorders. It is important to note that most of these are not free of charge, and several do not provide adolescent norms, although some have been developed in recent years (Smelror et al., 2019).

The Wechsler Intelligence Scales for children and adults

David Wechsler's test batteries, the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV) (Wechsler, 2008), and the Wechsler Intelligence Scale for Children, fifth edition (WISC−V) (Wechsler, 2014), are among the most widely used cognitive tests batteries for assessing intellectual/cognitive capacity, across contexts and clinical syndromes. In the WAIS-IV and WISC-V, the two-factor verbal and perceptual IQ has been replaced with four index scales (i.e., cognitive domains), in line with current intelligence research (Weiss et al., 2010), each including two to three subtests. The WAIS provides healthy reference norms from 16 to 90 years of age, while the WISC provides healthy norms from 6 to 16 years of age.

The MATRICS Consensus Cognitive Battery

One of the results from the NIMH initiative, mentioned previously in the chapter, was the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2004; Nuechterlein et al., 2004, 2008). The MCCB is a hybrid cognitive battery comprised of 10 existing tests selected from other batteries, across seven cognitive domains consistently found to be impaired in patients with schizophrenia. The developers of the MCCB have published healthy norms for adults from 20 to 65 years of age (Kern et al., 2008). However, as the MCCB also was increasingly used to assess cognition in adolescents EOP, there was a need to develop age-appropriate norms for this age group as well. To fill this gap, we developed standardized scores for the MCCB for adolescents from 11 to 19 years of age (Smelror et al., 2019). By providing a healthy adolescent reference for the MCCB, researchers can examine patterns of cognitive performance between domains, compare findings and combine clinical samples across research groups. Hopefully this can contribute to an improved understanding of the maturing neurobiological processes that underlie the cognitive functioning among adolescents with EOP.

Other cognitive batteries for schizophrenia

Other cognitive batteries relevant for schizophrenia are the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray et al., 1996; Robbins et al., 2004), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998), the CogState battery (Maruff et al., 2009; Pietrzak et al., 2009; Westerman et al., 2001), and the CogTest battery (Cogtest, 2022). Common for these batteries is that they provide digital tests, which may be an advantage in certain settings. The CogTest platform has also incorporated and digitalized the Brief Assessment of Cognition in Schizophrenia (BACS) battery (Keefe et al., 2004). To our knowledge, RBANS is the only of these batteries with available healthy reference data for adolescents.

Clinical implications

Pharmacological treatment

Current antipsychotic medications demonstrate no or minimal effect on improving cognitive functioning in individuals with psychotic disorders (Brown et al., 2016; Frazier et al., 2012; Goldberg et al., 2007). Adolescence is characterized by maturing neurotransmitter systems such as dopamine, stabilization and fine tuning of synapses, and integration between early- and late-maturing brain structures (Keshavan et al., 2014; Schalbetter et al., 2022). Thus, the use of pharmacological treatment in youth with EOP raises unique concerns regarding clinical response and potential side effects (Kumra et al.,

2008). As young individuals appear more sensitive to adverse side effects than adults (Bernagie et al., 2016; Cohen et al., 2012), second-generation antipsychotics are usually preferred for young people with EOP (Kumar et al., 2013; Kumra et al., 2008). Furthermore, second-generation antipsychotics have demonstrated better effects for improving cognitive functioning in adults relative to first-generation antipsychotics (Baldez et al., 2021). On the other side, a meta-analysis including randomized controlled trials of second-generation antipsychotics found no effects on cognitive performance for any of the included medications (Nielsen et al., 2015). There is limited evidence for which antipsychotic medication that is best for sparing or improving cognitive functioning in individuals with EOP (Kumar et al., 2013; Nielsen et al., 2015). Thus, development of new pharmacological agents targeting cognition and functional recovery in these patients continues to be important (Hofer & Fleischhacker, 2010).

Cognitive remediation

The Cognitive Remediation Experts Workshop has defined cognitive remediation as a "behavioral training-based intervention that aims to improve cognitive processes with the goal of durability and generalization" (Bowie et al., 2020). Core elements of cognitive remediation include repeated practice on cognitive exercises (paper and pencil or computer), the presence of an active therapist to facilitate training, employment of procedures to develop cognitive strategies, and to facilitate transfer from training to real world functioning (Bowie et al., 2020). Cognitive remediation is considered an evidence-based approach for improving cognition and functional outcome for adults with psychotic disorders (Vita et al., 2021). Several studies have shown positive effects of cognitive remediation in individuals at clinical high-risk for psychosis (Friedman-Yakoobian et al., 2019; Glenthøj et al., 2017) as well as in individuals with first-episode psychosis (Revell et al., 2015). Positive effects of cognitive remediation have also been found for cognition in adolescents with EOP, although results are mixed regarding functional outcome (Anagnostopoulou et al., 2019). In a study of adolescents with EOP, improved performance was found on one task measuring attention in the cognitive remediation group ($n = 14$) at 1-year follow-up (Ueland & Rund, 2005). No significant differences were found for other tasks measuring attention, memory, executive functions, or functional outcome (Ueland & Rund, 2005). Furthermore, in a randomized controlled trial of adolescents with early-onset schizophrenia, Puig et al. (2014) found significant improvements in verbal memory, executive functions, and functional outcome in the cognitive remediation group ($n = 25$). However, at 3-month follow-up the effect on functional outcome was diminished. In another randomized controlled trial of adolescents at clinical high-risk and EOP, Holzer et al. (2014) found significant improvements in visuospatial abilities in the cognitive remediation group ($n = 15$). No significant differences were found for other cognitive domains or functional outcome.

There is a strong rationale for implementing cognitive remediation in adolescents with EOP in terms of the established link between cognition and functional outcome and increased brain plasticity (Puig et al., 2014). In a meta-analysis of cognitive remediation for patients with early phase schizophrenia (3 of 11 studies included participants with EOP), Revell et al. (2015) found beneficial effects on cognition, symptoms, and functioning. As found in adults (Vita et al., 2021), the effects of cognitive remediation on daily functioning particularly applied when the interventions were delivered in combination with other psychosocial rehabilitation strategies. The effects were nevertheless smaller than what has been found in studies of participants with chronic schizophrenia. The authors argued that this was due to participant characteristics and methodological issues such as small sample sizes (Revell et al., 2015).

More recently, specific social cognitive training programs have also been developed. Social cognitive training programs use a variety of intervention methods such as drill and practice of tasks with social stimuli, role-playing, strategy training, and psychoeducation. Some programs target only one social cognitive domain while others are broad-based targeting several domains (Kurtz et al., 2016; Nijman et al., 2020). These programs show promise although less studied than traditional cognitive remediation programs targeting neurocognition. Several studies of social cognitive training for high-risk samples have been conducted (Friedman-Yakoobian et al., 2019; Glenthøj et al., 2020), but very few for young people with EOP. One recent study found that a combination of social cognition and interaction training (SCIT) and antipsychotic medication (paliperidone) was superior to antipsychotic medication alone for improving cognitive function (neuro- and social) in patients with early-onset schizophrenia (Li et al., 2020).

Psychoeducation

Psychoeducation can be defined as systematic, didactic psychotherapeutic interventions, aimed at informing patients and their families about their disorder and its treatment (Bäuml et al., 2006). Educating patients and families about cognition and how cognitive impairments can affect school performance, social interactions, and other aspects of daily living, should be an integral part of psychoeducation. This may improve awareness and provide an understanding of the adolescents' struggles beyond symptom management. Psychoeducation also aims to empower patients by helping them find meaning and constructive attitudes toward their illness (Morin & Franck, 2017). Hence, increased knowledge about their disorder, including knowledge about cognitive functioning, can facilitate increased motivation to learn supportive techniques and strategies to compensate for cognitive impairments.

Future directions

Moving forward, several areas of cognitive research in psychotic disorders have great potential. First, there is a need for increased knowledge about the neural mechanisms underlying cognitive functioning and to recognize cognition as a treatment target for patients with psychosis (McCleery & Nuechterlein, 2019). Second, more research on social cognition in adolescents with EOP is called for, particularly considering the documented association between social cognition and functional outcome (Fett et al., 2011). Third, with the development of advanced statistical models, we see a shift in focus from investigating group differences to examining subgroups and individual level performance (i.e., precision medicine). This also includes the development of improved prediction models ("risk calculators") with cognitive parameters (Koutsouleris et al., 2018). Fourth, the rapid development of digital technology may play an important role in future cognitive research. Cognitive training in virtual reality environments or as smartphone applications are examples of digital interventions that may prove useful for improving cognitive functioning (Bell et al., 2022). Furthermore, digital phenotyping, which is the momentary quantification of behavior using digital tools (Torous et al., 2016), can collect passive data from smartphone sensors and digital behavior, such as writing patterns and processing speed. This might be valuable for detecting emerging cognitive impairments, preventing illness onset, and improving treatment response and relapse prediction (Torous et al., 2020). Lastly, there is an increasing trend in academia to freely share datasets, codes, and research papers (open access). Cognitive research is depended on access to validated tools such as cognitive tests. Unfortunately, these tests or test batteries are often quite expensive. One possible solution could be that publishers offered freely available cognitive tests for research purposes as part of a social responsibility initiative.

Conclusion

Cognitive dysfunction is an important characteristic of early-onset psychosis. Many adolescents with EOP struggle with cognitive deficits across multiple domains with the largest impairments found in processing speed and verbal memory. Cognitive impairments are closely related to other aspects of the disorder, such as symptoms and impaired daily functioning. Thus, cognitive assessment should be a routine part of the overall assessment of these individuals and the results should be used for treatment and rehabilitation planning. Unfortunately, currently available antipsychotic medications have minimal treatment effect for improving cognitive performance, although they have indirect effects by reducing positive symptoms. As a more suitable alternative for treating cognitive deficits, cognitive remediation should be recommended. In the years to come, it is important to continue the research to identify the neurobiological factors underlying cognitive impairment and to continue refining and developing treatments targeting cognition.

Acknowledgments

This work was supported by the South-Eastern Norway Regional Health Authority (2019−099). The authors report no conflicts of interest.

References

Amminger, G. P., Henry, L. P., Harrigan, S. M., Harris, M. G., Alvarez-Jimenez, M., Herrman, H., Jackson, H. J., & Mcgorry, P. D. (2011). Outcome in early-onset schizophrenia revisited: Findings from the early psychosis prevention and intervention centre long-term follow-up study. *Schizophrenia Research, 131*(1−3), 112−119. https://doi.org/10.1016/j.schres.2011.06.009

Anagnostopoulou, N., Kyriakopoulos, M., & Alba, A. (2019). Psychological interventions in psychosis in children and adolescents: A systematic review. *European Child and Adolescent Psychiatry, 28*(6), 735−746. https://doi.org/10.1007/s00787-018-1159-3

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin, 24*(2), 203−218. https://doi.org/10.1093/oxfordjournals.schbul.a033321

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M. J., & McGuire, P. (2018). Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 86*, 166−175. https://doi.org/10.1016/j.neubiorev.2017.12.001

Baddeley, A., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation, 8*, 47−89. https://doi.org/10.1016/S0079-7421(08)60452-1

Baldez, D. P., Biazus, T. B., Rabelo-da-Ponte, F. D., Nogaro, G. P., Martins, D. S., Kunz, M., & Czepielewski, L. S. (2021). The effect of antipsychotics on the cognitive performance of individuals with psychotic disorders: Network meta-analyses of randomized controlled trials. *Neuroscience and Biobehavioral Reviews, 126*, 265−275. https://doi.org/10.1016/j.neubiorev.2021.03.028

Barch, D. M. (2005). The cognitive neuroscience of schizophrenia. *Annual Review of Clinical Psychology, 1*, 321−353. https://doi.org/10.1146/annurev.clinpsy.1.102803.143959

Barch, D. M., & Ceaser, A. (2012). Cognition in schizophrenia: Core psychological and neural mechanisms. *Trends in Cognitive Sciences, 16*(1), 27−34. https://doi.org/10.1016/j.tics.2011.11.015

Barkl, S. J., Lah, S., Harris, A. W. F., & Williams, L. M. (2014). Facial emotion identification in early-onset and first-episode psychosis: A systematic review with meta-analysis. *Schizophrenia Research, 159*(1), 62−69. https://doi.org/10.1016/j.schres.2014.07.049

Bäuml, J., Froböse, T., Kraemer, S., Rentrop, M., & Pitschel-Walz, G. (2006). Psychoeducation: A basic psychotherapeutic intervention for patients with schizophrenia and their families. *Schizophrenia Bulletin, 32*(1), S1−S9. https://doi.org/10.1093/schbul/sbl017

Bell, I., Pot-Kolder, R. M. C. A., Wood, S. J., Nelson, B., Acevedo, N., Stainton, A., Nicol, K., Kean, J., Bryce, S., Bartholomeusz, C. F., Watson, A., Schwartz, O., Daglas-Georgiou, R., Walton, C. C., Martin, D., Simmons, M., Zbukvic, I., Thompson, A., Nicholas, J., … Allott, K. (2022). Digital technology for addressing cognitive impairment in recent-onset psychosis: A perspective. *Schizophrenia Research: Cognition, 28*, 100247. https://doi.org/10.1016/j.scog.2022.100247

Bernagie, C., Danckaerts, M., Wampers, M., & De Hert, M. (2016). Aripiprazole and acute extrapyramidal symptoms in children and adolescents: A meta-analysis. *CNS Drugs, 30*(9), 807–818. https://doi.org/10.1007/s40263-016-0367-y

Binet, A., & Simon, T. (1948). In W. Dennis (Ed.), *The development of the Binet-Simon scale, 1905–1908* (pp. 412–424). https://doi.org/10.1037/11304-047

Bittner, R. A., Linden, D. E. J., Roebroeck, A., Härtling, F., Rotarska-Jagiela, A., Maurer, K., Goebel, R., Singer, W., & Haenschel, C. (2015). The when and where of working memory dysfunction in early-onset schizophrenia - a functional magnetic resonance imaging study. *Cerebral Cortex, 25*(9), 2494–2506. https://doi.org/10.1093/cercor/bhu050

Blakemore, S.-J., & Choudhury, S. (2006). Development of the adolescent brain: Implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry, 47*(3–4), 296–312. https://doi.org/10.1111/j.1469-7610.2006.01611.x

Bombin, I., Mayoral, M., Castro-Fornieles, J., Gonzalez-Pinto, A., De La Serna, E., Rapado-Castro, M., Barbeito, S., Parellada, M., Baeza, I., Graell, M., Payá, B., & Arango, C. (2013). Neuropsychological evidence for abnormal neurodevelopment associated with early-onset psychoses. *Psychological Medicine, 43*(4), 757–768. https://doi.org/10.1017/S0033291712001535

Bora, E., & Özerdem, A. (2017). Meta-Analysis of longitudinal studies of cognition in bipolar disorder: Comparison with healthy controls and schizophrenia. *Psychological Medicine, 47*(16), 2753–2766. https://doi.org/10.1017/S0033291717001490

Bora, E., & Pantelis, C. (2016). Social cognition in schizophrenia in comparison to bipolar disorder: A meta-analysis. *Schizophrenia Research, 175*(1–3), 72–78. https://doi.org/10.1016/j.schres.2016.04.018

Bowie, C. R., Bell, M. D., Fiszdon, J. M., Johannesen, J. K., Lindenmayer, J. P., McGurk, S. R., Medalia, A. A., Penadés, R., Saperstein, A. M., Twamley, E. W., Ueland, T., & Wykes, T. (2020). Cognitive remediation for schizophrenia: An expert working group white paper on core techniques. *Schizophrenia Research, 215*, 49–53. https://doi.org/10.1016/j.schres.2019.10.047

Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of real-world functional performance in schizophrenia subjects: Correlations with cognition, functional capacity, and symptoms. *American Journal of Psychiatry, 163*(3), 418–425. https://doi.org/10.1176/appi.ajp.163.3.418

Bozikas, V. P., & Andreou, C. (2011). Longitudinal studies of cognition in first episode psychosis: A systematic review of the literature. *Australian and New Zealand Journal of Psychiatry, 45*(2), 93–108. https://doi.org/10.3109/00048674.2010.541418

Braaten, E. B., Ward, A. K., Forchelli, G., Vuijk, P. J., Cook, N. E., McGuinness, P., Lee, B. A., Samkavitz, A., Lind, H., O'Keefe, S. M., & Doyle, A. E. (2020). Characteristics of child psychiatric outpatients with slow processing speed and potential mechanisms of academic impact. *European Child and Adolescent Psychiatry, 29*(10), 1453–1464. https://doi.org/10.1007/s00787-019-01455-w

Brown, H. E., Roffman, J. L., & Wood, J. K. (2016). Emerging treatments in schizophrenia: Highlights from recent supplementation and prevention trials. *Harvard Review of Psychiatry, 24*(2), e1–e7. https://doi.org/10.1097/HRP.0000000000000101

Burgess, P. W. (2010). *Assessment of executive function*. Oxford University Press (OUP). https://doi.org/10.1093/acprof:oso/9780199234110.003.018

Carrión, R. E., Walder, D. J., Auther, A. M., McLaughlin, D., Zyla, H. O., Adelsheim, S., Calkins, R., Carter, C. S., McFarland, B., Melton, R., Niendam, T., Ragland, J. D., Sale, T. G., Taylor, S. F., McFarlane, W. R., & Cornblatt, B. A. (2018). From the psychosis prodrome to

the first-episode of psychosis: No evidence of a cognitive decline. *Journal of Psychiatric Research, 96*, 231–238. https://doi.org/10.1016/j.jpsychires.2017.10.014

Cervellione, K. L., Burdick, K. E., Cottone, J. G., Rhinewine, J. P., & Kumra, S. (2007). Neurocognitive deficits in adolescents with schizophrenia: Longitudinal stability and predictive utility for short-term functional outcome. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(7), 867–878. https://doi.org/10.1097/chi.0b013e318054678d

Clemmensen, L., Vernal, D. L., & Steinhausen, H. C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry, 12*. https://doi.org/10.1186/1471-244X-12-150

Cogtest. (2022). www.cogtest.com.

Cohen, D., Bonnot, O., Bodeau, N., Consoli, A., & Laurent, C. (2012). Adverse effects of second-generation antipsychotics in children and adolescents: A bayesian meta-analysis. *Journal of Clinical Psychopharmacology, 32*(3), 309–316. https://doi.org/10.1097/JCP.0b013e3182549259

Conway, A. R. A., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends in Cognitive Sciences, 7*(12), 547–552. https://doi.org/10.1016/j.tics.2003.10.005

Demmo, C., Lagerberg, T. V., Aminoff, S. R., Hellvin, T., Kvitland, L. R., Simonsen, C., Andreassen, O. A., Melle, I., & Ueland, T. (2016). History of psychosis and previous episodes as potential explanatory factors for neurocognitive impairment in first-treatment bipolar I disorder. *Bipolar Disorders, 18*(2), 136–147. https://doi.org/10.1111/bdi.12377

Depp, C. A., Mausbach, B. T., Harmell, A. L., Savla, G. N., Bowie, C. R., Harvey, P. D., & Patterson, T. L. (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disorders, 14*(3), 217–226. https://doi.org/10.1111/j.1399-5618.2012.01011.x

Dickinson, D. (2008). Digit symbol coding and general cognitive ability in schizophrenia: Worth another look? *British Journal of Psychiatry, 193*(5), 354–356. https://doi.org/10.1192/bjp.bp.108.049387

Downs, J., Dean, H., Lechler, S., Sears, N., Patel, R., Shetty, H., Hotopf, M., Ford, T., Kyriakopoulos, M., Diaz-Caneja, C. M., Arango, C., MacCabe, J. H., Hayes, R. D., & Pina-Camacho, L. (2019). Negative symptoms in early-onset psychosis and their association with antipsychotic treatment failure. *Schizophrenia Bulletin, 45*(1), 69–79. https://doi.org/10.1093/schbul/sbx197

East-Richard, C., Mercier, A. R., Nadeau, D., & Cellard, C. (2020). Transdiagnostic neurocognitive deficits in psychiatry: A review of meta-analyses. *Canadian Psychology/Psychologie Canadienne, 61*(3), 190–214. https://doi.org/10.1037/cap0000196

Eckert, M. A., Keren, N. I., Roberts, D. R., Calhoun, V. D., & Harris, K. C. (2010). Age-related changes in processing speed: Unique contributions of cerebellar and prefrontal cortex. *Frontiers in Human Neuroscience, 4*. https://doi.org/10.3389/neuro.09.010.2010

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience, 3*(11), 1149–1152. https://doi.org/10.1038/80671

Elia, J., Gai, X., Xie, H. M., Perin, J. C., Geiger, E., Glessner, J. T., D'Arcy, M., Deberardinis, R., Frackelton, E., Kim, C., Lantieri, F., Muganga, B. M., Wang, L., Takeda, T., Rappaport, E. F., Grant, S. F. A., Berrettini, W., Devoto, M., Shaikh, T. H., … White, P. S. (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Molecular Psychiatry, 15*(6), 637–646. https://doi.org/10.1038/mp.2009.57

Elliott, R. (2003). Executive functions and their disorders. *British Medical Bulletin, 65*, 49−59. https://doi.org/10.1093/bmb/65.1.49

Epstein, K. A., Cullen, K. R., Mueller, B. A., Robinson, P., Lee, S., & Kumra, S. (2014). White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(3), 362−372.e2. https://doi.org/10.1016/j.jaac.2013.12.007

Fagerlund, B., Pagsberg, A. K., & Hemmingsen, R. P. (2006). Cognitive deficits and levels of IQ in adolescent onset schizophrenia and other psychotic disorders. *Schizophrenia Research, 85*(1−3), 30−39. https://doi.org/10.1016/j.schres.2006.03.004

Fett, A. K. J., Viechtbauer, W., Dominguez, M.d. G., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 35*(3), 573−588. https://doi.org/10.1016/j.neubiorev.2010.07.001

Frangou, S., Hadjulis, M., & Vourdas, A. (2008). The Maudsley early onset schizophrenia study: Cognitive function over a 4-year follow-up period. *Schizophrenia Bulletin, 34*(1), 52−59. https://doi.org/10.1093/schbul/sbm124

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuorpsychiatyric applications of CANTAB. *International Journal of Geriatric Psychiatry, 11*(4), 329−336. https://doi.org/10.1002/(SICI)1099-1166(199604)11:4<329::AID-GPS453>3.0.CO;2-6

Frazier, J. A., Giuliano, A. J., Johnson, J. L., Yakutis, L., Youngstrom, E. A., Breiger, D., Sikich, L., Findling, R. L., McClellan, J., Hamer, R. M., Vitiello, B., Lieberman, J. A., & Hooper, S. R. (2012). Neurocognitive outcomes in the treatment of early-onset Schizophrenia Spectrum Disorders study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(5), 496−505. https://doi.org/10.1016/j.jaac.2012.02.001

Friedman-Yakoobian, M., Parrish, E. M., Thomas, A., Lesser, R., Gnong-Granato, A., Eack, S., & Keshavan, M. S. (2019). An integrated neurocognitive and social-cognitive treatment for youth at clinical high risk for psychosis: Cognition for Learning and for Understanding Everyday Social Situations (CLUES). *Schizophrenia Research, 208*, 55−59. https://doi.org/10.1016/j.schres.2019.01.029

Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B. C., & Andreasen, N. C. (2002). Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *American Journal of Psychiatry, 159*(7), 1183−1189. https://doi.org/10.1176/appi.ajp.159.7.1183

Gillissie, E. S., Lui, L. M. W., Ceban, F., Miskowiak, K., Gok, S., Cao, B., Teopiz, K. M., Ho, R., Lee, Y., Rosenblat, J., & McIntyre, R. S. (2022). Deficits of social cognition in bipolar disorder: Systematic review and meta-analysis. *Bipolar Disorders, 24*(2), 137−148. https://doi.org/10.1111/bdi.13163

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2015). *Behavior Rating Inventory of Executive Function®, Second Edition (BRIEF®2)*. Lutz, FL: PAR Inc.

Glahn, D. C., Ragland, J. D., Abramoff, A., Barrett, J., Laird, A. R., Bearden, C. E., & Velligan, D. I. (2005). Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping, 25*(1), 60−69. https://doi.org/10.1002/hbm.20138

Glenthøj, L. B., Hjorthøj, C., Kristensen, T. D., Davidson, C. A., & Nordentoft, M. (2017). The effect of cognitive remediation in individuals at ultra-high risk for psychosis: A systematic review. *Npj Schizophrenia, 3*(1). https://doi.org/10.1038/s41537-017-0021-9

Glenthøj, L. B., Mariegaard, L. S., Fagerlund, B., Jepsen, J. M., Kristensen, T. D., Wenneberg, C., Krakauer, K., Medalia, A., Roberts, D. L., Hjorthøj, C., & Nordentoft, M. (2020).

Effectiveness of cognitive remediation in the ultra-high risk state for psychosis. *World Psychiatry, 19*(3), 401−402. https://doi.org/10.1002/wps.20760

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, 101*(21), 8174−8179. https://doi.org/10.1073/pnas.0402680101

Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia Research, 72*(1), 21−28. https://doi.org/10.1016/j.schres.2004.09.008

Goldberg, T. E., Goldman, R. S., Burdick, K. E., Malhotra, A. K., Lencz, T., Patel, R. C., Woerner, M. G., Schooler, N. R., Kane, J. M., & Robinson, D. G. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: Is it a practice effect? *Archives of General Psychiatry, 64*(10), 1115−1122. https://doi.org/10.1001/archpsyc.64.10.1115

de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J. P., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin, 135*(1), 157−171. https://doi.org/10.1037/a0014415

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry, 153*(3), 321−330. https://doi.org/10.1176/ajp.153.3.321

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., Fenton, W. S., Frese, F., Goldberg, T. E., Heaton, R. K., Keefe, R. S. E., Kern, R. S., Kraemer, H., Stover, E., Weinberger, D. R., Zalcman, S., & Marder, S. R. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological Psychiatry, 56*(5), 301−307. https://doi.org/10.1016/j.biopsych.2004.06.023

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. C., Kring, A. M., Park, S., Silverstein, S. M., & Heinssen, R. (2008). Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. *Schizophrenia Bulletin, 34*(6), 1211−1220. https://doi.org/10.1093/schbul/sbm145

Gur, R. C., Richard, J., Calkins, M. E., Chiavacci, R., Hansen, J. A., Bilker, W. B., Loughead, J., Connolly, J. J., Qiu, H., Mentch, F. D., Abou-Sleiman, P. M., Hakonarson, H., & Gur, R. E. (2012). Age group and sex differences in performance on a computerized neurocognitive battery in children age 8−21. *Neuropsychology, 26*(2), 251−265. https://doi.org/10.1037/a0026712

Harrison, P. J., & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. *Molecular Psychiatry, 10*(1), 40−68. https://doi.org/10.1038/sj.mp.4001558

Heinrichs, R. W. (2005). The primacy of cognition in schizophrenia. *American Psychologist, 60*(3), 229−242. https://doi.org/10.1037/0003-066x.60.3.229

Hofer, A., & Fleischhacker, W. W. (2010). In V. Roder, & A. Medalia (Eds.), *Pharmacological interventions* (Vol. 177, pp. 145−157). Karger Medical and Scientific Publishers.

Hollis, C. (2000). Adolescent schizophrenia. *Advances in Psychiatric Treatment, 6*(2), 83−92. https://doi.org/10.1192/apt.6.2.83

Holmén, A., Juuhl-Langseth, M., Thormodsen, R., Melle, I., & Rund, B. R. (2010). Neuropsychological profile in early-onset schizophrenia-spectrum disorders: Measured with the MATRICS battery. *Schizophrenia Bulletin, 36*(4), 852−859. https://doi.org/10.1093/schbul/sbn174

Holmén, A., Juuhl-Langseth, M., Thormodsen, R., Ueland, T., Agartz, I., Sundet, K., Andreassen, O. A., Rund, B. R., & Melle, I. (2012). Executive function in early- and adult onset schizophrenia. *Schizophrenia Research, 142*(1−3), 177−182. https://doi.org/10.1016/j.schres.2012.10.006

Holzer, L., Urben, S., Passini, C. M., Jaugey, L., Herzog, M. H., Halfon, O., & Pihet, S. (2014). A randomized controlled trial of the effectiveness of computer-assisted cognitive remediation (CACR) in adolescents with psychosis or at high risk of psychosis. *Behavioural and Cognitive Psychotherapy, 42*(4), 421−434. https://doi.org/10.1017/S1352465813000313

Horan, W. P., Green, M. F., Degroot, M., Fiske, A., Hellemann, G., Kee, K., Kern, R. S., Lee, J., Sergi, M. J., Subotnik, K. L., Sugar, C. A., Ventura, J., & Nuechterlein, K. H. (2012). Social cognition in schizophrenia, part 2: 12-month stability and prediction of functional outcome in first-episode patients. *Schizophrenia Bulletin, 38*(4), 865−872. https://doi.org/10.1093/schbul/sbr001

Huang, M., Huang, Y., Yu, L., Hu, J., Chen, J., Jin, P., Xu, W., Wei, N., Hu, S., Qi, H., & Xu, Y. (2016). Relationship between negative symptoms and neurocognitive functions in adolescent and adult patients with first-episode schizophrenia. *BMC Psychiatry, 16*(1). https://doi.org/10.1186/s12888-016-1052-x

Izhikevich, E. M., & Edelman, G. M. (2008). Large-scale model of mammalian thalamocortical systems. *Proceedings of the National Academy of Sciences, 105*(9), 3593−3598. https://doi.org/10.1073/pnas.0712231105

Jepsen, J. R. M., Fagerlund, B., Pagsberg, A. K., Christensen, A. M. R., Nordentoft, M., & Mortensen, E. L. (2010). Deficient maturation of aspects of attention and executive functions in early onset schizophrenia. *European Child and Adolescent Psychiatry, 19*(10), 773−786. https://doi.org/10.1007/s00787-010-0126-4

Jirsaraie, R. J., Sheffield, J. M., & Barch, D. M. (2018). Neural correlates of global and specific cognitive deficits in schizophrenia. *Schizophrenia Research, 201*, 237−242. https://doi.org/10.1016/j.schres.2018.06.017

Juuhl-Langseth, M., Hartberg, C. B., Holmén, A., Thormodsen, R., Groote, I. R., Rimol, L. M., Emblem, K. E., Agartz, I., Rund, B. R., & Soriano-Mas, C. (2015). Impaired verbal learning is associated with larger caudate volumes in early onset schizophrenia spectrum disorders. *Plos one, 10*(7), e0130435. https://doi.org/10.1371/journal.pone.0130435

Kahn, R. S., & Keefe, R. S. E. (2013). Schizophrenia is a cognitive illness: Time for a change in focus. *JAMA Psychiatry, 70*(10), 1107−1112. https://doi.org/10.1001/jamapsychiatry.2013.155

Keefe, R. S. E., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The brief assessment of cognition in schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research, 68*(2−3), 283−297. https://doi.org/10.1016/j.schres.2003.09.011

Kelleher, I., Clarke, M. C., Rawdon, C., Murphy, J., & Cannon, M. (2013). Neurocognition in the extended psychosis phenotype: Performance of a community sample of adolescents with psychotic symptoms on the matrics neurocognitive battery. *Schizophrenia Bulletin, 39*(5), 1018−1026. https://doi.org/10.1093/schbul/sbs086

Kelly, S., Guimond, S., Lyall, A., Stone, W. S., Shenton, M. E., Keshavan, M., & Seidman, L. J. (2019). Neural correlates of cognitive deficits across developmental phases of schizophrenia. *Neurobiology of Disease, 131*, 104353. https://doi.org/10.1016/j.nbd.2018.12.013

Kern, R. S., Green, M. F., Nuechterlein, K. H., & Deng, B. H. (2004). NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. *Schizophrenia Research, 72*(1), 11−19. https://doi.org/10.1016/j.schres.2004.09.004

Kern, R. S., Nuechterlein, K. H., Green, M. F., Baade, L. E., Fenton, W. S., Gold, J. M., Keefe, R. S. E., Mesholam-Gately, R., Mintz, J., Seidman, L. J., Stover, E., & Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 2: Co-norming and standardization. *American Journal of Psychiatry, 165*(2), 214–220. https://doi.org/10.1176/appi.ajp.2007.07010043

Keshavan, M. S., Giedd, J., Lau, J. Y. F., Lewis, D. A., & Paus, T. (2014). Changes in the adolescent brain and the pathophysiology of psychotic disorders. *The Lancet Psychiatry, 1*(7), 549–558. https://doi.org/10.1016/S2215-0366(14)00081-9

Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D. B., Paolini, M., Chisholm, K., Kambeitz, J., Haidl, T., Schmidt, A., Gillam, J., Schultze-Lutter, F., Falkai, P., Reiser, M., Riecher-Rössler, A., Upthegrove, R., Hietala, J., Salokangas, R. K. R., … Borgwardt, S. (2018). Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: A multimodal, multisite machine learning analysis. *JAMA Psychiatry, 75*(11), 1156–1172. https://doi.org/10.1001/jamapsychiatry.2018.2165

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangou, S. (2003). The maudsley early-onset schizophrenia study: Cognitive function in adolescent-onset schizophrenia. *Schizophrenia Research, 65*(2–3), 95–103. https://doi.org/10.1016/S0920-9964(03)00067-7

Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A., & Russell, P. S. (2013). Atypical antipsychotics for psychosis in adolescents. *Cochrane Database of Systematic Reviews, 2013*(10). https://doi.org/10.1002/14651858.CD009582.pub2

Kumra, S., Oberstar, J. V., Sikich, L., Findling, R. L., McClellan, J. M., Vinogradov, S., & Charles Schulz, S. (2008). Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophrenia Bulletin, 34*(1), 60–71. https://doi.org/10.1093/schbul/sbm109

Kurtz, M. M., Gagen, E., Rocha, N. B. F., Machado, S., & Penn, D. L. (2016). Comprehensive treatments for social cognitive deficits in schizophrenia: A critical review and effect-size analysis of controlled studies. *Clinical Psychology Review, 43*, 80–89. https://doi.org/10.1016/j.cpr.2015.09.003

Langner, R., & Eickhoff, S. B. (2013). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin, 139*(4), 870–900. https://doi.org/10.1037/a0030694

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience and Biobehavioral Reviews, 94*, 179–195. https://doi.org/10.1016/j.neubiorev.2018.09.005

Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: Clinical and functional outcomes in schizophrenia. *Canadian Journal of Psychiatry, 59*(1), 5–12. https://doi.org/10.1177/070674371405900103

Lesh, T. A., Niendam, T. A., Minzenberg, M. J., & Carter, C. S. (2011). Cognitive control deficits in schizophrenia: Mechanisms and meaning. *Neuropsychopharmacology, 36*(1), 316–338. https://doi.org/10.1038/npp.2010.156

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). Oxford University Press.

Lieberman, D. A. (2021). *Learning and memory* (2nd ed.). Cambridge University Press.

Li, Y., Sun, K., Liu, D., Chen, M. X., Li, G., Ma, J., & Zhang, X. (2020). The effects of combined social cognition and interaction training and paliperidone on early-onset schizophrenia. *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.525492

Marder, S. R., & Fenton, W. (2004). Measurement and treatment research to improve cognition in schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophrenia Research, 72*(1), 5−9. https://doi.org/10.1016/j.schres.2004.09.010

Martinez-Aran, A., Vieta, E., Torrent, C., Sanchez-Moreno, J., Goikolea, J. M., Salamero, M., Malhi, G. S., Gonzalez-Pinto, A., Daban, C., Alvarez-Grandi, S., Fountoulakis, K., Kaprinis, G., Tabares-Seisdedos, R., & Ayuso-Mateos, J. L. (2007). Functional outcome in bipolar disorder: The role of clinical and cognitive factors. *Bipolar Disorders, 9*(1−2), 103−113. https://doi.org/10.1111/j.1399-5618.2007.00327.x

Maruff, P., Thomas, E., Cysique, L., Brew, B., Collie, A., Snyder, P., & Pietrzak, R. H. (2009). Validity of the CogState brief battery: Relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Archives of Clinical Neuropsychology, 24*(2), 165−178. https://doi.org/10.1093/arclin/acp010

Mayer, J. S., & Park, S. (2012). Working memory encoding and false memory in schizophrenia and bipolar disorder in a spatial delayed response task. *Journal of Abnormal Psychology, 121*(3), 784−794. https://doi.org/10.1037/a0028836

Mayer, J., Salovey, P., & Caruso, D. (2002). *Mayer-salovey-caruso emotional intelligence test (MSCEIT) item booklet*. Multi-health systems.

McCleery, A., & Nuechterlein, K. H. (2019). Cognitive impairment in psychotic illness: Prevalence, profile of impairment, developmental course, and treatment considerations. *Dialogues in Clinical Neuroscience, 21*(3), 239−248. https://doi.org/10.31887/DCNS.2019.21.3/amccleery

Mollon, J., David, A. S., Zammit, S., Lewis, G., & Reichenberg, A. (2018). Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry, 75*(3), 270−279. https://doi.org/10.1001/jamapsychiatry.2017.4327

Mørch-Johnsen, L., Smelror, R. E., Andreou, D., Barth, C., Johannessen, C., Wedervang-Resell, K., Wortinger, L. A., Díaz, R., Victoria, G., Ueland, T., Andreassen, O. A., Myhre, A. M., Rund, B. R., Ulloa, R. E., & Agartz, I. (2022). Negative symptom domains are associated with verbal learning in adolescents with early onset psychosis. *Frontiers in Psychiatry, 12*. https://doi.org/10.3389/fpsyt.2021.825681

Morin, L., & Franck, N. (2017). Rehabilitation interventions to promote recovery from schizophrenia: A systematic review. *Frontiers in Psychiatry, 8*. https://doi.org/10.3389/fpsyt.2017.00100

Nielsen, R. E., Levander, S., Kjaersdam Telléus, G., Jensen, S. O. W., Østergaard Christensen, T., & Leucht, S. (2015). Second-generation antipsychotic effect on cognition in patients with schizophrenia-a meta-analysis of randomized clinical trials. *Acta Psychiatrica Scandinavica, 131*(3), 185−196. https://doi.org/10.1111/acps.12374

Nieto, R. G., & Castellanos, F. X. (2011). A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. *Journal of Clinical Child and Adolescent Psychology, 40*(2), 266−280. https://doi.org/10.1080/15374416.2011.546049

Nijman, S. A., Veling, W., van der Stouwe, E. C. D., & Pijnenborg, G. H. M. (2020). Social cognition training for people with a psychotic disorder: A network meta-analysis. *Schizophrenia Bulletin, 46*(5), 1086−1103. https://doi.org/10.1093/schbul/sbaa023

Nitzburg, G. C., DeRosse, P., Burdick, K. E., Peters, B. D., Gopin, C. B., & Malhotra, A. K. (2014). MATRICS cognitive consensus battery (MCCB) performance in children, adolescents,

and young adults. *Schizophrenia Research, 152*(1), 223–228. https://doi.org/10.1016/j.schres.2013.11.023

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research, 72*(1), 29–39. https://doi.org/10.1016/j.schres.2004.09.007

Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., Essock, S., Fenton, W. S., Frese, F. J., Gold, J. M., Goldberg, T., Heaton, R. K., Keefe, R. S. E., Kraemer, H., Mesholam-Gately, R., Seidman, L. J., Stover, E., Weinberger, D. R., Young, A. S., … Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *American Journal of Psychiatry, 165*(2), 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042

Øie, M. G., & Rund, B. R. (1999). Neuropsychological deficits in adolescent-onset schizophrenia compared with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 156*(8), 1216–1222.

Øie, M. G., Sundet, K., Haug, E., Zeiner, P., Klungsøyr, O., & Rund, B. R. (2021). Cognitive performance in early-onset schizophrenia and attention-deficit/hyperactivity disorder: A 25-year follow-up study. *Frontiers in Psychology, 11*. https://doi.org/10.3389/fpsyg.2020.606365

Øie, M. G., Sundet, K., & Rund, B. R. (2010). Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: Evidence from a 13-year follow-up study. *Schizophrenia Bulletin, 36*(3), 557–565. https://doi.org/10.1093/schbul/sbn127

Øie, M. G., Sundet, K., & Ueland, T. (2011). Neurocognition and functional outcome in early-onset schizophrenia and attention-deficit/hyperactivity disorder: A 13-year follow-up. *Neuropsychology, 25*(1), 25–35. https://doi.org/10.1037/a0020855

Paz-Alonso, P. M., Bunge, S. A., & Ghetti, S. (2014). *Emergence of higher cognitive functions: Reorganization of large-scale brain networks during childhood and adolescence*. Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199935291.013.003

Pérez-Garza, R., Victoria-Figueroa, G., & Ulloa-Flores, R. E. (2016). Sex differences in severity, social functioning, adherence to treatment, and cognition of adolescents with schizophrenia. *Schizophrenia Research and Treatment, 2016*. https://doi.org/10.1155/2016/1928747

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience, 35*, 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Pietrzak, R. H., Olver, J., Norman, T., Piskulic, D., Maruff, P., & Snyder, P. J. (2009). A comparison of the CogState schizophrenia battery and the measurement and treatment research to improve cognition in schizophrenia (MATRICS) battery in assessing cognitive impairment in chronic schizophrenia. *Journal of Clinical and Experimental Neuropsychology, 31*(7), 848–859. https://doi.org/10.1080/13803390802592458

Puig, O., Baeza, I., De La Serna, E., Cabrera, B., Mezquida, G., Bioque, M., Lobo, A., González-Pinto, A., Parellada, M., Corripio, I., Vieta, E., Bobes, J., Usall, J., Contreras, F., Cuesta, M. J., Bernardo, M., Castro-Fornieles, J., Amoretti, S., Garriga, M., … Balanzá-Martínez, V. (2017). Persistent negative symptoms in first-episode psychosis: Early cognitive and social functioning correlates and differences between early and adult onset. *Journal of Clinical Psychiatry, 78*(9), 1414–1422. https://doi.org/10.4088/JCP.16m11122

Puig, O., Penadés, R., Baeza, I., De La Serna, E., Sánchez-Gistau, V., Bernardo, M., & Castro-Fornieles, J. (2014). Cognitive remediation therapy in adolescents with early-onset schizophrenia: A randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(8), 859–868. https://doi.org/10.1016/j.jaac.2014.05.012

Rajji, T. K., Ismail, Z., & Mulsant, B. H. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *British Journal of Psychiatry, 195*(4), 286–293. https://doi.org/10.1192/bjp.bp.108.060723

Rajji, T. K., Miranda, D., & Mulsant, B. H. (2014). Cognition, function, and disability in patients with schizophrenia: A review of longitudinal studies. *Canadian Journal of Psychiatry, 59*(1), 13–17. https://doi.org/10.1177/070674371405900104

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological Status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology, 20*(3), 310–319. https://doi.org/10.1076/jcen.20.3.310.823

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., Poulton, R., & Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal of Psychiatry, 167*(2), 160–169. https://doi.org/10.1176/appi.ajp.2009.09040574

Revell, E. R., Neill, J. C., Harte, M., Khan, Z., & Drake, R. J. (2015). A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophrenia Research, 168*(1–2), 213–222. https://doi.org/10.1016/j.schres.2015.08.017

Rhinewine, J. P., Lencz, T., Thaden, E. P., Cervellione, K. L., Burdick, K. E., Henderson, I., Bhaskar, S., Keehlisen, L., Kane, J., Kohn, N., Fisch, G. S., Bilder, R. M., & Kumra, S. (2005). Neurocognitive profile in adolescents with early-onset schizophrenia: Clinical correlates. *Biological Psychiatry, 58*(9), 705–712. https://doi.org/10.1016/j.biopsych.2005.04.031

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., & Rabbitt, P. (2004). Cambridge neuropsychological test automated battery (CANTAB): A factor Analytic study of a large sample of normal elderly volunteers. *Dementia and Geriatric Cognitive Disorders, 5*(5), 266–281. https://doi.org/10.1159/000106735

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders, 93*(1–3), 105–115. https://doi.org/10.1016/j.jad.2006.02.016

Ruiz-Veguilla, M., Moreno-Granados, J., Salcedo-Marin, M. D., Barrigon, M. L., Blanco-Morales, M. J., Igunza, E., Cañabate, A., Garcia, M. D., Guijarro, T., Diaz-Atienza, F., & Ferrin, M. (2017). Sex-specific cognitive abnormalities in early-onset psychosis. *Revista Brasileira de Psiquiatria, 39*(1), 28–35. https://doi.org/10.1590/1516-4446-2015-1807

Savla, G. N., Vella, L., Armstrong, C. C., Penn, D. L., & Twamley, E. W. (2013). Deficits in domains of social cognition in schizophrenia: A meta-analysis of the empirical evidence. *Schizophrenia Bulletin, 39*(5), 979–992. https://doi.org/10.1093/schbul/sbs080

Schalbetter, S. M., Von Arx, A. S., Cruz-Ochoa, N., Dawson, K., Ivanov, A., Mueller, F. S., Lin, H. Y., Amport, R., Mildenberger, W., Mattei, D., Beule, D., Földy, C., Greter, M., Notter, T., & Meyer, U. (2022). Adolescence is a sensitive period for prefrontal microglia to act on cognitive development. *Science Advances, 8*(9). https://doi.org/10.1126/sciadv.abi6672

Seidman, L. J., & Mirsky, A. F. (2017). Evolving notions of schizophrenia as a developmental neurocognitive disorder. *Journal of the International Neuropsychological Society, 23*(9–10), 881–892. https://doi.org/10.1017/S1355617717001114

Seidman, L. J., Shapiro, D. I., Stone, W. S., Woodberry, K. A., Ronzio, A., Cornblatt, B. A., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Tsuang, M. T., Walker, E. F., & Woods, S. W. (2016). Association of neurocognition with transition to psychosis: Baseline functioning in the second

phase of the north American prodrome longitudinal study. *JAMA Psychiatry, 73*(12), 1239–1248. https://doi.org/10.1001/jamapsychiatry.2016.2479

Sheffield, J. M., Karcher, N. R., & Barch, D. M. (2018). Cognitive deficits in psychotic disorders: A lifespan perspective. *Neuropsychology Review, 28*(4), 509–533. https://doi.org/10.1007/s11065-018-9388-2

Smelror, R. E., Johannessen, C., Wedervang-Resell, K., Jørgensen, K. N., Barth, C., Andreou, D., Ueland, T., Andreassen, O. A., Myhre, A. M., Rund, B. R., & Agartz, I. (2021). Cognitive impairment profile in adolescent early-onset psychosis using the MATRICS Battery: Age and sex effects. *Neuropsychology, 35*(3), 300–309. https://doi.org/10.1037/neu0000723

Smelror, R. E., Jørgensen, K. N., Lonning, V., Kelleher, I., Cannon, M., DeRosse, P., Malhotra, A. K., Karlsgodt, K. H., Andreassen, O. A., Lundberg, M., Edbom, T., Cleland, N., Ueland, T., Myhre, A. M., Rund, B. R., & Agartz, I. (2019). Healthy adolescent performance with standardized scoring tables for the MATRICS consensus cognitive battery: A multisite study. *Schizophrenia Bulletin, 45*(4), 773–783. https://doi.org/10.1093/schbul/sby131

Smelror, R. E., Rund, B. R., Lonning, V., Jørgensen, K. N., Wedervang-Resell, K., Andreassen, O. A., Ueland, T., Myhre, A. M., & Agartz, I. (2020). Negative and disorganized symptoms mediate the relationship between verbal learning and global functioning in adolescents with early-onset psychosis. *European Child and Adolescent Psychiatry, 29*(12), 1693–1703. https://doi.org/10.1007/s00787-020-01479-7

Spearman, C. (1904). "General intelligence," objectively determined and measured. *The American Journal of Psychology, 15*(2), 201–292. https://doi.org/10.2307/1412107

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory, 82*(3), 171–177. https://doi.org/10.1016/j.nlm.2004.06.005

Stone, W. S., Mesholam-Gately, R. I., Giuliano, A. J., Woodberry, K. A., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Tsuang, M. T., Walker, E. F., Woods, S. W., McCarley, R. W., Heinssen, R., Green, M. F., Nuechterlein, K., & Seidman, L. J. (2016). Healthy adolescent performance on the MATRICS Consensus Cognitive Battery (MCCB): Developmental data from two samples of volunteers. *Schizophrenia Research, 172*(1–3), 106–113. https://doi.org/10.1016/j.schres.2016.02.003

Takehara-Nishiuchi, K. (2020). Prefrontal–hippocampal interaction during the encoding of new memories. *Brain and Neuroscience Advances, 4*.

Teigset, C. M., Mohn, C., Brunborg, C., Juuhl-Langseth, M., Holmén, A., & Rund, B. R. (2018). Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders? *Journal of Child Psychology and Psychiatry, 59*(9), 1012–1023. https://doi.org/10.1111/jcpp.12896

Torous, J., Choudhury, T., Barnett, I., Keshavan, M., & Kane, J. (2020). Smartphone relapse prediction in serious mental illness: A pathway towards personalized preventive care. *World Psychiatry, 19*(3), 308–309. https://doi.org/10.1002/wps.20805

Torous, J., Kiang, M. V., Lorme, J., & Onnela, J. P. (2016). New tools for new research in psychiatry: A scalable and customizable platform to empower data driven smartphone research. *JMIR Mental Health, 3*(2). https://doi.org/10.2196/mental.5165

Trotta, A., Murray, R. M., & Maccabe, J. H. (2015). Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. *Psychological Medicine, 45*(2), 381–394. https://doi.org/10.1017/S0033291714001512

Tuulio-Henriksson, A., Partonen, T., Suvisaari, J., Haukka, J., & Lönnqvist, J. (2004). Age at onset and cognitive functioning in schizophrenia. *British Journal of Psychiatry, 185*, 215–219. https://doi.org/10.1192/bjp.185.3.215

Ueland, T., Øie, M. G., Landrø, N. I., & Rund, B. R. (2004). Cognitive functioning in adolescents with schizophrenia spectrum disorders. *Psychiatry Research, 126*(3), 229–239. https://doi.org/10.1016/j.psychres.2004.02.014

Ueland, T., & Rund, B. R. (2005). Cognitive remediation for adolescents with early onset psychosis: A 1-year follow-up study. *Acta Psychiatrica Scandinavica, 111*(3), 193–201. https://doi.org/10.1111/j.1600-0447.2004.00503.x

Victoria, G., Apiquian, R., Rosetti, M. F., & Ulloa, R. E. (2019). Cognitive impairment and its improvement after six months in adolescents with schizophrenia. *Schizophrenia Research: Cognition, 17*. https://doi.org/10.1016/j.scog.2019.100135

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry, 78*(8), 848–858. https://doi.org/10.1001/jamapsychiatry.2021.0620

Vlad, M., Raucher-Chéné, D., Henry, A., & Kaladjian, A. (2018). Functional outcome and social cognition in bipolar disorder: Is there a connection? *European Psychiatry, 52*, 116–125. https://doi.org/10.1016/j.eurpsy.2018.05.002

Waber, D. P., De Moor, C., Forbes, P. W., Almli, C. R., Botteron, K. N., Leonarf, G., Molovan, D., Paus, T., & Rumsey, J. (2007). The NIH MRI study of normal brain development: Performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *Journal of the International Neuropsychological Society, 13*(5), 729–746. https://doi.org/10.1017/S1355617707070841

Wechsler, D. (2008). *Wechsler adult intelligence scale–fourth edition (WAIS-IV)*. Pearson.

Wechsler, D. (2014). *Wechsler intelligence scale for children–fifth edition (WISC-V)*. Pearson.

Weiss, L., Saklofske, D., Coalson, D., & Raiford, S. E. (2010). *WAIS-IV clinical use and interpretation: Scientist-practitioner perspectives*. Academic Press.

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 457–465. https://doi.org/10.1097/00004583-199105000-00017

Westerman, R., Darby, D., Maruff, P., & A, C. (2001). Computer-assisted cognitive function assessment of pilots. *ADF Health, 2*, 29–36.

Zabala, A., Rapado, M., Arango, C., Robles, O., De La Serna, E., González, C., Rodríguez-Sánchez, J. M., Andrés, P., Mayoral, M., & Bombín, I. (2010). Neuropsychological functioning in early-onset first-episode psychosis: Comparison of diagnostic subgroups. *European Archives of Psychiatry and Clinical Neuroscience, 260*(3), 225–233. https://doi.org/10.1007/s00406-009-0046-9

Chapter 7

The immunopsychiatry of early-onset psychosis

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Introduction

The notion that the two major organ systems of the body—the immune and the nervous systems—interact with each other was confirmed after a long period of cumulative scientific observations. This resulted in the birth of the field of psychoneuroimmunology about 4 decades ago. The term "psychoneuroimmunology" was coined by Robert Ader in 1980 to grasp the idea of convergent findings demonstrating the crosstalk of the immune system and the central nervous system (CNS) (Daruna, 2012). This new field emerged as a systems-level and integrative discipline aiming to explore the psychobiology and physiology of processes through which mental events influence or alter immune functions, and how, in turn, the immune system is able to modulate the function of the mind (Daruna, 2012; Szabo & Rajnavolgyi, 2013b). Of note, the emergence of modern psychoneuroimmunology research was preceded by purposeful investigations or incidental observations carried through many centuries.

Modern immunopsychiatry (a term recently used as a synonym for psychoneuroimmunology in preclinical and clinical contexts) can be distinguished from its forerunners by its novel theoretical design and methodology (Pariante, 2015). This new paradigm considers neuroimmune communication as an integrated, system-level biobehavioral entity with the brain and immune system being its two aspects. Furthermore, an understanding of the immune system is important in normal neurodevelopment and refinement of the CNS architecture and functional neural circuits has emerged. Recently, inflammation and dysregulated immune responses have been suggested to be involved in the pathophysiology of psychotic disorders, including early-onset psychosis (EOP; illness onset before age 18 years) (Khandaker et al., 2015; Miyaoka et al., 2017; Wedervang-Resell, Friis, et al., 2020; Wedervang-Resell, Ueland, et al.,

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00013-5

2020). *In utero* and perinatal infections, as well as CNS inflammation or autoimmunity presenting later in childhood, adolescence, or adult life, have all been implicated in the manifestation of the disease (Bechter et al., 2010; Benros et al., 2011; Brown & Patterson, 2011; Estes & McAllister, 2016). Moreover, increased levels of circulating inflammatory cytokines and other biomarkers were reported to be associated with the severity and symptom evolution of psychotic disorders (Borovcanin et al., 2017; Hope et al., 2013). However, the underlying pathophysiological role of inflammation and immune system activation in psychosis and EOP is still unclear. In this chapter, we provide an overview of the available literature about the immunopsychiatry of psychosis with a focus on EOP. We also discuss potential mechanisms, such as the immune system's role in neurodevelopment, innate immune dysregulation, or aberrant peripheral immune functions as possible biological correlates of EOP. Finally, we review novel and emerging therapeutic immune targets for adolescent psychosis, and potentially also in other neurodevelopmental disorders with psychotic features.

The immune system and neurodevelopment

Immune system functions and brain physiology

The immune system is a complex network of lymphatic tissues and organs that consists of various cell types and mediators. It is an intricate system of surveillance and protection that has evolved to protect the body from infections and endogenous malignancies. From a functional perspective, it can be thought of as a two-part defense system. Innate immunity is the first line of defense, which acts rapidly and in a nonspecific manner. Its receptors are germline-encoded, and innate immune cells (such as neutrophils and macrophages) are continuously monitoring the tissues looking for nonself or potentially dangerous molecular motifs (Sonnenberg & Hepworth, 2019). Inflammatory cytokines and chemokines that are produced by activated immune cells in this manner establish and support the first, acute phase of the immune response (Szabo & Rajnavolgyi, 2013a). Adaptive immunity, on the other hand, is slower, may take several days or weeks in its course, and is highly antigen-specific (i.e., the immune response is precisely directed against the foreign or self-molecular pattern (epitope) that has elicited it). Functionally, it is largely based on the activity of T and B lymphocytes, as well as the humoral "arm" of adaptive immunity that involves the secretion of antigen-specific antibodies by plasma cells (i.e., the activated B lymphocytes). Another important aspect of adaptive immunity is the generation of antigen-specific immunological memory that can protect the organism over long periods of time (for years or even decades in humans). As mentioned above, inflammatory pathologies and innate immune dysregulation are tightly connected and have been shown to play an important role in the

pathophysiology of psychosis (Khandaker et al., 2015). Thus, in this section, we will focus on the innate part of the immune system and its role in neurodevelopment and brain pathologies.

The innate immune system represents an ancient host defense mechanism that is directed against invading pathogens. The detection of potentially dangerous, nonself, pathogen-associated molecular patterns (PAMPs) is based on pattern recognition receptors that are widely expressed in immune cells and in various tissues. PAMPs are evolutionally conserved foreign patterns that are commonly found in larger microbial groups. Recognition of these molecular motifs by pattern recognition receptors typically initiates nuclear factor kappa-b (NF-κB)-mediated inflammatory chemokine, or interferon responses that depend on the type of invading microbe. In the recent 2 decades, a plethora of various pattern recognition receptors have been identified including Toll-like and C-type lectin receptors, cytosolic nucleotide-binding oligomerization domain containing (NOD)-like receptors, and many others (Riera Romo et al., 2016; Thaiss et al., 2016). NOD-like receptors are involved in the formation of an important innate immune effector mechanism, the *inflammasome*. Inflammasomes are complex, large, multicomponent platforms that control caspase-1 activation. Caspase-1 is a proteolytic enzyme that regulates the cleavage/maturation of the pro-inflammatory cytokines, interleukin-1beta (IL-1β) and IL-18 (Fig. 7.1), as well as mediates pyroptosis, an inflammatory form of cell death (Rathinam et al., 2012; Rathinam & Fitzgerald, 2016). The assembly of the inflammasome complex is triggered by cytosolic detection of PAMPs that enter the cytoplasm during microbial infection. In addition to this "classic" form of caspase-1 activation, self-derived endogenous damage-associated molecular patterns (DAMPs) can also trigger inflammasome activation. DAMPs that emerge during tissue damage, metabolic imbalance or psychological stress (Iwata et al., 2016) can drive pathological "sterile inflammation," an inflammatory phenomenon that is occurring in the absence of pathogenic microbes (Latz et al., 2013). Chronic inflammation provoked by either exogenous or endogenous stimuli can elicit considerable tissue damage that may subsequently lead to autoimmunity. This way, innate immunity has an important role in the etiology of several autoimmune diseases by initiating and sustaining autoinflammation, decreasing the immune tolerance threshold, and by contributing to the development of long-term adaptive immune responses against self-tissues, such as the brain parenchyma (Doria, Dayer, et al., 2012; Doria, Zen, et al., 2012). In genome-wide association studies, a strong relationship between schizophrenia and the major histocompatibility complex region has been identified. This region encompasses the human leukocyte antigen cluster, pivotal not only for normal immune functions and for the modulation of autoimmune processes, but also for physiological neurodevelopment (Ripke et al., 2014).

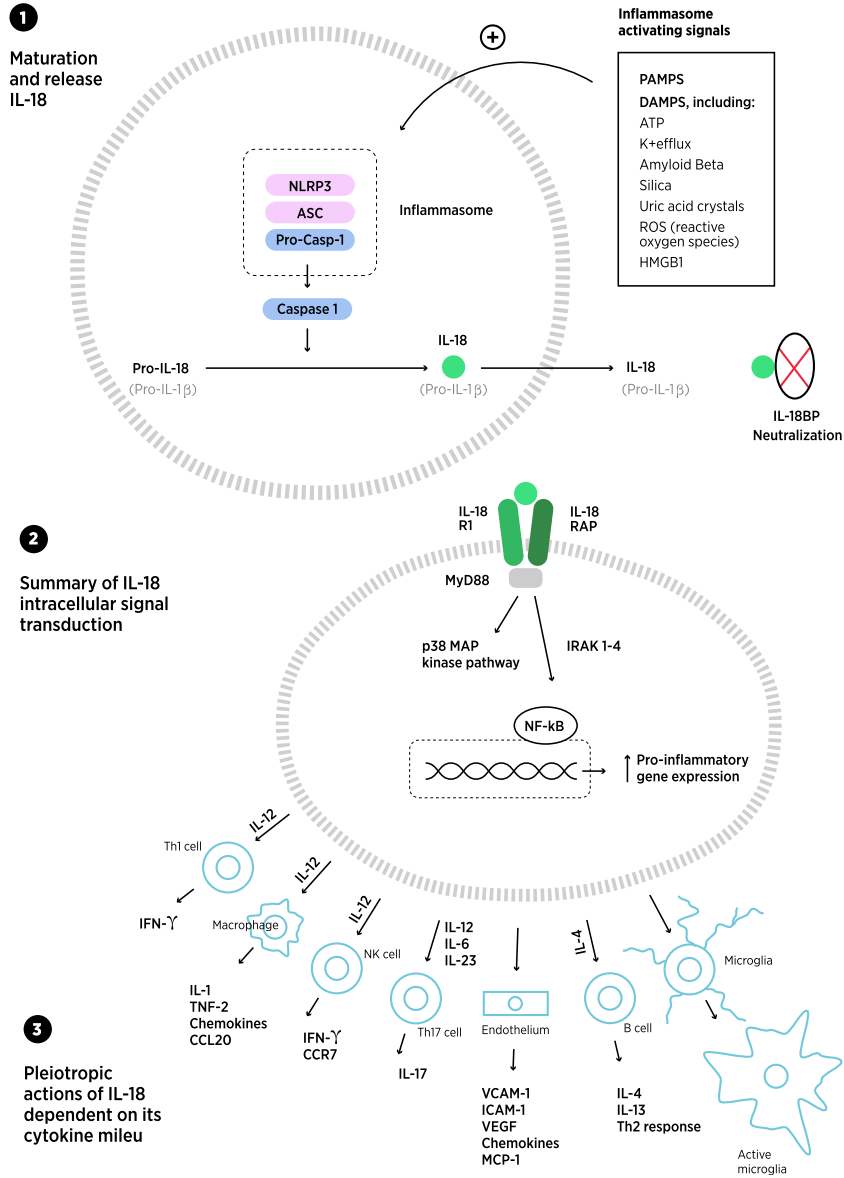

FIGURE 7.1 Schematic illustration of the inflammasome activating signals and caspase-1 assembly. (1) The inflammasome activating signals and caspase-1 assembly induce the maturation and release of IL-18 and IL-1β. To illustrate an example of inflammasome effector functions, the lower part of the figure summarizes (2) IL-18 intracellular signal transduction and (3) the pleiotropic actions of IL-18, which is dependent on its cytokine milieu. *Reproduced with permission from Wedervang-Resell, & Universitetet i Oslo Institutt for klinisk medisin. (2021). Immune and metabolic markers in early-onset psychosis. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo.*

Cytokines in CNS development, maintenance, and pathophysiology

Cytokines are immune signaling molecules, with predominantly pro- or antiinflammatory effects. They possess both neuropoietic properties, important in neurodevelopment, and significant neuromodulatory potential in acute and chronic neuroinflammatory states. Cytokines are also constitutively expressed in the brain, and play a crucial role in regulating homeostatic mechanisms, such as higher order cognition, memory, sleep, and CNS metabolism (Bilbo & Schwarz, 2012; Kubota et al., 2000; Vitkovic et al., 2000; Yirmiya & Goshen, 2011). The best known and most characterized effect of cytokines on brain functions is the so-called sickness behavior. Sick mammals manifest various, well-known changes in their behavior, such as reduced activity, food intake, social and sexual interactions, increased sleep, and disturbances in cognition (Dantzer & Kelley, 2007). These behavioral alterations are mediated by the activated immune system via orchestrated cytokine release. This gives rise to adaptive strategies that serve the survival of the host and the protection of the population (by preventing contagion) and are not mere pathological consequences of the infectious microbes themselves (Bilbo & Schwarz, 2012; Dantzer & Kelley, 2007). Thus, sickness behavior is a prototypical example of complex changes in cognition/behavior elicited by organized and fine-tuned changes in the nervous system, endocrine-, and immune system activities.

Cytokine-specific receptors are widely expressed in neurons and brain endothelial cells, as well as in glial cells, that is, in microglia, astrocytes, and oligodendrocytes. The relative rate of expression and densities for individual cytokines and cytokine receptors is time and region-dependent in the mammalian brain, suggesting a physiological role in the development of specific brain circuits (Deverman & Patterson, 2009; Rostène et al., 2011). Cytokines can be released by many cell types, mostly by resident or infiltrating immune cells, but also by glial and endothelial cells at the blood–brain barrier. Their production is an important element of CNS development and physiology. However, pathological cytokine dysregulation can be a result of virtually any sort of perturbations in brain homeostasis, such as infections, stroke, trauma, psychological stress, neurodegenerative processes, etc. (Hopkins & Rothwell, 1995; Rothwell & Hopkins, 1995). Cytokine signals can also be transmitted to the brain from the periphery. This can happen through various routes and processes, including: (1) direct neurotransmission by cytokines binding to their specific receptors on vagal afferents (Andersson & Tracey, 2012); (2) via signaling through the blood-brain barrier (Hopkins & Rothwell, 1995; Rostène et al., 2011); (3) by active transport mechanisms (Banks et al., 1995); or (4) by crossing into the brain at circumventricular organs with higher permeability or at leaky blood-brain barrier sites (Bilbo & Schwarz, 2012; Wuchert et al., 2008).

Preclinical studies have provided valuable data on the possible mechanisms of immune dysregulation in psychosis. Circulating IL-6 can bind to its cognate receptor on the vagus nerve, and the signal is transmitted to the hypothalamic brain nuclei via retrograde axonal transport. Within the CNS, inflammatory cytokine signals are amplified, resulting in microglia activation leading to the secretion of additional inflammatory cytokines, chemokines and glia-specific proteases in the brain parenchyma (Dantzer et al., 2008). This signaling cascade leads to the activation of Indoleamine 2,3-dioxygenase (IDO1), the enzyme that metabolizes tryptophan in the kynurenine pathway, resulting in elevated concentrations of kynurenic acid and quinolonic acid (its metabolite). Both kynurenic and quinolonic acid are involved in glutamatergic neurotransmission, as well as in neurotoxic inflammation and neurodegeneration (Sellgren, Gracias, Jungholm, et al., 2019; Sellgren et al., 2021; Walker et al., 2013). Dysregulated CNS cytokine levels can also increase oxidative stress through elevated toxic nitric oxide levels, which, in turn, modulates the hypothalamic-pituitary-adrenal axis (HPA-axis) and the systemic release of cortisol (Miller et al., 2009). These mechanisms could play a role in individuals with schizophrenia by contributing to the positive, negative, and cognitive symptoms of the disorder, and also by altering mood and social perception. Mental and cognitive effects have been observed in healthy volunteers, where nonspecific immune activation, elicited by intravenous bacterial lipopolysaccharide, increased serum IL-6 while also inducing dysphoria, anxiety, and markedly reduced cognitive performance (Reichenberg et al., 2001). Cytokines also exert significant modulatory effects on microglia that, besides their role in immunosurveillance, are crucial in neurodevelopment and the maintenance of synaptic health in the mammalian brain (Hanisch & Kettenmann, 2007).

Glial cells in CNS development, maintenance, and pathophysiology

Microglia constitute about 10%−12% of the glial compartment of the brain. These brain-resident immunocompetent cells originate from yolk-sac fetal macrophages, while peripheral macrophages arise from precursors generated later in development (Hoeffel et al., 2015; Sheng et al., 2015). In early embryonic life, microglial colonization, migration, and maturation within the developing brain is an orchestrated event related to the maturation of the nervous system in a sex-, time-, and region-specific manner (Bilbo & Schwarz, 2009; Ginhoux et al., 2010; Lenz & Nelson, 2018). During homeostatic conditions in the adult CNS, microglia display a downregulated, resting phenotype, while continuously monitoring and responding to the tissue microenvironment of the brain (Ransohoff & Perry, 2009). In contrast, microglia show a distinct morphology during early neurodevelopment, featuring a larger, round, ameboid shape similar to adult-activated microglia

usually seen in pathological states (Bilbo & Schwarz, 2009). In adults, microglia acquire this activated phenotype in response to injury, trauma, infections, or systemic inflammatory stimuli. This activated state is characterized by the secretion of inflammatory mediators and increased expression of surface markers involved in immune cell migration, adhesion, and antigen-presentation (Perry et al., 2010). However, during adolescent neurodevelopment, physiologically active microglia are involved in synaptic pruning by phagocytosis of complement-marked synapses intended for elimination, thus contributing to brain connectivity. Any dysfunction in these immune-related processes may disrupt the physiological neurodevelopmental process. Indeed, Sekar et al. (2016) reported complement C4 gene variants to be associated with schizophrenia risk and showed that increased levels of complement C4A expression in the brain enhance microglial-dependent synaptic pruning with a consequent reduction in gray matter thickness.

Cytokines and glial cells in adults with psychotic disorders

Several cross-sectional studies and meta-analyses have shown that individuals with schizophrenia are characterized by a disrupted cytokine regulation in the peripheral immune compartment that promotes inflammatory states (Khandaker et al., 2015; Miller et al., 2011; Potvin et al., 2008; Upthegrove et al., 2014). Longitudinal studies are needed to corroborate if the elevated plasma levels of inflammatory cytokines in patients with schizophrenia and other psychotic disorders represent the cause or consequence of the illness. However, the majority of the available findings so far indicate a causal mechanism. Adults with first-episode psychosis (in antipsychotic-naïve patients) and acute psychotic relapse are characterized by increased circulating levels of inflammatory cytokines, such as IL-6, TNF-α, IL-1β, interferon-γ, and decreased blood levels of the antiinflammatory cytokine IL-10 (Miller et al., 2011; Upthegrove et al., 2014). These alterations are normalized after treatment with antipsychotic medication or following symptom remission (Miller et al., 2011). In agreement with these results, T cells from adult patients with schizophrenia displayed decreased IL-2 production in *in vitro* studies suggesting potential autoimmune causes of psychosis (Ganguli et al., 1993). Several reports indicate that blood IL-6 concentrations are associated with the duration and severity of psychosis, and antipsychotic treatment (Miller et al., 2011). However, more studies are required to better understand the associations between cytokine concentrations, symptom evolution, disease progression, and pharmacological treatment response.

Activated microglia, a hallmark of neuroinflammation, are associated with increased translocator protein expression. Molecular neuroimaging studies using positron emission tomography and translocator protein radioligand found neuroinflammation in patients with acute psychotic episodes (van Berckel et al., 2008) and recent-onset schizophrenia (Upthegrove et al., 2014).

The same studies also reported binding of the translocator protein ligand in the entire gray matter and hippocampus. These findings indicate that the observed neuroinflammatory process might play a role in gray matter atrophy and cognitive decline in patients with schizophrenia (Doorduin et al., 2009; van Berckel et al., 2008). Another explanation for increased translocator protein signals in the related brain areas could be the ligand's affinity for activated astrocytes, which are also immunocompetent and crucially important neuro-supportive glial cells of the mammalian CNS (Dietz et al., 2020; Khandaker et al., 2015).

Astrocytes have also been proposed to play a role in altered neuro-inflammatory responses in patients with schizophrenia. Induced pluripotent stem cell-derived astrocytes display decreased inflammatory regulatory capacity and stress resilience when challenged by IL-1β stimulation in adults with schizophrenia compared to healthy controls (Akkouh et al., 2020). Furthermore, altered microglia-astrocyte crosstalk and abnormal inflammatory coregulation may also contribute to neuroinflammation and neurodegenerative processes in patients with schizophrenia (Dietz et al., 2020).

Finally, previously primed microglia are able to respond to a new stimulus in a much stronger and more rapid way (Schroder et al., 2006). This can possibly retain immune memory regarding specific neuropathological signals, which could lead to increased responsiveness to future systemic inflammatory inputs (Khandaker et al., 2015; Perry et al., 2010). Thus, early insults during neurodevelopment (e.g., severe infections in the perinatal or childhood period) could hypothetically have a priming effect on microglia thereby enhancing glial activation and psychosis risk following infections and/or systemic inflammatory events later in life (Khandaker et al., 2015). Recent studies using induced pluripotent stem cell technology demonstrated diminished neuronal activity, decreased neurite numbers, and glutamatergic signaling (Brennand et al., 2011), as well as substantially increased synaptic pruning by microglia, in individuals with schizophrenia (Sellgren, Gracias, Watmuff, et al., 2019). Similar technologies are emerging as useful tools in revealing the underlying, disease-specific molecular and cellular mechanisms of psychotic disorders.

The neurodevelopmental aspects of immune activation in psychosis

The first link between psychiatric disorders and perinatal infection was proposed in 1891 by Thomas Clouston, who suggested that there might be an infectious basis of determinants to severe mental disorders with onset during adolescence (Bilbo & Schwarz, 2012). Since then, several studies have demonstrated a strong connection between perinatal or early-life infections and later-life onset of schizophrenia (Fruntes & Limosin, 2008; Meyer et al., 2005). The developing nervous system is sensitive to immune activation because immune and inflammatory signals (both exogenous and endogenous)

can influence the developmental trajectory of all major CNS cell types, the glial network and neural connectome, and the associated behavioral patterns. There is increasing evidence that various immune stressors during the pre- and postnatal periods, such as maternal immune activation or inflammatory disorders, can greatly alter how developing neural circuits are formed (Bilbo & Schwarz, 2009; Fatemi & Folsom, 2009). This can, for instance, affect the proteome of neurons and disrupt the proteostasis in the fetal brain (Kalish et al., 2021). The adult behavioral consequences of these immune-neurodevelopmental factors are often significant and permanent. Other underlying mechanisms by which infections and immune activation may cause psychopathology include the: (1) direct infection of the fetus and consequent abnormalities in neurodevelopment; (2) activation of the maternal immune system and the production of auto-antibodies that target fetal neural tissues; and (3) dysregulation of cytokine production, which can be a common denominator of all three mechanisms (Bilbo & Schwarz, 2009; Khandaker et al., 2015; Pearce, 2001).

Increased circulating pro-inflammatory cytokine levels induced by maternal immune activation have been associated with aberrant fetal brain development and increased risk of many neurodevelopmental disorders (Meyer, 2014). For example, increased IL-1β, IL-6, and TNFα levels in infants with bacterial meningitis show strong correlations with the manifestation of neurological and psychiatric abnormalities later in life (Bilbo & Schwarz, 2012). Several studies in humans have shown that maternal immune activation, through maternal infections, modulates the production of high inflammatory cytokine levels, both in the maternal and fetal immune systems, and the placenta (Estes & McAllister, 2016; Han et al., 2021). These mechanisms have been linked to increased risk of schizophrenia in the offspring (Brown & Derkits, 2010). Recent developments in clinical medicine have tremendously increased survival rates among mothers and babies who suffered from infections. However, despite the lowered mortality rates, infections have an impact on the neuropsychiatric sequelae (Bilbo, 2011). One of the major clinical consequences of maternal immune activation and/or early-life immune dysregulation could be the development of EOP.

In the last 2 decades, links between immune activation and the neurodevelopmental aspects of several psychiatric disorders have been found (Dantzer et al., 2008; Dantzer & Kelley, 2007). This indicates that many psychiatric disorders may share or involve some form of immune dysregulation, even if the explicit immune challenge is not present (Bilbo & Schwarz, 2012). This immune link has been well-described in psychiatric disorders such as depression, schizophrenia, autism spectrum disorder, anxiety, and learning/cognitive disabilities (Hornig et al., 2018; Jiang et al., 2016; Khandaker et al., 2018; Severance & Yolken, 2016; Shi et al., 2009). Moreover, patients with posttraumatic stress disorder and positive psychotic symptoms also have elevated circulating levels of inflammatory markers, abnormal T cell counts,

enhanced immune reactivity during skin tests, and altered global methylation of a large set of immune genes (Bauer et al., 2010; Bilbo & Schwarz, 2012; Pace & Heim, 2011). Importantly, the majority of these disorders have developmental origins.

Abnormal levels of IL-1β, IL-6, neuregulin, and brain-derived neurotropic factor (BDNF) were also found in the brain and peripheral tissues of people with schizophrenia, suggesting a two-sided pathology affecting both the immune system and important regulatory pathways that are involved in synapse formation, maintenance, and function during neurodevelopment (Müller & Ackenheil, 1998; Müller & Schwarz, 2010; Nawa & Takei, 2006).

Clinical findings on immune system dysregulation in individuals with psychotic disorders

As presented above, the immune system takes part in neurodevelopment and in the interplay between environmental and genetic susceptibility factors conferring risk for neuropsychiatric disorders. Indeed, converging findings from epidemiological, genetic, and clinical studies in adults with psychotic disorders indicate that immune system dysregulation may contribute to the pathophysiology (Comer et al., 2020; Khandaker et al., 2015; Kroken et al., 2019). Studies of immune functions in adult patients with psychotic disorders show alterations in several immune-inflammatory markers in peripheral blood and cerebrospinal fluid including higher levels of pro-inflammatory cytokines, C-reactive protein (CRP), various antibodies, and changes in leukocyte subpopulation counts. Some of these alterations are present in subjects only at specific psychotic stages, such as at first episode of psychosis, while others may be considered trait markers (Khandaker et al., 2015; Kroken et al., 2019). However, knowledge of the molecular mechanisms and origin of these findings is still insufficient.

Because the immune system and peripheral levels of immune-inflammatory markers may also be influenced by lifestyle factors (e.g., obesity, smoking, poor diet and reduced physical activity), comorbid somatic diseases, and antipsychotic medication, studies in adolescents with EOP are especially valuable. These patients tend to have less confounders, as they are usually somatically healthy, have short or no exposure to antipsychotic medication and few unhealthy lifestyle factors. Moreover, adolescent patients with EOP are in an early phase of their disorder and neurodevelopment is still taking place, offering an opportunity to explore potential stage- or age-specific events. Despite this, studies on immune system dysregulation in patients with EOP are unfortunately still scarce.

Immune-inflammatory markers in longitudinal studies of psychosis

The notion that exposure to elevated inflammatory markers in fetal life, childhood and adolescence has important roles in the pathogenesis of

psychosis is supported by results from several longitudinal studies. First, a recent large-scale American longitudinal study examined the effects of perinatal factors on infant and child development. Based on their findings, the authors suggest that exposure to aberrant immune signaling can affect crucial elements of neural embryology to increase the risk of psychosis (Allswede et al., 2020). Further, the authors showed that concentrations of pro-inflammatory cytokines, TNF-α, IL-1β and IL-6, were significantly higher in the maternal serum of offspring who later developed psychosis compared with matched healthy controls. They also showed that these differences were greatest in the first half of pregnancy (7−20 weeks) thereby placing the prenatal timing of psychosis risk associated with maternal inflammation at a very early stage in fetal neurodevelopment (Allswede et al., 2020). A prospective study in a British population birth cohort (n = 2528) found a positive association between higher IL-6 serum levels in children at age 9 years and subsequent psychotic experiences (operationally defined, including both psychotic experiences and those with a psychotic disorder) at age 18 years (n = 101) (Khandaker et al., 2014). For each standard deviation increase in IL-6 level, the odds ratio for psychotic experiences was 1.24, thereby demonstrating a longitudinal association between a circulating pro-inflammatory marker in childhood and future risk of psychosis in a dose-dependent manner (Khandaker et al., 2014). In yet another prospective birth cohort study (n = 6362), the authors found a positive relationship between higher CRP levels in adolescents at age 15−16 years and subsequent risk of schizophrenia at follow-up until age 27 years (n = 22). They described an adjusted odds ratio of 1.25 for schizophrenia by age 27 years for each standard deviation increase in CRP levels at age 15−16 years, consistent with a linear, dose-response relationship (Metcalf et al., 2017). They also found that higher adolescent CRP levels were correlated with earlier age of onset (Spearman's r = −0.40).

Predictive value of immune-inflammatory markers in individuals with clinical high risk for psychosis

Several studies have reported altered inflammatory profiles in individuals at clinical high risk for psychosis (CHR). A review of 15 studies on inflammatory markers in samples with CHR found that plasma levels of cortisol, IL-1β, IL-7, IL-8 and matrix metalloproteinase (MMP)-8 are promising predictors of psychotic transition in the CHR group (Khoury & Nasrallah, 2018). In the same review, baseline CRP and IL-6 were not shown to discriminate between converters and nonconverters to psychosis. However, due to small sample sizes, lack of adequate design in the longitudinal studies, and heterogeneity in the duration of follow-up and statistical methods to detect discriminatory biomarkers, the authors concluded that more studies are needed (Khoury & Nasrallah, 2018). Moreover, in the North American Prodrome Longitudinal Study, the researchers found a positive relationship between the pro-inflammatory cytokine TNF and

the longitudinal 12 months-course of negative symptoms (Goldsmith et al., 2019). In contrast, higher baseline levels of cytokine IL-6 predicted a greater decrease in negative symptoms over time in the same group (Goldsmith et al., 2019). A recent meta-analysis also reported higher levels of IL-6 in individuals with CHR compared to healthy controls, but not in those with familial high-risk only, suggesting that familial liability to psychosis is not associated with subclinical inflammation (Misiak et al., 2021). Importantly, the authors concluded that based on existing data they could not find evidence that single immune-inflammatory markers can be used to predict transition to psychosis in individuals at CHR. However, results from studies combining peripheral immune markers and MRI data in groups with CHR have suggested that immune system signaling may have a role in the differential brain tissue loss between people who convert and not convert to psychosis. Cannon et al. (2015) reported that higher levels of an aggregate measure of plasma pro-inflammatory cytokines (such as TNF-α, IL-2, INF-γ) at baseline significantly correlated with a steeper rate of gray matter volume reduction in right prefrontal cortex among individuals who converted to psychosis. Given that pro-inflammatory cytokines can activate microglia into the M1 cytotoxic phenotype that result in increased synaptic pruning, this finding suggests a hypothesis of a mechanistic link between immune activation and progressive gray matter loss. However, the field needs studies examining more direct indicators of in-vivo CNS microglial activity in individuals with CHR to test this hypothesis.

Immune-inflammatory markers in adolescents with early-onset psychosis

Few studies have explored peripheral inflammatory markers in adolescents with EOP, and due to the rarity of these disorders, the sample sizes are frequently small, rendering the analyses vulnerable to false negative statistical errors. A recent review had to refrain from making a meta-analysis of inflammatory markers in adolescents with EOP due to insufficient data (Fraguas et al., 2017). However, there are single studies suggesting immune system dysregulation in patients with EOP, although conflicting reports also exist.

Falcone et al. (2015) found increased levels of monocytes in patients with EOP ($n = 28$) compared to inpatient controls without psychosis ($n = 66$). Moreover, the patients with EOP displayed elevated levels of several immune-inflammatory markers (TNF-α, IL-1β, IL-6, IL-5, IL-10, IFN-γ, and S100 B) compared to healthy controls ($n = 8$) (Falcone et al., 2015). While higher levels of the astrocyte-specific, circulating S100B point to blood−brain barrier impairment in youth with EOP, the explored cytokine levels suggest a pro-inflammatory profile. In line, our group found elevated peripheral levels of the pro-inflammatory cytokine IL-18 in patients with EOP ($n = 31$) compared to healthy controls ($n = 68$) (Wedervang-Resell, Friis, et al., 2020). Higher activity in the IL-18 system was also demonstrated, as derived from the IL-18/

IL-18BP-ratio, which reflects the biologically active proportion (unbound free IL-18) (Wedervang-Resell, Friis, et al., 2020). In contrast, a transcriptome expression profile of peripheral blood mononuclear cells from adolescents with EOP (n = 14) showed increased expression of IL-18 mRNA, but a greater decrease in IL-18R1 mRNA, suggesting reduced overall IL-18 signaling among patients with EOP (Xu et al., 2016).

Contradictory results have also been reported in a previous study of antipsychotic naïve patients with EOP aged 10−17 years (n = 30) (Simşek et al., 2016). The authors found no differences between patients and healthy controls concerning levels of Th1 helper T cell cytokines (TNF-α, IFN-γ, IL-2), Th2 cytokines (IL-4 and IL-10), Th17 cytokine IL-17A, and the pro-inflammatory IL-6. However, the authors did find large significant correlations between levels of IL-4 and IL-10 and levels of negative symptoms, as well as a significant negative correlation between disease severity and TNF-α levels (Simşek et al., 2016). Moreno et al. (2019) found that adolescents with EOP exhibited a higher pro-inflammatory status than adults with a first-episode psychotic disorder, by comparing differences in trajectories of pro-/anti-inflammatory balance in plasma and peripheral blood mononuclear cells between the groups. Compared to the adult patients, the adolescents with EOP had higher levels of NF-κβ, a master regulator of the inflammatory and oxidative status of cells. This was present both at baseline and at 6-month follow-up, without upregulation of compensatory antiinflammatory responses. Given that activation of NF-κβ might contribute to higher oxidative stress and cell damage by membrane lipid peroxidation, as well as influence cell survival, neuroprotection, neuronal transmission, and plasticity, this may confer risk for developing psychosis (Moreno et al., 2019). In adolescents with early-onset bipolar disorder (n = 18), a pattern of increased activation of spontaneous levels of NF-κβ in their peripheral blood mononuclear cells, and within the monocyte and lymphocyte subpopulations, occurred after stimulation, compared to healthy controls (Miklowitz et al., 2016). Moreover, IL-1β levels were elevated in the patient group, but not levels of IL-6, IL-8, TNF-α.

Although the presented results focus on patients with EOP, immune system dysregulation is not specific to adolescents with psychotic disorders. A previous review suggests that elevated peripheral inflammatory markers (e.g., IL-1β and IL-6) are common across youth populations (n = 3952) with a broad spectrum of neuropsychiatric disorders (Mitchell & Goldstein, 2014), underscoring the overlap of environmental and genetic susceptibility risk factors across diagnostic categories. A recent study including child and adolescent inpatients across various acute psychiatric conditions requiring hospitalization (n = 77, of which 30 with EOP), found that IL-1β, IL-6, IL-8, INF-γ-induced protein-10, MCP-1 and monocyte count were elevated across all diagnoses in the total sample and the diagnostic subgroups compared to healthy controls (Gariup et al., 2015).

Relationships between immune-inflammatory markers and clinical phenotypes in individuals with early-onset psychosis

Simşek et al. (2016) found that a higher level of negative psychotic symptoms were associated with lower levels of IL-10 and higher levels of IL-4 in patients with EOP (n = 30). These are pleiotropic antiinflammatory cytokines that function mainly by suppressing a pro-inflammatory milieu. Interestingly, in a study of adult patients with chronic schizophrenia (n = 210), lower levels of IL-4 were found to discriminate between those with an early-onset (n = 84) and adult-onset schizophrenia (n = 126), and was also significantly correlated with the presence of neurological soft signs in the early-onset group (Liu et al., 2020).

Gariup and colleagues explored relationships between pro-inflammatory markers and psychological stress, measured by self- and parent-rating questionnaires. They found significant correlations between subjective and parent-rated psychosocial stress and elevations in pro-inflammatory markers (IL-1β, IL-8, MCP-1, and monocyte counts) in young patients (n = 77) across several acute psychiatric disorders, including psychosis (n = 30) (Gariup et al., 2015). In line with this, our group found that levels of serum cortisol independently contributed to explain the variance of IL-18 system activity in adolescents with EOP (n = 31). We found a strong significant correlation between cortisol and IL-18 activity among the patients but not the healthy controls, suggesting an interaction between stress and IL-18 system activity in patients with EOP (Wedervang-Resell, Friis, et al., 2020).

Together these results suggest two hypotheses that should be further explored in future studies of patients with EOP. First, the relationship between aberrant levels of cytokine IL-4 and negative symptoms and neurological soft signs may point to an imbalance in pro- and anti-inflammatory cytokines in these patients, with consequences for neurodevelopment and psychosis risk. Notably, IL-4 has anti-inflammatory and immune regulatory properties and has been shown to be neuroprotective and secure better cognitive outcomes in both rodent experimental studies and in children (Jiang et al., 2018). Second, the relationship found between higher levels of stress markers (cortisol and psychological stress) and pro-inflammatory immune activation in adolescents with EOP also warrants further scrutiny.

Scientific implications

The immune dysregulation seen in psychotic disorders is manifold and partly overlapping, involving different immune components. It is to note that the observed heterogeneity between studies might suggest heterogeneity in the etiology and pathogenesis of the schizophrenia syndrome (Khandaker et al., 2015). Shifting the focus of investigations from syndrome to symptoms might be beneficial to fully understand the potential role of immune mechanisms in psychosis. The focus of the current studies has mostly been

polarized toward blood rather than brain/CNS immune markers, and only a fraction of investigations has examined associations between cognition or symptom characteristics and immune markers in patients with schizophrenia (Hope et al., 2013; Khandaker et al., 2015; O'Connell et al., 2021). Furthermore, studies on stress, neuroendocrine hormone levels, and immune marker associations are also rare, and the underlying mechanisms are not yet fully understood. Nevertheless, despite these gaps in current knowledge, there is a consensus regarding the importance of immune system mechanisms in the development of psychosis that is supported by both preclinical and clinical data.

However, clinical reports of immune-inflammatory changes in youth with EOP are still warranted, as studies in this group are scarce. At the same time, specific mechanisms linking immune system dysregulation to altered neurodevelopment and the emergence of psychotic symptoms/disorders remain largely undetermined. Therefore, to develop experimental models exploring these factors will be key to understanding underlying mechanisms. Immunopsychiatry is a new and emerging field with important implications in a broader biomedical, translational, and therapeutic context. Indeed, if immune system dysregulation can be established as a major contributor to the development of psychosis in youth, it is expected that novel therapeutics directed against decreasing inflammation or regulating immune system homeostasis will be beneficial. Maybe even more than in adult groups, as there are indications that young patients with EOP feature a greater immune imbalance than adults (Moreno et al., 2019). As such, randomized controlled trials of agents targeting immune-inflammatory imbalance in EOP, such as add-on antiinflammatory drugs, antioxidants, immunosuppressants, or specific cytokine-receptor antagonists, would be most valuable.

Clinical implications

The peripheral pro-inflammatory dysregulation that has been described in patients with EOP exerts negative effects on the cardiovascular system and development of atherosclerosis (Bohman et al., 2020), making this group especially vulnerable to long-term risk of future cardiovascular disease (Szabo et al., 2022). In addition, most patients with EOP will receive antipsychotic medication with metabolic side effects and are also susceptible to develop an unhealthy lifestyle, which together further increase cardiovascular disease risk. Hence, in clinical practice attention to reducible cardiovascular disease risk factors such as smoking, obesity, sedentary lifestyle, and poor dietary choices should be part of the treatment plan for patients with EOP.

References

Akkouh, I. A., Ueland, T., Hansson, L., Inderhaug, E., Hughes, T., Steen, N. E., Aukrust, P., Andreassen, O. A., Szabo, A., & Djurovic, S. (2020). Decreased IL-1β-induced CCL20 response in human iPSC-astrocytes in schizophrenia: Potential attenuating effects on recruitment of regulatory T cells. *Brain, Behavior, and Immunity, 87*, 634−644. https://doi.org/10.1016/j.bbi.2020.02.008

Allswede, D. M., Yolken, R. H., Buka, S. L., & Cannon, T. D. (2020). Cytokine concentrations throughout pregnancy and risk for psychosis in adult offspring: A longitudinal case-control study. *The Lancet Psychiatry, 7*(3), 254−261. https://doi.org/10.1016/S2215-0366(20)30006-7

Andersson, U., & Tracey, K. J. (2012). Reflex principles of immunological homeostasis. *Annual Review of Immunology, 30*, 313−335. https://doi.org/10.1146/annurev-immunol-020711-075015

Banks, W. A., Kastin, A. J., & Broadwell, R. D. (1995). Passage of cytokines across the blood-brain barrier. *Neuro immunomodulation, 2*(4), 241−248. https://doi.org/10.1159/000097202

Bauer, M. E., Wieck, A., Lopes, R. P., Teixeira, A. L., & Grassi-Oliveira, R. (2010). Interplay between neuroimmunoendocrine systems during post-traumatic stress disorder: A minireview. *Neuroimmunomodulation, 17*(3), 192−195. https://doi.org/10.1159/000258721

Bechter, K., Reiber, H., Herzog, S., Fuchs, D., Tumani, H., & Maxeiner, H. G. (2010). Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: Identification of subgroups with immune responses and blood-CSF barrier dysfunction. *Journal of Psychiatric Research, 44*(5), 321−330. https://doi.org/10.1016/j.jpsychires.2009.08.008

Benros, M. E., Nielsen, P. R., Nordentoft, M., Eaton, W. W., Dalton, S. O., & Mortensen, P. B. (2011). Autoimmune diseases and severe infections as risk factors for schizophrenia: A 30-year population-based register study. *American Journal of Psychiatry, 168*(12), 1303−1310. https://doi.org/10.1176/appi.ajp.2011.11030516

van Berckel, B. N., Bossong, M. G., Boellaard, R., Kloet, R., Schuitemaker, A., Caspers, E., Luurtsema, G., Windhorst, A. D., Cahn, W., Lammertsma, A. A., & Kahn, R. S. (2008). Microglia activation in recent-onset schizophrenia: A quantitative (R)-[11C]PK11195 positron emission tomography study. *Biological Psychiatry, 64*(9), 820−822. https://doi.org/10.1016/j.biopsych.2008.04.025

Bilbo, S. D. (2011). How cytokines leave their mark: The role of the placenta in developmental programming of brain and behavior. *Brain, Behavior, and Immunity, 25*(4), 602−603. https://doi.org/10.1016/j.bbi.2011.01.018

Bilbo, S. D., & Schwarz, J. M. (2009). Early-life programming of later-life brain and behavior: A critical role for the immune system. *Frontiers in Behavioral Neuroscience, 3*. https://doi.org/10.3389/neuro.08.014.2009

Bilbo, S. D., & Schwarz, J. M. (2012). The immune system and developmental programming of brain and behavior. *Frontiers in Neuroendocrinology, 33*(3), 267−286. https://doi.org/10.1016/j.yfrne.2012.08.006

Bohman, H., Agartz, I., Mansouri, S., Naessen, T., & Lundberg, M. (2020). Preclinical atherosclerosis in adolescents with psychotic or bipolar disorders investigated with carotid high-frequency ultrasound. *Brain and Behavior, 10*(12). https://doi.org/10.1002/brb3.1862

Borovcanin, M. M., Jovanovic, I., Radosavljevic, G., Pantic, J., Janicijevic, S. M., Arsenijevic, N., & Lukic, M. L. (2017). Interleukin-6 in schizophrenia-is there a therapeutic relevance? *Frontiers in Psychiatry, 8*. https://doi.org/10.3389/fpsyt.2017.00221

Brennand, K. J., Simone, A., Jou, J., Gelboin-Burkhart, C., Tran, N., Sangar, S., Li, Y., Mu, Y., Chen, G., Yu, D., McCarthy, S., Sebat, J., & Gage, F. H. (2011). Modelling schizophrenia

using human induced pluripotent stem cells. *Nature, 473*(7346), 221–225. https://doi.org/10.1038/nature09915

Brown, A. S., & Derkits, E. J. (2010). Prenatal infection and schizophrenia: A review of epidemiologic and translational studies. *American Journal of Psychiatry, 167*(3), 261–280. https://doi.org/10.1176/appi.ajp.2009.09030361

Brown, A. S., & Patterson, P. H. (2011). Maternal infection and schizophrenia: Implications for prevention. *Schizophrenia Bulletin, 37*(2), 284–290. https://doi.org/10.1093/schbul/sbq146

Cannon, T. D., Chung, Y., He, G., Sun, D., Jacobson, A., Van Erp, T. G. M., McEwen, S., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D. H., McGlashan, T., Perkins, D., Jeffries, C., Seidman, L. J., Tsuang, M., Walker, E., Woods, S. W., & Heinssen, R. (2015). Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biological Psychiatry, 77*(2), 147–157. https://doi.org/10.1016/j.biopsych.2014.05.023

Comer, A. L., Carrier, M., Tremblay, M.È., & Cruz-Martín, A. (2020). The inflamed brain in schizophrenia: The convergence of genetic and environmental risk factors that lead to uncontrolled neuroinflammation. *Frontiers in Cellular Neuroscience, 14*. https://doi.org/10.3389/fncel.2020.00274

Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity, 21*(2), 153–160. https://doi.org/10.1016/j.bbi.2006.09.006

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience, 9*(1), 46–56. https://doi.org/10.1038/nrn2297

Daruna, J. H. (2012). *Introduction to psychoneuroimmunology* (2nd ed.). Elsevier Academic Press. https://doi.org/10.1016/B978-0-12-382049-5.00002-4

Deverman, B. E., & Patterson, P. H. (2009). Cytokines and CNS development. *Neuron, 64*(1), 61–78. https://doi.org/10.1016/j.neuron.2009.09.002

Dietz, A. G., Goldman, S. A., & Nedergaard, M. (2020). Glial cells in schizophrenia: A unified hypothesis. *The Lancet Psychiatry, 7*(3), 272–281. https://doi.org/10.1016/S2215-0366(19)30302-5

Doorduin, J., De Vries, E. F. J., Willemsen, A. T. M., De Groot, J. C., Dierckx, R. A., & Klein, H. C. (2009). Neuroinflammation in schizophrenia-related psychosis: A PET study. *Journal of Nuclear Medicine, 50*(11), 1801–1807. https://doi.org/10.2967/jnumed.109.066647

Doria, A., Dayer, J. M., & Punzi, L. (2012). Autoinflammatory diseases: How to put the fire inside the body out? *Autoimmunity Reviews, 12*(1), 1–4. https://doi.org/10.1016/j.autrev.2012.07.013

Doria, A., Zen, M., Bettio, S., Gatto, M., Bassi, N., Nalotto, L., Ghirardello, A., Iaccarino, L., & Punzi, L. (2012). Autoinflammation and autoimmunity: Bridging the divide. *Autoimmunity Reviews, 12*(1), 22–30. https://doi.org/10.1016/j.autrev.2012.07.018

Estes, M. L., & McAllister, A. K. (2016). Maternal immune activation: Implications for neuropsychiatric disorders. *Science, 353*(6301), 772–777. https://doi.org/10.1126/science.aag3194

Falcone, T., Carlton, E., Lee, C., Janigro, M., Fazio, V., Forcen, F. E., Franco, K., & Janigro, D. (2015). Does systemic inflammation play a role in pediatric psychosis? *Clinical Schizophrenia and Related Psychoses, 9*(2), 65–78. https://doi.org/10.3371/CSRP.FACA.030813

Fatemi, S. H., & Folsom, T. D. (2009). The neurodevelopmental hypothesis of Schizophrenia, revisited. *Schizophrenia Bulletin, 35*(3), 528–548. https://doi.org/10.1093/schbul/sbn187

Fraguas, D., Díaz-Caneja, C. M., Rodríguez-Quiroga, A., & Arango, C. (2017). Oxidative stress and inflammation in early onset first episode psychosis: A systematic review and meta-

analysis. *International Journal of Neuropsychopharmacology, 20*(6), 435−444. https://doi.org/10.1093/ijnp/pyx015

Fruntes, V., & Limosin, F. (2008). Schizophrenia and viral infection during neurodevelopment: A pathogenesis model? *Medical Science Monitor, 14*(6), RA71−RA77. http://www.medscimonit.com/fulltxt.php?ICID=859025.

Ganguli, R., Brar, J. S., Roy Chengappa, K. N., Yang, Z. W., Nimgaonkar, V. L., & Rabin, B. S. (1993). Autoimmunity in schizophrenia: A review of recent findings. *Annals of Medicine, 25*(5), 489−496. https://doi.org/10.3109/07853899309147317

Gariup, M., Gonzalez, A., Lázaro, L., Torres, F., Serra-Pagès, C., & Morer, A. (2015). IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology. *Psychoneuroendocrinology, 62*, 233−242. https://doi.org/10.1016/j.psyneuen.2015.08.017

Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., Mehler, M. F., Conway, S. J., Ng, L. G., Stanley, E. R., Samokhvalov, I. M., & Merad, M. (2010). Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science, 330*(6005), 841−845. https://doi.org/10.1126/science.1194637

Goldsmith, D. R., Haroon, E., Miller, A. H., Addington, J., Bearden, C., Cadenhead, K., Cannon, T., Cornblatt, B., Mathalon, D., McGlashan, T., Seidman, L., Tsuang, M., Woods, S. W., Walker, E. F., & Perkins, D. O. (2019). Association of baseline inflammatory markers and the development of negative symptoms in individuals at clinical high risk for psychosis. *Brain, Behavior, and Immunity, 76*, 268−274. https://doi.org/10.1016/j.bbi.2018.11.315

Hanisch, U. K., & Kettenmann, H. (2007). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience, 10*(11), 1387−1394. https://doi.org/10.1038/nn1997

Han, V. X., Patel, S., Jones, H. F., & Dale, R. C. (2021). Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. *Nature Reviews Neurology, 17*(9), 564−579. https://doi.org/10.1038/s41582-021-00530-8

Hoeffel, G., Chen, J., Lavin, Y., Low, D., Almeida, F. F., See, P., Beaudin, A. E., Lum, J., Low, I., Forsberg, E. C., Poidinger, M., Zolezzi, F., Larbi, A., Ng, L. G., Chan, J. K. Y., Greter, M., Becher, B., Samokhvalov, I. M., Merad, M., & Ginhoux, F. (2015). C-Myb+ erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. *Immunity, 42*(4), 665−678. https://doi.org/10.1016/j.immuni.2015.03.011

Hope, S., Ueland, T., Steen, N. E., Dieset, I., Lorentzen, S., Berg, A. O., Agartz, I., Aukrust, P., & Andreassen, O. A. (2013). Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. *Schizophrenia Research, 145*(1−3), 36−42. https://doi.org/10.1016/j.schres.2012.12.023

Hopkins, S. J., & Rothwell, N. J. (1995). Cytokines and the nervous system I: Expression and recognition. *Trends in Neurosciences, 18*(2), 83−88. https://doi.org/10.1016/0166-2236(95)80029-2

Hornig, M., Bresnahan, M. A., Che, X., Schultz, A. F., Ukaigwe, J. E., Eddy, M. L., Hirtz, D., Gunnes, N., Lie, K. K., Magnus, P., Mjaaland, S., Reichborn-Kjennerud, T., Schjølberg, S., Øyen, A. S., Levin, B., Susser, E. S., Stoltenberg, C., & Lipkin, W. I. (2018). Prenatal fever and autism risk. *Molecular Psychiatry, 23*(3), 759−766. https://doi.org/10.1038/mp.2017.119

Iwata, M., Ota, K. T., Li, X. Y., Sakaue, F., Li, N., Dutheil, S., Banasr, M., Duric, V., Yamanashi, T., Kaneko, K., Rasmussen, K., Glasebrook, A., Koester, A., Song, D., Jones, K. A., Zorn, S., Smagin, G., & Duman, R. S. (2016). Psychological stress activates the inflammasome via release of adenosine triphosphate and stimulation of the purinergic type

2X7 receptor. *Biological Psychiatry, 80*(1), 12–22. https://doi.org/10.1016/j.biopsych.2015.11.026

Jiang, N. M., Cowan, M., Moonah, S. N., & Petri, W. A. (2018). The impact of systemic inflammation on neurodevelopment. *Trends in Molecular Medicine, 24*(9), 794–804. https://doi.org/10.1016/j.molmed.2018.06.008

Jiang, H. Y., Xu, L. L., Shao, L., Xia, R. M., Yu, Z. H., Ling, Z. X., Yang, F., Deng, M., & Ruan, B. (2016). Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. *Brain, Behavior, and Immunity, 58*, 165–172. https://doi.org/10.1016/j.bbi.2016.06.005

Kalish, B. T., Kim, E., Finander, B., Duffy, E. E., Kim, H., Gilman, C. K., Yim, Y. S., Tong, L., Kaufman, R. J., Griffith, E. C., Choi, G. B., Greenberg, M. E., & Huh, J. R. (2021). Maternal immune activation in mice disrupts proteostasis in the fetal brain. *Nature Neuroscience, 24*(2), 204–213. https://doi.org/10.1038/s41593-020-00762-9

Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. *The Lancet Psychiatry, 2*(3), 258–270. https://doi.org/10.1016/S2215-0366(14)00122-9

Khandaker, G. M., Dalman, C., Kappelmann, N., Stochl, J., Dal, H., Kosidou, K., Jones, P. B., & Karlsson, H. (2018). Association of childhood infection with IQ and adult nonaffective psychosis in Swedish men a population-based longitudinal cohort and co-relative study. *JAMA Psychiatry, 75*(4), 356–362. https://doi.org/10.1001/jamapsychiatry.2017.4491

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life a population-based longitudinal study. *JAMA Psychiatry, 71*(10), 1121–1128. https://doi.org/10.1001/jamapsychiatry.2014.1332

Khoury, R., & Nasrallah, H. A. (2018). Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): State or trait? *Schizophrenia Research, 199*, 31–38. https://doi.org/10.1016/j.schres.2018.04.017

Kroken, R. A., Sommer, I. E., Steen, V. M., Dieset, I., & Johnsen, E. (2019). Constructing the immune signature of schizophrenia for clinical use and research; an integrative review translating descriptives into diagnostics. *Frontiers in Psychiatry, 10*. https://doi.org/10.3389/fpsyt.2018.00753

Kubota, T., Kushikata, T., Fang, J., & Krueger, J. M. (2000). Nuclear factor-kappaB inhibitor peptide inhibits spontaneous and interleukin-1beta-induced sleep. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology, 279*(2), 404–413.

Latz, E., Xiao, T. S., & Stutz, A. (2013). Activation and regulation of the inflammasomes. *Nature Reviews Immunology, 13*(6), 397–411. https://doi.org/10.1038/nri3452

Lenz, K. M., & Nelson, L. H. (2018). Microglia and beyond: Innate immune cells as regulators of brain development and behavioral function. *Frontiers in Immunology, 9*. https://doi.org/10.3389/fimmu.2018.00698

Liu, J. Y., Chen, H. Y., Lin, J. J., Lu, M. K., Tan, H. P., Jang, F. L., & Lin, S. H. (2020). Alterations of plasma cytokine biomarkers for identifying age at onset of schizophrenia with neurological soft signs. *International Journal of Medical Sciences, 17*(2), 255–262. https://doi.org/10.7150/ijms.38891

Metcalf, S. A., Jones, P. B., Nordstrom, T., Timonen, M., Mäki, P., Miettunen, J., Jääskeläinen, E., Järvelin, M. R., Stochl, J., Murray, G. K., Veijola, J., & Khandaker, G. M. (2017). Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study. *Brain, Behavior, and Immunity, 59*, 253–259. https://doi.org/10.1016/j.bbi.2016.09.008

Meyer, U. (2014). Prenatal Poly(I:C) exposure and other developmental immune activation models in rodent systems. *Biological Psychiatry, 75*(4), 307−315. https://doi.org/10.1016/j.biopsych.2013.07.011

Meyer, U., Feldon, J., Schedlowski, M., & Yee, B. K. (2005). Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. *Neuroscience and Biobehavioral Reviews, 29*(6), 913−947. https://doi.org/10.1016/j.neubiorev.2004.10.012

Miklowitz, D. J., Portnoff, L. C., Armstrong, C. C., Keenan-Miller, D., Breen, E. C., Muscatell, K. A., Eisenberger, N. I., & Irwin, M. R. (2016). Inflammatory cytokines and nuclear factor-kappa B activation in adolescents with bipolar and major depressive disorders. *Psychiatry Research, 241*, 315−322. https://doi.org/10.1016/j.psychres.2016.04.120

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry, 70*(7), 663−671. https://doi.org/10.1016/j.biopsych.2011.04.013

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732−741. https://doi.org/10.1016/j.biopsych.2008.11.029

Misiak, B., Bartoli, F., Carrà, G., Stańczykiewicz, B., Gładka, A., Frydecka, D., Samochowiec, J., Jarosz, K., Hadryś, T., & Miller, B. J. (2021). Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis. *Psychoneuroendocrinology, 127*, 105200. https://doi.org/10.1016/j.psyneuen.2021.105200

Mitchell, R. H. B., & Goldstein, B. I. (2014). Inflammation in children and adolescents with neuropsychiatric disorders: A systematic review. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(3), 274−296. https://doi.org/10.1016/j.jaac.2013.11.013

Miyaoka, T., Wake, R., Hashioka, S., Hayashida, M., Oh-Nishi, A., Azis, I. A., Izuhara, M., Tsuchie, K., Araki, T., Arauchi, R., Abdullah, R. A., & Horiguchi, J. (2017). Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: A case report. *Frontiers in Psychiatry, 8*. https://doi.org/10.3389/fpsyt.2017.00174

Moreno, C., Parellada, M., MacDowell, K. S., García-Bueno, B., Cabrera, B., González-Pinto, A., Saiz, P., Lobo, A., Rodriguez-Jimenez, R., Berrocoso, E., Bernardo, M., & Leza, J. C. (2019). Differences in the regulation of inflammatory pathways in adolescent- and adult-onset first-episode psychosis. *European Child and Adolescent Psychiatry, 28*(10), 1395−1405. https://doi.org/10.1007/s00787-019-01295-8

Müller, N., & Ackenheil, M. (1998). Psychoneuroimmunology and the cytokine action in the CNS: Implications for psychiatric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 22*(1), 1−33. https://doi.org/10.1016/S0278-5846(97)00179-6

Müller, N., & Schwarz, M. J. (2010). The role of immune system in schizophrenia. *Current Immunology Reviews, 6*(3), 213−220. https://doi.org/10.2174/157339510791823673

Nawa, H., & Takei, N. (2006). Recent progress in animal modeling of immune inflammatory processes in schizophrenia: Implication of specific cytokines. *Neuroscience Research, 56*(1), 2−13. https://doi.org/10.1016/j.neures.2006.06.002

O'Connell, K. S., Sønderby, I. E., Frei, O., Van Der Meer, D., Athanasiu, L., Smeland, O. B., Alnæs, D., Kaufmann, T., Westlye, L. T., Steen, V. M., Andreassen, O. A., Hughes, T., & Djurovic, S. (2021). Association between complement component 4A expression, cognitive performance and brain imaging measures in UK Biobank. *Psychological Medicine*. https://doi.org/10.1017/S0033291721000179

Pace, T. W. W., & Heim, C. M. (2011). A short review on the psychoneuroimmunology of posttraumatic stress disorder: From risk factors to medical comorbidities. *Brain, Behavior, and Immunity, 25*(1), 6−13. https://doi.org/10.1016/j.bbi.2010.10.003

Pariante, C. M. (2015). Psychoneuroimmunology or immunopsychiatry? *The Lancet Psychiatry, 2*(3), 197−199. https://doi.org/10.1016/S2215-0366(15)00042-5

Pearce, B. D. (2001). Schizophrenia and viral infection during neurodevelopment: A focus on mechanisms. *Molecular Psychiatry, 6*(6), 634−646. https://doi.org/10.1038/sj.mp.4000956

Perry, V. H., Nicoll, J. A. R., & Holmes, C. (2010). Microglia in neurodegenerative disease. *Nature Reviews Neurology, 6*(4), 193−201. https://doi.org/10.1038/nrneurol.2010.17

Potvin, S., Stip, E., Sepehry, A. A., Gendron, A., Bah, R., & Kouassi, E. (2008). Inflammatory cytokine alterations in schizophrenia: A systematic quantitative review. *Biological Psychiatry, 63*(8), 801−808. https://doi.org/10.1016/j.biopsych.2007.09.024

Ransohoff, R. M., & Perry, V. H. (2009). Microglial physiology: Unique stimuli, specialized responses. *Annual Review of Immunology, 27*, 119−145. https://doi.org/10.1146/annurev.immunol.021908.132528

Rathinam, V. A. K., & Fitzgerald, K. A. (2016). Inflammasome complexes: Emerging mechanisms and effector functions. *Cell, 165*(4), 792−800. https://doi.org/10.1016/j.cell.2016.03.046

Rathinam, V. A. K., Vanaja, S. K., & Fitzgerald, K. A. (2012). Regulation of inflammasome signaling. *Nature Immunology, 13*(4), 333−342. https://doi.org/10.1038/ni.2237

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollmächer, T. (2001). Cytokine-associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry, 58*(5), 445−452. https://doi.org/10.1001/archpsyc.58.5.445

Riera Romo, M., Pérez-Martínez, D., & Castillo Ferrer, C. (2016). Innate immunity in vertebrates: An overview. *Immunology, 148*(2), 125−139. https://doi.org/10.1111/imm.12597

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Belliveau, R. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421−427. https://doi.org/10.1038/nature13595

Rostène, W., Guyon, A., Kular, L., Godefroy, D., Barbieri, F., Bajetto, A., Banisadr, G., Callewaere, C., Conductier, G., Rovère, C., Mélik-Parsadaniantz, S., & Florio, T. (2011). Chemokines and chemokine receptors: New actors in neuroendocrine regulations. *Frontiers in Neuroendocrinology, 32*(1), 10−24. https://doi.org/10.1016/j.yfrne.2010.07.001

Rothwell, N. J., & Hopkins, S. J. (1995). Cytokines and the nervous system II: Actions and mechanisms of action. *Trends in Neurosciences, 18*(3), 130−136. https://doi.org/10.1016/0166-2236(95)93890-A

Schroder, K., Sweet, M. J., & Hume, D. A. (2006). Signal integration between IFNγ and TLR signalling pathways in macrophages. *Immunobiology, 211*(6−8), 511−524. https://doi.org/10.1016/j.imbio.2006.05.007

Sekar, A., Bialas, A. R., De Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S. A., Handsaker, R. E., Daly, M. J., Carroll, M. C., Stevens, B., & McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature, 530*(7589), 177−183. https://doi.org/10.1038/nature16549

Sellgren, C. M., Gracias, J., Jungholm, O., Perlis, R. H., Engberg, G., Schwieler, L., Landen, M., & Erhardt, S. (2019). Peripheral and central levels of kynurenic acid in bipolar disorder subjects and healthy controls. *Translational Psychiatry, 9*(1). https://doi.org/10.1038/s41398-019-0378-9

Sellgren, C. M., Gracias, J., Watmuff, B., Biag, J. D., Thanos, J. M., Whittredge, P. B., Fu, T., Worringer, K., Brown, H. E., Wang, J., Kaykas, A., Karmacharya, R., Goold, C. P., Sheridan, S. D., & Perlis, R. H. (2019). Increased synapse elimination by microglia in

schizophrenia patient-derived models of synaptic pruning. *Nature Neuroscience, 22*(3), 374−385. https://doi.org/10.1038/s41593-018-0334-7

Sellgren, C. M., Imbeault, S., Larsson, M. K., Oliveros, A., Nilsson, I. A. K., Codeluppi, S., Orhan, F., Bhat, M., Tufvesson-Alm, M., Gracias, J., Kegel, M. E., Zheng, Y., Faka, A., Svedberg, M., Powell, S. B., Caldwell, S., Kamenski, M. E., Vawter, M. P., Schulmann, A., … Erhardt, S. (2021). GRK3 deficiency elicits brain immune activation and psychosis. *Molecular Psychiatry, 26*(11), 6820−6832. https://doi.org/10.1038/s41380-021-01106-0

Severance, E. G., & Yolken, R. H. (2016). Role of immune and autoimmune dysfunction in schizophrenia. In *Handbook of behavioral neuroscience* (Vol 23, pp. 501−516). Elsevier B.V. https://doi.org/10.1016/B978-0-12-800981-9.00029-8

Sheng, J., Ruedl, C., & Karjalainen, K. (2015). Most tissue-resident macrophages except microglia are derived from fetal hematopoietic stem cells. *Immunity, 43*(2), 382−393. https://doi.org/10.1016/j.immuni.2015.07.016

Shi, L., Smith, S. E. P., Malkova, N., Tse, D., Su, Y., & Patterson, P. H. (2009). Activation of the maternal immune system alters cerebellar development in the offspring. *Brain, Behavior, and Immunity, 23*(1), 116−123. https://doi.org/10.1016/j.bbi.2008.07.012

Simşek, S., Yıldırım, V., Çim, A., & Kaya, S. (2016). Serum IL-4 and IL-10 levels correlate with the symptoms of the drug-naive adolescents with first episode, early onset schizophrenia. *Journal of Child and Adolescent Psychopharmacology, 26*(8), 721−726. https://doi.org/10.1089/cap.2015.0220

Sonnenberg, G. F., & Hepworth, M. R. (2019). Functional interactions between innate lymphoid cells and adaptive immunity. *Nature Reviews Immunology, 19*(10), 599−613. https://doi.org/10.1038/s41577-019-0194-8

Szabo, A., O'Connell, K. S., Ueland, T., Sheikh, M. A., Agartz, I., Andreou, D., Aukrust, P., Boye, B., Bøen, E., Drange, O. K., Elvsåshagen, T., Engh, J. A., Hope, S., Collier Høegh, M., Joa, I., Johnsen, E., Kroken, R. A., Vik Lagerberg, T., Lekva, T., … Djurovic, S. (2022). Increased circulating IL-18 levels in severe mental disorders indicate systemic inflammasome activation. *Brain, Behavior, and Immunity, 99*, 299−306. https://doi.org/10.1016/j.bbi.2021.10.017

Szabo, A., & Rajnavolgyi, E. (2013a). Collaboration of toll-like and RIG-I-like receptors in human dendritic cells: tRIGgering antiviral innate immune responses. *Am J Clin Exp Immunol, 2*(3), 195−207.

Szabo, A., & Rajnavolgyi, E. (2013b). The brain-immune-gut triangle: Innate immunity in psychiatric and neurological disorders. *Current Immunology Reviews, 9*(4), 241−248. https://doi.org/10.2174/15733955096661312032256 59

Thaiss, C. A., Zmora, N., Levy, M., & Elinav, E. (2016). The microbiome and innate immunity. *Nature, 535*(7610), 65−74. https://doi.org/10.1038/nature18847

Upthegrove, R., Manzanares-Teson, N., & Barnes, N. M. (2014). Cytokine function in medication-naive first episode psychosis: A systematic review and meta-analysis. *Schizophrenia Research, 155*(1−3), 101−108. https://doi.org/10.1016/j.schres.2014.03.005

Vitkovic, L., Bockaert, J., & Jacque, C. (2000). "Inflammatory" cytokines' neuromodulators in normal brain? *Journal of Neurochemistry, 74*(2), 457−471. https://doi.org/10.1046/j.1471-4159.2000.740457.x

Walker, A. K., Budac, D. P., Bisulco, S., Lee, A. W., Smith, R. A., Beenders, B., Kelley, K. W., & Dantzer, R. (2013). NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology, 38*(9), 1609−1616. https://doi.org/10.1038/npp.2013.71

Wedervang-Resell, K., Friis, S., Lonning, V., Smelror, R. E., Johannessen, C., Reponen, E. J., Lyngstad, S. H., Lekva, T., Aukrust, P., Ueland, T., Andreassen, O. A., Agartz, I., & Myhre, A. M. (2020). Increased interleukin 18 activity in adolescents with early-onset psychosis is associated with cortisol and depressive symptoms. *Psychoneuroendocrinology, 112*, 104513. https://doi.org/10.1016/j.psyneuen.2019.104513

Wedervang-Resell, K., Ueland, T., Aukrust, P., Friis, S., Holven, K. B., H. Johannessen, C., Lekva, T., Lonning, V., Smelror, R. E., Szabo, A., Andreassen, O. A., Myhre, A. M., & Agartz, I. (2020). Reduced levels of circulating adhesion molecules in adolescents with early-onset psychosis. *NPJ Schizophrenia, 6*(1). https://doi.org/10.1038/s41537-020-00112-5

Wuchert, F., Ott, D., Murgott, J., Rafalzik, S., Hitzel, N., Roth, J., & Gerstberger, R. (2008). Rat area postrema microglial cells act as sensors for the toll-like receptor-4 agonist lipopolysaccharide. *Journal of Neuroimmunology, 204*(1−2), 66−74. https://doi.org/10.1016/j.jneuroim.2008.07.017

Xu, Y., Yue, W., Shugart, Y. Y., Yuan, J., Wang, G., Wang, H. Z., Lehrman, B., Zhang, F., & Zhang, D. (2016). Potential involvement of the interleukin-18 pathway in schizophrenia. *Journal of Psychiatric Research, 74*, 10−16. https://doi.org/10.1016/j.jpsychires.2015.12.013

Yirmiya, R., & Goshen, I. (2011). Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain, Behavior, and Immunity, 25*(2), 181−213. https://doi.org/10.1016/j.bbi.2010.10.015

Chapter 8

Structural brain imaging in early-onset psychosis

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Introduction

Early-onset psychosis (EOP) is a clinically heterogeneous category of psychotic disorders, with symptoms of psychosis typically emerging in early adolescence (before the age of 18 years). During this sensitive period for brain maturation, the brain undergoes dynamic change toward increased specialization and optimization (Giedd & Rapoport, 2010). There is insufficient knowledge on how brain maturation and the emergence of psychosis are linked (Vijayakumar et al., 2018), and neuroimaging studies of these cooccurring processes are important. An advantage of studying the adolescent brain is the relative absence of confounding factors affecting the brain in adults with psychotic disorders, such as lengthy duration of illness, exposure to pharmacological treatment, and substance use. Thus, studying these disorders during adolescence provides the opportunity to uncover the neural mechanisms underlying psychosis development and to discover factors that may be unique to the early-onset form of the illness.

To date, neuroimaging studies in youth with EOP are relatively sparse in comparison with studies of adults with psychotic disorders, and mainly focus on youth with early-onset schizophrenia (EOS). Pioneering studies of children with schizophrenia (childhood-onset schizophrenia (COS); age of onset before 13 years), emerged in the 1990s from the US National Institute of Mental Health (Rapoport & Gogtay, 2011). Despite early exceptions from Spain (Fraguas et al., 2016), most studies of youth with EOP have typically included less than 50 patients, which limits the power of detecting true effects. To overcome the problem of small sample sizes, including overestimation of effect sizes and poor replicability, large-scale collaborative efforts such as the Enhancing Neuro

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00011-1

Imaging Genetics through Meta-Analysis Consortium (ENIGMA, 2021) are of critical importance. ENIGMA creates the possibility to pool neuroimaging data from multiples sites worldwide, using harmonized analysis protocols.

While such efforts have been successfully applied to studies of adults with psychosis, large consortium studies examining brain structural alterations in adolescent populations are critically needed. In this chapter, we first briefly describe central magnetic resonance imaging (MRI) methods and then review findings on subcortical and cortical brain morphology, and white matter structure, and connectivity in adolescents with EOP.

Structural MRI methods

Neuroimaging of brain anatomy and tissue composition is important in both brain disorders research and clinical imaging. In vivo MRI is today the most extensively used method to obtain new knowledge about the central nervous system, and MR scanners are available at most radiology centers in the world. The MR investigation is noninvasive, does not involve ionizing radiation, and can be repeated without adverse effects. Current MRI setups use 1.5 or 3 T magnets. Tesla (abbreviated T) is the unit used to measure magnetic field strength. In MRI, the object to be imaged is placed in a strong static magnetic field. Radio-frequency pulses are applied at the resonance frequency of hydrogen protons. The dynamic application of radio-frequency pulses leads to the emission of MR signals, which can be captured with receiver coils and are used for image reconstruction. The contrast in the image is typically based on tissue differences in proton density, blood flow, and the relaxation time constants; T1 and T2, which determine the rate at which the excited protons return to equilibrium. Particularly T1-weighted images are used to identify and quantify anatomic structures (see Fig. 8.1 for main MRI sequences). Other

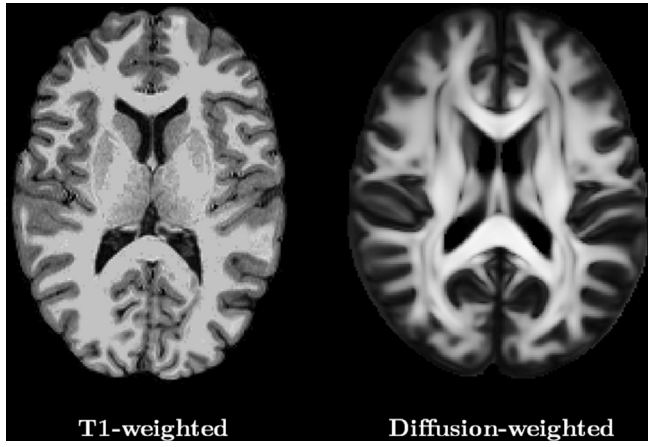

FIGURE 8.1 Visualization of common MRI sequences.

types of sequences are also available. For instance, diffusion weighted imaging is sensitive to water molecule movement in the brain and provides indirect measures of tissue microstructure that can be used to make inferences about structural connectivity. The high contrast and spatial resolution, non-invasiveness, and multimodal applications of MRI have led to a large number of fundamental discoveries in brain disorders research.

Subcortical and cortical morphometry

Open-source software packages, such as FreeSurfer (Fischl, 2012), are used to process and analyze brain MRI images. Using these software packages, gray matter (i.e., neuronal cell bodies) and white matter (i.e., neuronal axons/myelin) are segmented into anatomical parcels based on tissue contrast and spatial information. Further, they are quantitated at submillimeter level to enable measures of cortical or subcortical structure volumes, cortical surface area, cortical thickness, and cortical folding patterns. From anatomical brain atlases, their spatial positions are mapped in 3D space. At the structural level, MRI allows for excellent contrast and spatial resolution, rendering quantitative measurements of tissue composition in discrete anatomical areas. Commonly used methods to investigate morphological brain changes on a macroscopic scale are voxel-based morphometry and surface-based morphometry. While voxel-based morphometry conducts a voxel-by-voxel comparison of image intensity (e.g., tissue concentration or volume), surface-based morphometry estimates the shape of the cortical surfaces and generates more specific metrics such as cortical thickness, pial surface area and cortical curvature (i.e., sulci and gyri).

White matter microstructure and connectivity

Diffusion weighted imaging data can be modeled in different ways, but a commonly used approach is diffusion tensor imaging (DTI). DTI provides a three-dimensional model of diffusion distribution within each voxel, quantifying the diffusivity along three orthogonal axes. The most common diffusion metrics extracted are fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. While mean diffusivity reflects overall diffusion, fractional anisotropy characterizes the degree of diffusion directionality. Axial and radial diffusivities further describe diffusion along the primary axis and diffusion perpendicular to it, respectively. DTI metrics are sensitive to multiple aspects of white matter microstructure, including myelination, axonal packing, axon coherence, axon diameter, membrane permeability, and water content (Beaulieu, 2002).

Subcortical brain morphology

Subcortical structures are a group of diverse centrally located neural formations or nuclei in the basal brain, such as the diencephalon, basal ganglia, and limbic structures. The definition of subcortical structures on MRI can differ depending on

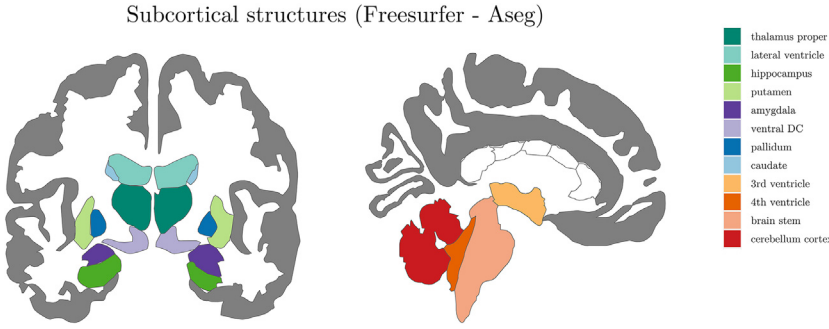

FIGURE 8.2 **Subcortical segmentation based on FreeSurfer** Abbreviation: *DC* = diencephalon. *Images were generated with ggseg in R, from Mowinckel, A. M., & Vidal-Piñeiro, D. (2020). Visualization of brain statistics with R packages ggseg and ggseg3d.* Advances in Methods and Practices in Psychological Science, 3*(4), 466–483. https://doi.org/10.1177/2515245920928009.*

software packages and/or brain segmentation atlases used. Based on work by Fischl and colleagues (see Fig. 8.2), subcortical morphology here refers to structures including the basal ganglia, hippocampus, amygdala, and cerebellum (Fischl et al., 2002). The *basal ganglia* are a centrally located and integrated network of subcortical nuclei and comprises the striatum (the caudate, putamen, and accumbens nuclei) and the pallidum (globus pallidus and ventral pallidum) as well as the subthalamic nucleus and the ventral tegmentum/substantia nigra complex. The *striatum* has been implicated in the development of psychosis, and antipsychotic medication targets the receptors in the striatum. The basal ganglia connect interchangeably to the cortex, thalamus, brainstem, and cerebellum. They are involved in many central functions, such as motor control, emotional/motivational and cognitive processing, sensory gating, and learning. The *hippocampus* is located deep in the temporal lobe and is generally included with the subcortical segmentation. The hippocampus has particularly close connections with the *amygdala* and the cortex.

All brain structure volumes have a proportional relationship to head size, which varies between the sexes. Females have smaller head sizes than males. The intracranial volume (ICV; i.e., the volume inside the dura mater) is commonly used to statistically adjust for inter-individual differences in head size. ICV is also an important marker for early brain development, as it reaches about 90% of its full size around the age of 5 years (Sgouros et al., 1999), and remains relatively stable throughout the adult lifespan. Generally, age is also a powerful determinant of variation in brain volumes.

Intracranial-, subcortical, and cerebellar structure volumes

Widespread differences in subcortical volumes have been reported for both adults and adolescents with psychotic disorders, relative to healthy controls. A large-scale ENIGMA meta-analysis of adult individuals with schizophrenia

(van Erp et al., 2016) and a mega-analysis of adults with bipolar disorders (Hibar et al., 2016) reported both lower hippocampal, amygdala and thalamus, and higher lateral ventricle volumes. In schizophrenia, van Erp and colleagues also found lower ICV and accumbens volumes, and higher pallidum volume (van Erp et al., 2016). The volumetric differences were less marked in bipolar disorder than in schizophrenia, a finding corroborated by a direct comparison study between the disorders and healthy controls (Rimol et al., 2010).

Similar to adult individuals with schizophrenia, smaller whole brain volume, thalamus volume, and larger caudate, putamen, pallidum and ventricular volumes have been reported in both youth with EOS (El-Sayed et al., 2010; Juuhl-Langseth et al., 2012) and COS (Frazier, Hamburger, et al., 1996; Kumra et al., 2000), compared to healthy controls. One study indicated similar magnitudes of subcortical volume differences in children with COS relative to adults with schizophrenia (Frazier, Hamburger, et al., 1996). A recent ENIGMA mega-analysis of 263 adolescents with EOP (70% EOS) and 359 healthy controls revealed overlapping patterns of subcortical volume differences in youth with EOP, relative to adults with psychotic disorders (Gurholt, Lonning, et al., 2020). Youth with EOP had significantly lower ICV and hippocampal volumes; higher caudate and pallidum volumes; and nominally significant lower amygdala, and higher lateral ventricular volumes, compared to healthy controls. Lower ICV was present in both youth with EOS and affective psychosis, while lower hippocampal and higher pallidum volumes were limited to youth with EOS. A notable finding was the negative effect size of ICV observed in both youth with EOS and affective psychosis which was greater than reported in the meta-analysis of adults with schizophrenia (van Erp et al., 2016). No such effect was reported for adults with bipolar disorders (Hibar et al., 2016). ICV expands rapidly in early age, driven by brain growth, and reaches its final volume by mid-to-late adolescence (Courchesne et al., 2000; Haijma et al., 2013; Mills et al., 2016). Given the relative stability of ICV from adolescence onwards, a low ICV in adolescents with psychosis suggests a deviant early neurodevelopment, which could be more severe and/or established earlier than in the adult counterparts.

In line with findings from studies of adults with psychotic disorders, the *hippocampus* showed the lowest volume of all the subcortical structures in adolescents with EOP, relative to controls, but this effect was limited to youth with EOS (Gurholt, Lonning, et al., 2020). Lower hippocampal volume has been reported in adolescents with attention-deficit/hyperactivity disorder (Hoogman et al., 2017) and in adults with affective, psychotic, stress-, and neurodegenerative disorders (Sämann et al., 2020). However, from MRI, it is unclear whether mechanisms leading to lower hippocampal volumes are shared or distinct across disorders. Improved methodologies (e.g., higher magnetic field strengths, advanced image analysis algorithms) allowing for a segmentation of the hippocampus into cell-specific anatomical subunits (subfields) might shed light on this question (Sämann et al., 2020). The

enlarged *pallidum* and *caudate* volumes and trends toward enlarged *putamen* volumes in patients with EOP treated with antipsychotic medication, suggest similar antipsychotic medication effects on brain structure as in adults with psychotic disorders. But there can also be factors that are specific to adolescence. In a previous study of youth with EOS, the enlarged caudate volumes were not linked to antipsychotic medication use (Juuhl-Langseth et al., 2012). However, in a follow-up study of adolescents with COS, who at baseline were on typical neuroleptics, caudate enlargement declined following a switch to clozapine treatment (Frazier, Kaysen, et al., 1996).

Neuroimaging studies in adults have suggested a role of the *cerebellum* in psychotic disorders, due to its involvement in sensorimotor control and higher-level cognitive function (Lawyer et al., 2009; Moberget & Ivry, 2019) that show impairment in individuals with schizophrenia (Moberget & Ivry, 2019). Furthermore, some studies suggest that the cerebellar cortex is one of the later maturing brain structures, reaching a peak at around 16 years of age (Tiemeier et al., 2010), potentially making it more vulnerable to later environmental influences. Smaller bilateral cerebellar volumes were reported in adults with schizophrenia relative to adults with bipolar I disorder and healthy controls (Laidi et al., 2015). In contrast to healthy controls, patients with COS showed a progressive loss of cerebellar volume during adolescence, consistent with previously reported lower total cerebral and cortical gray matter (Keller et al., 2003). Improved automated segmentation methods can trace the details of the lobulated cerebellar cortex and may improve our understanding of the putative cerebellar involvement in adolescent psychosis and its covariance with other brain structures, which remains to be determined (Wang et al., 2020).

Subcortical structures in bipolar disorder

Studies of youth with early-onset bipolar disorder (EOBD) are far fewer than in youth with EOS and include equally small sample sizes. Generally, the magnitude of subcortical volume differences in adolescents with EOBD relative to healthy controls is less than in youth with EOS. A review of 11 publications from 1990 to 2005 reported structural abnormalities in total cerebral, white matter, superior temporal gyrus, putamen, thalamus, amygdala, and hippocampal volumes (Frazier et al., 2005). These findings suggest that the limbic system is involved in the pathophysiology of EOBD. In contrast, a study of youth (6−17 years) with EOBD with and without psychosis, EOS, and healthy controls, did not find limbic volumetric differences between the diagnostic groups (Frazier et al., 2008). This discrepancy between studies may stem from phenotypic heterogeneity such as differences in disease severity and duration, medication history, and comorbidities and whether psychosis is part of the disease history or not.

Cortical brain morphology

Altered cortical structures and development

Cortical structural abnormalities are well established in adults with psychosis, including volumetric deficits (van Erp et al., 2018), cortical thinning (Kuperberg et al., 2003), and abnormal cortical folding (Sallet et al., 2003). A recent meta-analysis from the ENIGMA-consortium reported widespread thinner cortex and smaller cortical surface area, with the largest effect sizes for both frontal and temporal lobe regions, in adults with schizophrenia relative to healthy controls (van Erp et al., 2018). While large-scale collaborative efforts have been applied to adults with psychosis, large consortium studies examining cortical brain structural alterations in adolescents with psychosis are currently missing.

Most studies of adolescents with psychosis to date have focused on EOS, specifically, and few have characterized the cerebral cortex in youth with affective psychotic disorders. Throughout typical adolescent brain development, cortical gray matter dynamically changes with substantial thinning during childhood and adolescence, in general progressing in a posterior-to-anterior temporal pattern (age range 7−29 years (Tamnes et al., 2017)). The largest decreases in cortical thickness have been observed in the parietal lobe (Tamnes et al., 2013). Cortical surface area develops until approximately 12 years of age and remains relatively stable afterward (Amlien et al., 2016). As symptoms occur early in adolescence, researchers suggest a neurodevelopmental basis for the emergence of EOP. Yet, the nature and timing of putatively aberrant trajectories in adolescent brain development in youth with EOP are debated.

Cross-sectional studies in adolescents with EOP report on morphological abnormalities similar to adults with psychosis, relative to healthy controls; mainly in frontal and temporal regions, which are central for cognitive control functions and the processing of emotional stimuli (see Fig. 8.3 as reference image for most commonly used cortical parcellation). Using voxel-based morphometry, Douaud and colleagues reported widespread gray matter reductions in youth with EOS, including auditory and language areas (e.g., Heschl gyrus), sensorimotor and premotor areas, and prefrontal regions such as the dorsolateral prefrontal cortex (DLPFC) (Douaud et al., 2007). A more recent voxel-based morphometry study examined cortical gray matter in adolescent- and adult-onset, first-episode treatment-naïve individuals with schizophrenia, and found differential patterns of gray matter abnormalities. In adults with schizophrenia, gray matter deficits were focused on the cingulo-fronto-temporal module and right occipital regions. However, in adolescents with EOS, gray matter deficits were found in the left parietal postcentral gyrus, parahippocampal gyrus and right cerebellum posterior pyramis (Zhang et al., 2017). These gray matter changes can be interpreted as a result of locally

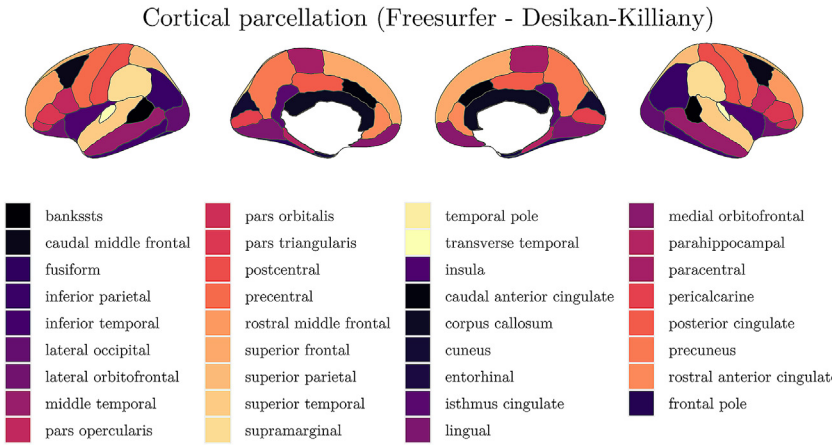

FIGURE 8.3 **Cortical parcellation based on FreeSurfer** Abbreviation: *bankssts* = banks of superior temporal sulcus. *Images were generated with ggseg in R, from Mowinckel, A. M., & Vidal-Piñeiro, D. (2020). Visualization of Brain Statistics With R Packages ggseg and ggseg3d.* Advances in Methods and Practices in Psychological Science, 3*(4), 466–483.* https://doi.org/10.1177/2515245920928009.

lower cortical thickness or lower cortical surface area. In addition, differential cortical folding, involving changes in sulco-gyral morphology, may also impact observed gray matter changes. Studies of youth with EOP suggest deficits in all measures of cortical brain anatomy. By means of surface-based morphometry, Voets and colleagues found widespread cortical pathology in youth with EOS, particularly involving the prefrontal cortex and superior temporal gyrus (Voets et al., 2008). The authors found that lower cortical surface area accounted for previously established voxel-based morphometry changes by Douaud and colleagues. Similarly, another study using surface-based morphometry also found bilateral cortical thinning and smaller volumes in both the gyri and sulci of the superior temporal cortex, and the inferior, middle, medial, and superior prefrontal cortices (Janssen et al., 2009). Cortical thinning in the right superior frontal cortex overlapped with diminished cortical folding in youth with EOP. Furthermore, White and colleagues showed that adolescents with EOS had significantly more flattened curvature in the sulci of frontal and parietal lobes, and more steeped curvature in the gyri of the occipital lobe (White et al., 2003). Investigating cortical folding is of particular interest as gyri and sulci predominantly develop prenatally (Armstrong et al., 1995). If abnormal cortical folding overlaps with areas of thinner cortices, one might speculate that aberrant cortical thinning occurs in early stages of cortical development (Janssen et al., 2009), lending further support to the early neurodevelopmental disturbances in adolescents with EOP.

Relative to cross-sectional studies, longitudinal designs assessing the development of the cerebral cortex within individuals with EOP are limited. James and colleagues demonstrated lower prefrontal cortex volumes in adolescents with EOS relative to healthy controls, which remained stable over two time points (average 2−3 years apart) (James et al., 2004). Another study found distributed reductions in cortical thickness at illness onset in individuals with EOS (Palaniyappan et al., 2019). However, these differences were nullified after a 2-year follow-up period, during which the healthy controls showed continued cortical thinning. This finding indicates a distinct lack of the expected progressive cortical thinning in individuals with EOS during adolescence, indicating converging cortical maturation trajectories (Palaniyappan et al., 2019). On the contrary, compared with healthy controls, another study found greater gray matter volume loss in the frontal lobe during a 2-year follow-up in youth with EOP (Arango et al., 2012). Furthermore, findings from individuals with COS indicated four times higher progressive reduction in cortical gray matter volume when scanned during adolescence relative to healthy controls over 2 years (Rapoport et al., 1999). A landmark study by Thompson and colleagues in youth with COS (aged 13.9 ± 0.8 years at first scan) indicated dynamic waves of brain tissue loss over a 5-year follow-up period, spreading from parietal cortices at disease onset to encompass temporal and frontal regions later in the disease (Thompson et al., 2001). This pattern seems to resemble an exaggeration of normal cortical gray matter development and may eventually mimic patterns observed in individuals with adult-onset psychosis (Gogtay et al., 2011), with more localized gray matter loss in prefrontal and temporal cortices. While the mechanisms underlying a putative deviation of normal cortical development are mostly unknown, one hypothesis states that excessive synaptic pruning during adolescence may lead to the observed gray matter deficits (Feinberg, 1982; Gogtay et al., 2011), and an earlier age at onset of psychotic symptoms. However, other mechanisms such as increased myelination during adolescence, which correlates with cortical thinning, might be also at play (Natu et al., 2019). Interestingly, healthy siblings of individuals with COS also showed lower prefrontal and temporal gray matter volumes during early adolescence, relative to healthy controls. However, these deficits disappeared by age 20 years (Gogtay et al., 2011), highlighting a shared genetic vulnerability for aberrant cortical brain development. The normalization of gray matter abnormalities in late adolescence could be indicative of unknown genetic/environmental protective factors (Gogtay et al., 2011), which may result in resilience in unaffected siblings. However, it is currently unclear whether and how neurodevelopmental patterns seen in individuals with COS during adolescence translate to individuals with later age at onset of psychosis. More longitudinal studies are warranted to examine the timing of deviant cortical trajectories across the entire neurodevelopmental period.

Cortical structures in bipolar disorder

Similar to adults with schizophrenia, a recent ENIGMA-consortium study in adults with bipolar disorder found bilaterally thinner cortical gray matter in frontal, temporal and parietal regions (Hibar et al., 2018). In youth, large-scale collaborative efforts are so far missing. However, a few studies have examined cortical brain changes in youth with EOBD, mostly focusing on specific regions of interest. For instance, Kaur and colleagues limited their analysis to the cingulate cortex, due to its involvement in mood regulation, and reported smaller cingulate cortex volume in individuals with EOBD (75% type I) relative to healthy controls (Kaur et al., 2005). Preliminary evidence links abnormalities in the cingulate cortex in individuals with EOBD type I to lower glutamine levels, a marker for glial integrity (Moore et al., 2007). Besides the cingulate cortex, Wang and colleagues focused on the olfactocentric paralimbic cortex: a conglomerate of cortices important for the regulation of affect, circadian rhythm, sleep, and appetite (Wang et al., 2011). These functions are often disrupted early in the development of bipolar disorder. Indeed, smaller volumes were found in this region in youth with EOBD (37% with psychotic features), including orbitofrontal, insular, and temporopolar cortices. Other studies, selecting different regions of interest, further found volume deficits in the dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus in individuals with EOBD, relative to healthy controls, most prominently in the left hemisphere (Chen et al., 2004; Dickstein et al., 2005). Volumetric abnormalities in the DLPFC have also been linked to reduced levels of N-acetylaspartate, a marker of neuronal integrity, in individuals with EOBD (Sassi et al., 2005). Najt and colleagues further found sex differences in orbitofrontal cortex abnormalities in EOBD (79% bipolar type 1), with males showing smaller and females showing larger volumes in some subregions (Najt et al., 2007). Other studies also showed sex-by-diagnostic group interactions, further indicating that normative sex differences (brain volumes: male > female) may be disrupted in individuals with EOBD (Mitchell et al., 2018). While a number of region-of-interest studies suggest widespread cortical brain abnormalities in youth with EOBD, predominantly in frontal regions, other studies fail to replicate these findings (Baloch et al., 2010; Chang et al., 2005; Sanches et al., 2005). Hence, conclusive results from whole-brain studies in well-powered samples are urgently needed. Furthermore, studies barely differentiate between bipolar disorder type I and type II, or between bipolar disorder with and without psychotic features, both factors which may influence brain structure. For instance, Toma and colleagues found lower cortical thickness in the bilateral superior frontal and left caudal middle frontal gyrus, in adolescents with bipolar disorder type II, but not with type I (Toma et al., 2019). Furthermore, in adults with bipolar disorder, reduced cortical surface area was associated with a history of psychosis, but not with mood state at time of scanning, indicating differential effects in the presence of psychotic features (Hibar et al., 2018).

Similar to individuals with EOS, longitudinal studies of youth with EOBD are limited. Findings from a longitudinal study (2-year follow-up) of 10 individuals with EOBD type I suggest accelerated volume loss in the prefrontal cortex, relative to healthy controls (Kalmar et al., 2009). However, results should be interpreted with caution due to the small sample size. Another study found larger reductions in anterior cortical volumes including insula and orbitofrontal, rostral and dorsolateral prefrontal cortices over a 2-year follow-up period, suggesting diverging patterns of gray and white matter development in EOBD (Najt et al., 2016). Further studies are needed to draw firm conclusions.

White matter microstructure and connectivity

White matter microstructure and connectivity in psychosis

The spatially distributed nature of the regional differences in gray matter subcortical and cortical structures observed between adolescents with EOP and healthy controls suggests a need to consider the connectivity between the implicated brain regions. Connectivity is facilitated by increasing myelination of white matter tracts during typical development. World-leading researchers, such as Karl Friston, Chris Frith, and Nancy Andreasen, have suggested that a central feature of psychotic disorders is neural dysconnectivity, in which core psychotic symptoms arise from disruption of structural or functional connectivity and interaction between key brain regions (Andreasen et al., 1998; Friston & Frith, 1995).

Brain *structural connectivity* as studied by MRI refers to the physical properties of white matter tracts and networks interconnecting brain regions (Fig. 8.4). The *functional connectivity* across brain regions is discussed in Chapter 9. *Microstructural* properties of white matter and its major tracts associated with psychosis have been most commonly investigated using DTI, and the vast majority of the studies have been on adults with psychotic disorders. A meta-analysis of 59 studies of adolescent and adult individuals with schizophrenia found white matter alterations in regions with long projection fibers, callosal and commissural fibers, part of motor descending fibers, and fronto-temporal-limbic pathways (Vitolo et al., 2017). A meta-analysis of 15 studies of adult individuals with bipolar disorder found effects for all major classes of tracts (Nortje et al., 2013). The ENIGMA Schizophrenia Working Group recently reported widespread lower fractional anisotropy and higher mean and radial diffusivity in adults with schizophrenia relative to healthy controls (Kelly et al., 2018). The effect sizes varied by region, but the strongest effects were seen for fractional anisotropy in the anterior corona radiata and the corpus callosum. Similarly, work from the ENIGMA Bipolar Disorders Working Group has shown widespread lower fractional anisotropy in adults with bipolar disorders relative to healthy controls (Favre et al., 2019). Another

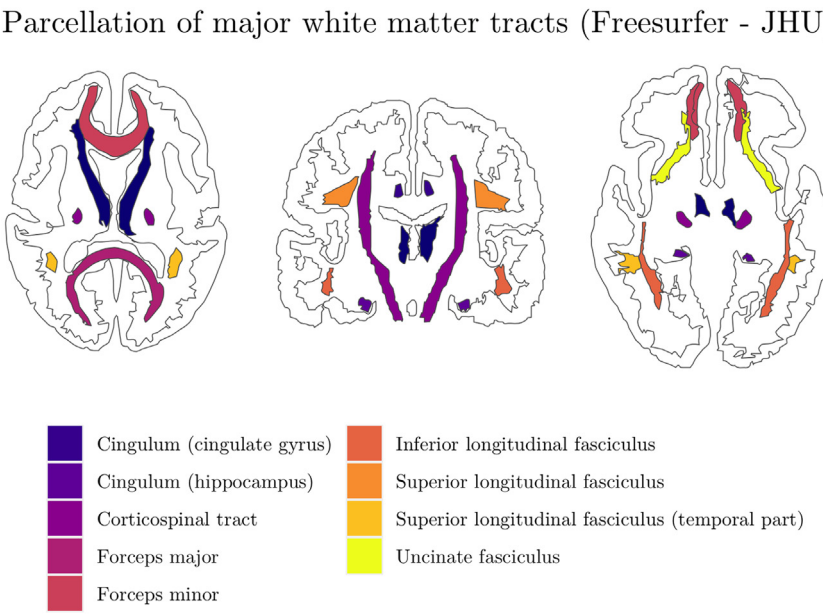

FIGURE 8.4 Parcellation of major white matter tracts based on FreeSurfer Abbreviation: *JHU* = Johns Hopkins University. *Images were generated with ggseg in R, from Mowinckel, A. M., & Vidal-Piñeiro, D. (2020). Visualization of Brain Statistics With R Packages ggseg and ggseg3d.* Advances in Methods and Practices in Psychological Science, 3*(4), 466–483. https://doi.org/10.1177/2515245920928009.*

recent large multisite study compared white matter microstructural differences between healthy controls and adult individuals with schizophrenia, bipolar disorder, autism spectrum disorder, or major depressive disorder (Koshiyama et al., 2020). Individuals with schizophrenia and bipolar disorder shared similar differences in the body of the corpus callosum, the fornix and the cingulum, while differences in the uncinate fasciculus were only present in individuals with schizophrenia. In a direct comparison, there were, however, no differences between individuals with schizophrenia and bipolar disorder (Koshiyama et al., 2020). Together, these results support the conclusion that psychotic disorders in adults involve microstructural deficits in white matter connections. We will next discuss whether similar patterns of connectivity disruption are seen in individuals with onset of schizophrenia or bipolar disorder during adolescence, when brain connections are still maturing.

White matter microstructure and connectivity in early-onset psychosis

A number of studies, albeit mostly small in sample size, have used DTI to compare white matter microstructure between youth with EOP and healthy

controls. In 2016, we published a systematic review of youth with EOS, covering 21 studies from 2004 to 2015 (Tamnes & Agartz, 2016). We found that significantly lower regional fractional anisotropy was consistently reported in youth with EOS (sample sizes ranging from 12 to 55), compared to healthy controls, but that the white matter tracts implicated were highly variable across studies. Lower fractional anisotropy values were reported in white matter regions in all cerebral lobes, corpus callosum, cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, fronto-occipital fasciculus, cortico-spinal tract, anterior thalamic radiation, optic radiation, fornix, posterior hippocampus, and cerebellum. Notably, however, there were also negative findings for several of these regions and tracts. Other common DTI indices, such as mean-, radial-, and axial diffusivity, were only explored in a few studies (Tamnes & Agartz, 2016).

In addition to static case–control differences in DTI measures, it is critical to investigate cross-sectional age-related differences or preferably longitudinal change over time, as this can help elucidate the neurodevelopmental pathophysiology of psychotic disorders. To date, it is unclear whether white matter microstructural abnormalities in youth with psychotic disorders are stable over time or whether they show a dynamic evolution reflecting altered trajectories of white matter development relative to typical development patterns. In typically developing youth, fractional anisotropy increases as well as mean- and radial diffusivity decreases decelerated over time. So far, only a few studies have examined white matter microstructural development in youth with EOS. The results are mixed, with the available studies reporting diverging, converging, or parallel developmental fractional anisotropy trajectories between individuals with EOP and healthy controls (Douaud et al., 2009; Epstein & Kumra, 2015; Kumra et al., 2005).

White matter microstructure and connectivity in bipolar disorder

Relatively few and mostly studies with small sample sizes have used DTI to probe white matter microstructure in youth with EOBD. Similar to youth with EOS, these studies have consistently reported lower fractional anisotropy. However, different studies have analyzed or found effects in different tracts, including in prefrontal white matter, corpus callosum, the superior longitudinal fasciculus, the cingulate, the anterior corona radiata, and fornix (Adler et al., 2006; Barnea-Goraly et al., 2009; Frazier et al., 2007; Gao et al., 2013; Gönenç et al., 2010; Kafantaris et al., 2009; Pavuluri et al., 2009; Roberts et al., 2016). Lower fractional anisotropy in many of the same tracts has also been reported for adolescents with subthreshold bipolar symptoms (Paillère Martinot et al., 2014).

A few studies have compared case–control differences in DTI indices in youth and adults with bipolar disorder. One study including adolescent and adult individuals with bipolar I disorder found greater deviations in fractional

anisotropy in the left anterior limb of the internal capsule in the young individuals compared to adult individuals with psychosis (Lu et al., 2012). Another study found different spatial patterns of fractional anisotropy differences in adolescents with EOBD relative to young adults with bipolar disorder, with more posterior white matter effects seen in the former group and more anterior effects in the latter (Ren et al., 2020). Together, these studies suggest some differences in white matter abnormalities between individuals with early- and adult-onset bipolar disorder.

Concerning white matter microstructural development in individuals with EOBD, Weathers and colleagues performed a longitudinal DTI study including adolescents and young adults with bipolar disorder (~50% with psychotic features), and healthy controls (Weathers et al., 2018). The researchers focused specifically on the uncinate fasciculus, which provides the major connections between the amygdala and ventral prefrontal cortex and is important in emotion regulation. The results showed interactions between diagnosis, age and time, with healthy controls showing increases in fractional anisotropy with age and over time, whereas no significant changes were observed in individuals with bipolar disorder (Weathers et al., 2018). This developmental pattern is also supported by the findings in a cross-sectional study that showed lower age-related fractional anisotropy increases in the anterior corpus callosum in youth with EOBD, although no group-by-age interaction effects were found for the uncinate fasciculus or the corticospinal tract (Cabeen et al., 2018; Linke et al., 2020).

Relationships with symptom profiles and functioning

While a number of brain structural and cognitive abnormalities have been reported in individuals with EOP, robust associations between the two are largely missing. Juuhl-Langseth and colleagues found that larger caudate volumes were associated with lower verbal learning performance in individuals with EOP relative to healthy controls (Juuhl-Langseth et al., 2015). Despite marked ventricular enlargements in EOP, the authors found comparable correlations between the lateral ventricular volume and cognitive domains among individuals with EOP and healthy controls. Antipsychotic medication was related to ventricular enlargements but did not affect the brain structure−function relationship (Juuhl-Langseth et al., 2012). In individuals with EOS, age of onset was positively correlated with regional gray matter volume in the right superior parietal lobule (Brodmann area 7), while duration of illness was negatively associated with regional gray matter volume in the left inferior frontal gyrus (Brodmann area 11/47) (Burke et al., 2008). Our review of DTI studies in individuals with EOS showed that consistent evidence for associations between DTI indices and measures of symptomatology or cognition was weak or lacking (Tamnes & Agartz, 2016).

While most studies of individuals with EOP have not found associations between cortical brain measures and symptom profiles or cognitive outcome,

some studies have linked suicidal behavior in adolescents with EOBD with brain structure. For instance, one study found an association between reduced left lateral orbitofrontal cortex volumes and increased suicidal lethality in currently depressed individuals with EOBD (Huber et al., 2019). Furthermore, individuals with EOBD (46% with psychotic features) who attempted suicide showed decreased structural connectivity in a ventral frontolimbic neural system subserving emotion regulation (Johnston et al., 2017). Besides behavioral outcomes, altered cortical brain morphology has also been linked to environmental factors in youths with EOP. Individuals with EOBD using cannabis exhibited larger volume and surface area in parietal regions, and smaller cortical thickness in frontal regions, relative to healthy controls and nonusing individuals with EOBD (Sultan et al., 2021). Genetic factors such as single nucleotide polymorphisms (SNPs) could further contribute to the heterogeneity seen in cortical findings among individuals with EOP. For instance, rs1006737 SNP on the calcium channel voltage-dependent L-type alpha 1C subunit (CACNA1C) gene may confer risk for bipolar disorder and schizophrenia, along with major depressive disorder, and has been linked to distinct brain structural phenotypes in individuals with EOBD. Individuals with EOBD who were carriers of the aforementioned SNP were found to have greater surface area in prefrontal and occipital regions relative to individuals with EOBD who were noncarriers. Interestingly, healthy control carriers showed the reversed pattern compared to healthy control noncarriers (Shonibare et al., 2021). A recent DTI study of individuals with EOBD type I and healthy controls found differential relationships between fractional anisotropy and cognitive flexibility performance in EOBD compared to healthy controls in several white matter regions (Radoeva et al., 2020). Replication of these findings and new studies with larger samples are needed to understand the clinical and cognitive relevance of brain structural and microstructural effects in individuals with adolescent psychosis.

Impact of medication

Antipsychotic drugs are cornerstones in the treatment of individuals with schizophrenia (Keepers et al., 2020). Basal ganglia volume increases occur already after a few weeks of treatment. This is thought to be a compensatory response to the antipsychotic medication induced dopamine D2 receptor antagonism, which leads to an up-regulation of the D2 receptors in the striatum (Chua et al., 2009). The propensity of antipsychotic type to bind to D2 receptors (Jørgensen et al., 2016) and the dose (Di Sero et al., 2019) shaped the magnitude of the basal ganglia volume increase. As shown in animal studies, the neurobiological responses may also differ as a function of neurodevelopmental phase (Moe et al., 2017), and it is an interesting, yet unanswered question, how antipsychotics can influence brain development in adolescents with EOP long-term. As mentioned above, transfer to clozapine treatment from typical antipsychotics resulted in reduction in caudate volumes

(Frazier, Kaysen, et al., 1996). In individuals with COS, globus pallidus enlargement correlated with neuroleptic medication exposure and with age of onset of psychosis (Frazier, Hamburger, et al., 1996). In adults with schizophrenia, cortical gray matter reductions have been observed over 6 months to 2 years (Huhtaniska et al., 2017), yet long-term medication studies of youth with EOP are missing. Treatment response in individuals with EOP has, however, been linked to cortical measures. Decreased cortical thickness in medial frontal areas was associated with a history of poor antipsychotic treatment response in individuals with COS (Gogtay et al., 2004). To the contrary, Thormodsen and colleagues found no significant effects of antipsychotic medication on cortical thickness in adolescents with EOP (Thormodsen et al., 2013). In individuals with EOBD, current use of mood stabilizers was linked to larger volumes in the right subgenual prefrontal cortex (Baloch et al., 2010). Using DTI, a recent study found a significant association between antipsychotic mediation status and fractional anisotropy in the left anterior corona radiata, with higher fractional anisotropy in medicated compared to nonmedicated individuals with EOP (Barth et al., 2020). Studies aiming at identifying neuroimaging biomarkers of treatment outcome are urgently needed to predict functional long-term outcomes in individuals with EOP.

Clinical implications

Identifying neuroimaging biomarkers of psychosis risk and treatment outcomes after disease onset has gained momentum in clinical brain research over the last decades. In adult psychosis populations, however, results are mostly equivocal, and studies in youth with EOP are largely missing. A recent prospective longitudinal multicenter study found that exaggerated deviation in neuroanatomical maturity, measured as brain age, in youth at clinical high-risk for psychosis, aged 12−17 years at the first scan, was associated with a greater risk for developing psychosis and a pattern of poor functioning (Chung et al., 2018). This association was not found in individuals at high-risk who developed psychosis at the age of 18 years or older. These individuals, however, showed accelerated reduction in cortical thickness, which was not the case in the adolescents at high risk. In sum, these results suggest that neuroanatomical measures may be useful in estimating onset of psychosis, especially among individuals at high-risk during adolescence. Concerning treatment outcomes, a recent study by Zang and colleagues found two distinct subgroups of individuals with EOBD, as defined by patterns of cortical thickness. The subgroup of EOBD with greater cortical thickness relative to healthy controls showed better treatment response to quetiapine than the EOBD subgroup with cortical thinning in superior temporal and superior parietal regions (Zhang et al., 2018). While promising, these results need to be interpreted with caution due to the small sample size, and replications in larger samples are warranted to inform medical decision-making.

Future directions

Large samples of individuals with EOP are needed to stratify for clinical subgroups, their functional outcome and treatment response in relationship to brain structure. Likewise, longitudinal studies are called for to understand the origin, emergence, and possible degenerative characteristics of brain structural differences associated with EOP, and the timing of these differences relative to familiar, genetic, clinical risk-status, and clinical manifestations in adolescence versus in adult age. Examining the interplay of clinical, environmental, and genetic variation for structural brain development in youth with EOP is an interesting avenue for future studies. Transdiagnostic comparison of brain structures across neurodevelopmental syndromes in youth might facilitate the search for clues to neurobiological processes underlying psychosis development. There is also a need to expand representative psychosis cohorts to parts of the world outside the Western hemisphere.

So far, previous cortical studies including individuals with EOP used traditional methods such as voxel-based morphometry, relying on coarse volume-based measures. Surface-based approaches provide powerful alternatives, which enable more precise spatial localization of potential alternations in cortical morphology (reviewed by Coalson et al., 2018). Furthermore, older studies tend to be biased by low-resolution images. To reliably quantify cortical abnormalities in adolescents with EOP, future studies should acquire high-resolution images (higher than the typical 1-mm acquisition) and use robust, high-quality cortical surface models in well-powered samples.

As we have reviewed, most diffusion weighted imaging studies on adolescents with psychosis have used DTI models and focused almost exclusively on fractional anisotropy, while other DTI indices are not consistently explored. DTI has numerous limitations and interpretation of its parameters is not necessarily straightforward. Advancements in diffusion weighted imaging acquisition and modeling, as discussed elsewhere (Pasternak et al., 2018; Tamnes et al., 2018), may give new knowledge about the brain structural basis of psychosis development during childhood and adolescence. These methods have in recent years been used in a few studies of adult individuals with psychosis (Gurholt, Haukvik, et al., 2020), but studies including adolescents with psychosis are so far scarce. Tractography (Tournier et al., 2011) and graph theory analysis (Bullmore & Bassett, 2011) also hold promise for further probing white matter connectivity and networks.

Conclusion

Subcortical brain structures are smaller in adolescents with EOP, with structural profiles mainly similar to adults with psychotic disorders. Basal ganglia volumes show increases concordant with antipsychotic medication use. The developmental trajectories of the cortex might provide important clues to the

neurodevelopment and brain pathology underlying EOP. DTI studies document lower regional fractional anisotropy in youth with EOP, but the implicated regions or tracts remain unclear. Attempts to associate specific brain structural changes to disease symptoms, cognition, and clinical outcome have so far shown limited success.

References

Adler, C. M., Adams, J., DelBello, M. P., Holland, S. K., Schmithorst, V., Levine, A., Jarvis, K., & Strakowski, S. M. (2006). Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: A diffusion tensor imaging study. *American Journal of Psychiatry,* 163(2), 322−324. https://doi.org/10.1176/appi.ajp.163.2.322

Amlien, I. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Krogsrud, S. K., Chaplin, T. A., Rosa, M. G. P., & Walhovd, K. B. (2016). Organizing principles of human cortical development - thickness and area from 4 to 30 Years: Insights from comparative primate neuroanatomy. *Cerebral Cortex,* 26(1), 257−267. https://doi.org/10.1093/cercor/bhu214

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin,* 24(2), 203−218. https://doi.org/10.1093/oxfordjournals.schbul.a033321

Arango, C., Rapado-Castro, M., Reig, S., Castro-Fornieles, J., González-Pinto, A., Otero, S., Baeza, I., Moreno, C., Graell, M., Janssen, J., Parellada, M., Moreno, D., Bargalló, N., & Desco, M. (2012). Progressive brain changes in children and adolescents with first-episode psychosis. *Archives of General Psychiatry,* 69(1), 16−26. https://doi.org/10.1001/archgenpsychiatry.2011.150

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., & Zilles, K. (1995). The ontogeny of human gyrification. *Cerebral Cortex, 5*(1), 56−63. https://doi.org/10.1093/cercor/5.1.56

Baloch, H. A., Hatch, J. P., Olvera, R. L., Nicoletti, M., Caetano, S. C., Zunta-Soares, G. B., & Soares, J. C. (2010). Morphology of the subgenual prefrontal cortex in pediatric bipolar disorder. *Journal of Psychiatric Research,* 44(15), 1106−1110. https://doi.org/10.1016/j.jpsychires.2010.04.005

Barnea-Goraly, N., Chang, K. D., Karchemskiy, A., Howe, M. E., & Reiss, A. L. (2009). Limbic and corpus callosum aberrations in adolescents with bipolar disorder: A tract-based spatial statistics analysis. *Biological Psychiatry,* 66(3), 238−244. https://doi.org/10.1016/j.biopsych.2009.02.025

Barth, C., Lonning, V., Gurholt, T. P., Andreassen, O. A., Myhre, A. M., & Agartz, I. (2020). Exploring white matter microstructure and the impact of antipsychotics in adolescent-onset psychosis. *PLoS ONE,* 15(5). https://doi.org/10.1371/journal.pone.0233684

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine,* 15(7−8), 435−455. https://doi.org/10.1002/nbm.782

Bullmore, E. T., & Bassett, D. S. (2011). Brain graphs: Graphical models of the human brain connectome. *Annual Review of Clinical Psychology,* 7, 113−140. https://doi.org/10.1146/annurev-clinpsy-040510-143934

Burke, L., Androutsos, C., Jogia, J., Byrne, P., & Frangou, S. (2008). The maudsley early onset schizophrenia study: The effect of age of onset and illness duration on fronto-parietal gray matter. *European Psychiatry,* 23(4), 233−236. https://doi.org/10.1016/j.eurpsy.2008.03.007

Cabeen, R. P., Laidlaw, D. H., Ruggieri, A., & Dickstein, D. P. (2018). Preliminary mapping of the structural effects of age in pediatric bipolar disorder with multimodal MR imaging. *Psychiatry Research - Neuroimaging,* 273, 54−62. https://doi.org/10.1016/j.pscychresns.2017.12.006

Chang, K., Barnea-Goraly, N., Karchemskiy, A., Simeonova, D. I., Barnes, P., Ketter, T., & Reiss, A. L. (2005). Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. *Biological Psychiatry,* 58(3), 197−203. https://doi.org/10.1016/j.biopsych.2005.03.039

Chen, H. H., Nicoletti, M. A., Hatch, J. P., Sassi, R. B., Axelson, D., Brambilla, P., Monkul, E. S., Keshavan, M. S., Ryan, N. D., Birmaher, B., & Soares, J. C. (2004). Abnormal left superior temporal gyrus volumes in children and adolescents with bipolar disorder: A magnetic resonance imaging study. *Neuroscience Letters,* 363(1), 65−68. https://doi.org/10.1016/j.neulet.2004.03.042

Chua, S. E., Deng, Y., Chen, E. Y. H., Law, C. W., Chiu, C. P. Y., Cheung, C., Wong, J. C. H., Lienenkaëmper, N., Cheung, V., Suckling, J., & McAlonan, G. M. (2009). Early striatal hypertrophy in first-episode psychosis within 3 weeks of initiating antipsychotic drug treatment. *Psychological Medicine,* 39(5), 793−800. https://doi.org/10.1017/S0033291708004212

Chung, Y., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D. H., McGlashan, T., Perkins, D., Seidman, L. J., Tsuang, M., Walker, E., Woods, S. W., McEwen, S., Van Erp, T. G. M., & Cannon, T. D. (2018). Use of machine learning to determine deviance in neuroanatomical maturity associated with future psychosis in youths at clinically high risk. *JAMA Psychiatry,* 75(9), 960−968. https://doi.org/10.1001/jamapsychiatry.2018.1543

Coalson, T. S., Van Essen, D. C., & Glasser, M. F. (2018). The impact of traditional neuroimaging methods on the spatial localization of cortical areas. *Proceedings of the National Academy of Sciences of the United States of America,* 115(27), E6356−E6365. https://doi.org/10.1073/pnas.1801582115

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., Harwood, M., Hinds, S., & Press, G. A. (2000). Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology,* 216(3), 672−682. https://doi.org/10.1148/radiology.216.3.r00au37672

Di Sero, A., Jørgensen, K. N., Nerland, S., Melle, I., Andreassen, O. A., Jovicich, J., & Agartz, I. (2019). Antipsychotic treatment and basal ganglia volumes: Exploring the role of receptor occupancy, dosage and remission status. *Schizophrenia Research,* 208, 114−123. https://doi.org/10.1016/j.schres.2019.04.002

Dickstein, D. P., Milham, M. P., Nugent, A. C., Drevets, W. C., Charney, D. S., Pine, D. S., & Leibenluft, E. (2005). Frontotemporal alterations in pediatric bipolar disorder: Results of a voxel-based morphometry study. *Archives of General Psychiatry,* 62(7), 734−741. https://doi.org/10.1001/archpsyc.62.7.734

Douaud, G., MacKay, C., Andersson, J., James, S., Quested, D., Ray, M. K., Connell, J., Roberts, N., Crow, T. J., Matthews, P. M., Smith, S., & James, A. (2009). Schizophrenia delays and alters maturation of the brain in adolescence. *Brain,* 132(9), 2437−2448. https://doi.org/10.1093/brain/awp126

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., James, S., Voets, N., Watkins, K., Matthews, P. M., & James, A. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain,* 130(9), 2375−2386. https://doi.org/10.1093/brain/awm184

El-Sayed, M., Grant Steen, R., Poe, M. D., Carter Bethea, T., Gerig, G., Lieberman, J., & Sikich, L. (2010). Brain volumes in psychotic youth with schizophrenia and mood disorders. *Journal of Psychiatry and Neuroscience,* 35(4), 229–236. https://doi.org/10.1503/jpn.090051

ENIGMA. (2021). *Enhancing neuro imaging genetics through meta-analysis consortium.* http://enigma.ini.usc.edu.

Epstein, K. A., & Kumra, S. (2015). White matter fractional anisotropy over two time points in early onset schizophrenia and adolescent cannabis use disorder: A naturalistic diffusion tensor imaging study. *Psychiatry Research - Neuroimaging,* 232(1), 34–41. https://doi.org/10.1016/j.pscychresns.2014.10.010

van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., Agartz, I., Westlye, L. T., Haukvik, U. K., Dale, A. M., Melle, I., Hartberg, C. B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D. W., … Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry,* 21(4), 547–553. https://doi.org/10.1038/mp.2015.118, 585–585.

van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., Pearlson, G. D., Yao, N., Fukunaga, M., Hashimoto, R., Okada, N., Yamamori, H., Bustillo, J. R., Clark, V. P., Agartz, I., Mueller, B. A., Cahn, W., de Zwarte, S. M. C., Hulshoff Pol, H. E., … Turner, J. A. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing Neuro imaging genetics through meta analysis (ENIGMA) consortium. *Biological Psychiatry,* 84(9), 644–654. https://doi.org/10.1016/j.biopsych.2018.04.023

Favre, P., Pauling, M., Stout, J., Hozer, F., Sarrazin, S., Abé, C., Alda, M., Alloza, C., Alonso-Lana, S., Andreassen, O. A., Baune, B. T., Benedetti, F., Busatto, G. F., Canales-Rodríguez, E. J., Caseras, X., Chaim-Avancini, T. M., Ching, C. R. K., Dannlowski, U., Deppe, M., … Houenou, J. (2019). Widespread white matter microstructural abnormalities in bipolar disorder: Evidence from mega- and meta-analyses across 3033 individuals. *Neuropsychopharmacology,* 44(13), 2285–2293. https://doi.org/10.1038/s41386-019-0485-6

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research,* 17(4), 319–334. https://doi.org/10.1016/0022-3956(82)90038-3

Fischl, B. (2012). FreeSurfer. *NeuroImage,* 62(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron,* 33(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Fraguas, D., Díaz-Caneja, C. M., Pina-Camacho, L., Janssen, J., & Arango, C. (2016). Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies. *Schizophrenia Research,* 173(3), 132–139. https://doi.org/10.1016/j.schres.2014.12.022

Frazier, J. A., Ahn, M. S., DeJong, S., Bent, E. K., Breeze, J. L., & Giuliano, A. J. (2005). Magnetic resonance imaging studies in early-onset bipolar disorder: A critical review. *Harvard Review of Psychiatry,* 13(3), 125–140. https://doi.org/10.1080/10673220591003597

Frazier, J. A., Breeze, J. L., Papadimitriou, G., Kennedy, D. N., Hodge, S. M., Moore, C. M., Howard, J. D., Rohan, M. P., Caviness, V. S., & Makris, N. (2007). White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorders,* 9(8), 799–809. https://doi.org/10.1111/j.1399-5618.2007.00482.x

Frazier, J. A., Giedd, J. N., Hamburger, S. D., Albus, K. E., Kassen, D., Vaituzis, A. C., Rajapakse, J. C., Lenane, M. C., McKenna, K., Jacobsen, L. K., Gordon, C. T., Breier, A., & Rapoport, J. L. (1996). Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. *Archives of General Psychiatry,* 53(7), 617–624. https://doi.org/10.1001/archpsyc.1996.01830070065010

Frazier, J. A., Giedd, J. N., Kaysen, D., Albus, K., Hamburger, S., Alaghband-Rad, J., Lenane, M. C., McKenna, K., Breier, A., & Rapoport, J. L. (1996). Childhood-onset schizophrenia: Brain MRI rescan after 2 years of clozapine maintenance treatment. *American Journal of Psychiatry,* 153(4), 564–566. https://doi.org/10.1176/ajp.153.4.564

Frazier, J. A., Hodge, S. M., Breeze, J. L., Giuliano, A. J., Terry, J. E., Moore, C. M., Kennedy, D. N., Lopez-Larson, M. P., Caviness, V. S., Seidman, L. J., Zablotsky, B., & Makris, N. (2008). Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. *Schizophrenia Bulletin,* 34(1), 37–46. https://doi.org/10.1093/schbul/sbm120

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience (New York, N.Y.), 3*(2), 89–97.

Gao, W., Jiao, Q., Qi, R., Zhong, Y., Lu, D., Xiao, Q., Lu, S., Xu, C., Zhang, Y., Liu, X., Yang, F., Lu, G., & Su, L. (2013). Combined analyses of gray matter voxel-based morphometry and white matter tract-based spatial statistics in pediatric bipolar mania. *Journal of Affective Disorders,* 150(1), 70–76. https://doi.org/10.1016/j.jad.2013.02.021

Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: What have we learned and where are we going? *Neuron,* 67(5), 728–734. https://doi.org/10.1016/j.neuron.2010.08.040

Gogtay, N., Sporn, A., Clasen, L. S., Nugent, T. F., Greenstein, D., Nicolson, R., Giedd, J. N., Lenane, M., Gochman, P., Evans, A., & Rapoport, J. L. (2004). Comparison of progressive cortical gray matter loss in childhood-onset schizophrenia with that in childhood-onset atypical psychoses. *Archives of General Psychiatry,* 61(1), 17–22. https://doi.org/10.1001/archpsyc.61.1.17

Gogtay, N., Vyas, N. S., Testa, R., Wood, S. J., & Pantelis, C. (2011). Age of onset of schizophrenia: Perspectives from structural neuroimaging studies. *Schizophrenia Bulletin,* 37(3), 504–513. https://doi.org/10.1093/schbul/sbr030

Gönenç, A., Frazier, J. A., Crowley, D. J., & Moore, C. M. (2010). Combined diffusion tensor imaging and transverse relaxometry in early-onset bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry,* 49(12), 1260–1268. https://doi.org/10.1016/j.jaac.2010.08.015

Gurholt, T. P., Haukvik, U. K., Lonning, V., Jönsson, E. G., Pasternak, O., & Agartz, I. (2020). Microstructural white matter and links with subcortical structures in chronic schizophrenia: A free-water imaging approach. *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.00056

Gurholt, T. P., Lonning, V., Nerland, S., Jørgensen, K. N., Haukvik, U. K., Alloza, C., Arango, C., Barth, C., Bearden, C. E., Berk, M., Bohman, H., Dandash, O., Díaz-Caneja, C. M., Edbom, C. T., van Erp, T. G. M., Fett, A. K. J., Frangou, S., Goldstein, B. I., Grigorian, A., … Agartz, I. (2020). Intracranial and subcortical volumes in adolescents with early-onset psychosis: A multisite mega-analysis from the ENIGMA consortium. *Human Brain Mapping, 43*, 373–384. https://doi.org/10.1002/hbm.25212

Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C. M. P., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin,* 39(5), 1129–1138. https://doi.org/10.1093/schbul/sbs118

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., Versace, A., Bilderbeck, A. C., Uhlmann, A., Mwangi, B., Krämer, B., Overs, B., Hartberg, C. B., Abe, C., Dima, D., Grotegerd, D., Sprooten, E., Ben, E., Jimenez, E., … Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular Psychiatry,* 23(4), 932−942. https://doi.org/10.1038/mp.2017.73

Hibar, D. P., Westlye, L. T., Van Erp, T. G. M., Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., Agartz, I., Dale, A. M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C. J., Ingvar, M., Landén, M., … Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular Psychiatry, 21*(12), 1710−1716. https://doi.org/10.1038/mp.2015.227

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S. J., van Hulzen, K. J. E., Medland, S. E., Shumskaya, E., Jahanshad, N., Zeeuw, P. D., Szekely, E., Sudre, G., Wolfers, T., Onnink, A. M. H., Dammers, J. T., Mostert, J. C., Vives-Gilabert, Y., Kohls, G., … Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *The Lancet Psychiatry,* 4(4), 310−319. https://doi.org/10.1016/S2215-0366(17)30049-4

Huber, R. S., Subramaniam, P., Kondo, D. G., Shi, X., Renshaw, P. F., & Yurgelun-Todd, D. A. (2019). Reduced lateral orbitofrontal cortex volume and suicide behavior in youth with bipolar disorder. *Bipolar Disorders,* 21(4), 321−329. https://doi.org/10.1111/bdi.12729

Huhtaniska, S., Jääskeläinen, E., Hirvonen, N., Remes, J., Murray, G. K., Veijola, J., Isohanni, M., & Miettunen, J. (2017). Long-term antipsychotic use and brain changes in schizophrenia − a systematic review and meta-analysis. *Human Psychopharmacology,* 32(2). https://doi.org/10.1002/hup.2574

James, A. C., James, S., Smith, D. M., & Javaloyes, A. (2004). Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. *American Journal of Psychiatry,* 161(6), 1023−1029. https://doi.org/10.1176/appi.ajp.161.6.1023

Janssen, J., Reig, S., Alemán, Y., Schnack, H., Udias, J. M., Parellada, M., Graell, M., Moreno, D., Zabala, A., Balaban, E., Desco, M., & Arango, C. (2009). Gyral and sulcal cortical thinning in adolescents with first episode early-onset psychosis. *Biological Psychiatry,* 66(11), 1047−1054. https://doi.org/10.1016/j.biopsych.2009.07.021

Johnston, J. A. Y., Wang, F., Liu, J., Blond, B. N., Wallace, A., Liu, J., Spencer, L., Lippard, E. T. C., Purves, K. L., Landeros-Weisenberger, A., Hermes, E., Pittman, B., Zhang, S., King, R., Martin, A., Oquendo, M. A., & Blumberg, H. P. (2017). Multimodal neuroimaging of frontolimbic structure and function associated with suicide attempts in adolescents and young adults with bipolar disorder. *American Journal of Psychiatry,* 174(7), 667−675. https://doi.org/10.1176/appi.ajp.2016.15050652

Jørgensen, K. N., Nesvåg, R., Gunleiksrud, S., Raballo, A., Jönsson, E. G., & Agartz, I. (2016). First- and second-generation antipsychotic drug treatment and subcortical brain morphology in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience,* 266(5), 451−460. https://doi.org/10.1007/s00406-015-0650-9

Juuhl-Langseth, M., Hartberg, C. B., Holmén, A., Thormodsen, R., Groote, I. R., Rimol, L. M., Emblem, K. E., Agartz, I., & Rund, B. R. (2015). Impaired verbal learning is associated with larger caudate volumes in early onset schizophrenia spectrum disorders. *PLoS ONE,* 10(7). https://doi.org/10.1371/journal.pone.0130435

Juuhl-Langseth, M., Rimol, L. M., Rasmussen, I. A., Thormodsen, R., Holmén, A., Emblem, K. E., Due-Tønnessen, P., Rund, B. R., & Agartz, I. (2012). Comprehensive segmentation of subcortical brain volumes in early onset schizophrenia reveals limited structural abnormalities.

Psychiatry Research - Neuroimaging, 203(1), 14–23. https://doi.org/10.1016/j.pscychresns.2011.10.005

Kafantaris, V., Kingsley, P., Ardekani, B., Saito, E., Lencz, T., Lim, K., & Szeszko, P. (2009). Lower orbital frontal white matter integrity in adolescents with bipolar I disorder. *Journal of the American Academy of Child and Adolescent Psychiatry,* 48(1), 79–86. https://doi.org/10.1097/CHI.0b013e3181900421

Kalmar, J. H., Wang, F., Spencer, L., Edmiston, E., Lacadie, C. M., Martin, A., Constable, T. R., Duncan, J. S., Staib, L. H., Papademetris, X., & Blumberg, H. P. (2009). Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *Journal of the International Neuropsychological Society,* 15(3), 476–481. https://doi.org/10.1017/S1355617709090584

Kaur, S., Sassi, R. B., Axelson, D., Nicoletti, M., Brambilla, P., Monkul, E. S., Hatch, J. P., Keshavan, M. S., Ryan, N., Birmaher, B., & Soares, J. C. (2005). Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. *American Journal of Psychiatry,* 162(9), 1637–1643. https://doi.org/10.1176/appi.ajp.162.9.1637

Keepers, G. A., Fochtmann, L. J., Anzia, J. M., Benjamin, S., Lyness, J. M., Mojtabai, R., Servis, M., Walaszek, A., Buckley, P., Lenzenweger, M. F., Young, A. S., Degenhardt, A., & Hong, S. H. (2020). The American psychiatric association practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry,* 177(9), 868–872. https://doi.org/10.1176/appi.ajp.2020.177901

Keller, A., Castellanos, F. X., Vaituzis, A. C., Jeffries, N. O., Giedd, J. N., & Rapoport, J. L. (2003). Progressive loss of cerebellar volume in childhood-onset schizophrenia. *American Journal of Psychiatry,* 160(1), 128–133. https://doi.org/10.1176/appi.ajp.160.1.128

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O. A., Arango, C., Banaj, N., Bouix, S., Bousman, C. A., Brouwer, R. M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., … Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA Schizophrenia DTI Working Group. *Molecular Psychiatry,* 23(5), 1261–1269. https://doi.org/10.1038/mp.2017.170

Koshiyama, D., Fukunaga, M., Okada, N., Morita, K., Nemoto, K., Usui, K., Yamamori, H., Yasuda, Y., Fujimoto, M., Kudo, N., Azechi, H., Watanabe, Y., Hashimoto, N., Narita, H., Kusumi, I., Ohi, K., Shimada, T., Kataoka, Y., Yamamoto, M., … Hashimoto, R. (2020). White matter microstructural alterations across four major psychiatric disorders: Mega-analysis study in 2937 individuals. *Molecular Psychiatry,* 25(4), 883–895. https://doi.org/10.1038/s41380-019-0553-7

Kumra, S., Ashtari, M., Cervellione, K. L., Henderson, I., Kester, H., Roofeh, D., Wu, J., Clarke, T., Thaden, E., Kane, J. M., Rhinewine, J., Lencz, T., Diamond, A., Ardekani, B. A., & Szeszko, P. R. (2005). White matter abnormalities in early-onset schizophrenia: A voxel-based diffusion tensor imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*(9), 934–941. https://doi.org/10.1097/01.chi.0000170553.15798.94

Kumra, S., Giedd, J. N., Vaituzis, A. C., Jacobsen, L. K., McKenna, K., Bedwell, J., Hamburger, S., Nelson, J. E., Lenane, M., & Rapoport, J. L. (2000). Childhood-onset psychotic disorders: Magnetic resonance imaging of volumetric differences in brain structure. *American Journal of Psychiatry,* 157(9), 1467–1474. https://doi.org/10.1176/appi.ajp.157.9.1467

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., Goff, D., West, W. C., Williams, S. C. R., Van der Kouwe, A. J. W., Salat, D. H., Dale, A. M., & Fischl, B. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry,* 60(9), 878–888. https://doi.org/10.1001/archpsyc.60.9.878

Laidi, C., d'Albis, M. A., Wessa, M., Linke, J., Phillips, M. L., Delavest, M., Bellivier, F., Versace, A., Almeida, J., Sarrazin, S., Poupon, C., Le Dudal, K., Daban, C., Hamdani, N., Leboyer, M., & Houenou, J. (2015). Cerebellar volume in schizophrenia and bipolar I disorder with and without psychotic features. *Acta Psychiatrica Scandinavica,* 131(3), 223−233. https://doi.org/10.1111/acps.12363

Lawyer, G., Nesvåg, R., Varnäs, K., Okugawa, G., & Agartz, I. (2009). Grey and white matter proportional relationships in the cerebellar vermis altered in schizophrenia. *Cerebellum,* 8(1), 52−60. https://doi.org/10.1007/s12311-008-0071-7

Linke, J. O., Stavish, C., Adleman, N. E., Sarlls, J., Towbin, K. E., Leibenluft, E., & Brotman, M. A. (2020). White matter microstructure in youth with and at risk for bipolar disorder. *Bipolar Disorders,* 22(2), 163−173. https://doi.org/10.1111/bdi.12885

Lu, L. H., Zhou, X. J., Fitzgerald, J., Keedy, S. K., Reilly, J. L., Passarotti, A. M., Sweeney, J. A., & Pavuluri, M. (2012). Microstructural abnormalities of white matter differentiate pediatric and adult-onset bipolar disorder. *Bipolar Disorders,* 14(6), 597−606. https://doi.org/10.1111/j.1399-5618.2012.01045.x

Mills, K. L., Goddings, A. L., Herting, M. M., Meuwese, R., Blakemore, S. J., Crone, E. A., Dahl, R. E., Güroğlu, B., Raznahan, A., Sowell, E. R., & Tamnes, C. K. (2016). Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. *NeuroImage,* 141, 273−281. https://doi.org/10.1016/j.neuroimage.2016.07.044

Mitchell, R. H. B., Metcalfe, A. W. S., Islam, A. H., Toma, S., Patel, R., Fiksenbaum, L., Korczak, D., MacIntosh, B. J., & Goldstein, B. I. (2018). Sex differences in brain structure among adolescents with bipolar disorder. *Bipolar Disorders,* 20(5), 448−458. https://doi.org/10.1111/bdi.12663

Moberget, T., & Ivry, R. B. (2019). Prediction, psychosis, and the cerebellum. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging,* 4(9), 820−831. https://doi.org/10.1016/j.bpsc.2019.06.001

Moe, A. A. K., Medely, G. A., Reeks, T., Burne, T. H. J., & Eyles, D. W. (2017). Short- and long-term effects of risperidone on catalepsy sensitisation and acquisition of conditioned avoidance response: Adolescent vs adult rats. *Pharmacological Research,* 121, 1−13. https://doi.org/10.1016/j.phrs.2017.04.013

Moore, C. M., Frazier, J. A., Glod, C. A., Breeze, J. L., Dieterich, M., Finn, C. T., Frederick, B. D., & Renshaw, P. F. (2007). Glutamine and glutamate levels in children and adolescents with bipolar disorder: A 4.0-T proton magnetic resonance spectroscopy study of the anterior cingulate cortex. *Journal of the American Academy of Child and Adolescent Psychiatry,* 46(4), 524−534. https://doi.org/10.1097/chi.0b013e31802f5f2c

Najt, P., Nicoletti, M., Chen, H. H., Hatch, J. P., Caetano, S. C., Sassi, R. B., Axelson, D., Brambilla, P., Keshavan, M. S., Ryan, N. D., Birmaher, B., & Soares, J. C. (2007). Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. *Neuroscience Letters,* 413(3), 183−186. https://doi.org/10.1016/j.neulet.2006.10.016

Najt, P., Wang, F., Spencer, L., Johnston, J. A. Y., Cox Lippard, E. T., Pittman, B. P., Lacadie, C., Staib, L. H., Papademetris, X., & Blumberg, H. P. (2016). Anterior cortical development during adolescence in bipolar disorder. *Biological Psychiatry,* 79(4), 303−310. https://doi.org/10.1016/j.biopsych.2015.03.026

Natu, V. S., Gomez, J., Barnett, M., Jeska, B., Kirilina, E., Jaeger, C., Zhen, Z., Cox, S., Weiner, K. S., Weiskopf, N., & Grill-Spector, K. (2019). Apparent thinning of human visual cortex during childhood is associated with myelination. *Proceedings of the National Academy of Sciences of the United States of America,* 116(41), 20750−20759. https://doi.org/10.1073/pnas.1904931116

Nortje, G., Stein, D. J., Radua, J., Mataix-Cols, D., & Horn, N. (2013). Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. *Journal of Affective Disorders,* 150(2), 192–200. https://doi.org/10.1016/j.jad.2013.05.034

Paillère Martinot, M. L., Lemaitre, H., Artiges, E., Miranda, R., Goodman, R., Penttilä, J., Struve, M., Fadai, T., Kappel, V., Poustka, L., Conrod, P., Banaschewski, T., Barbot, A., Barker, G. J., Büchel, C., Flor, H., Gallinat, J., Garavan, H., Heinz, A., … Martinot, J. L. (2014). White-matter microstructure and gray-matter volumes in adolescents with subthreshold bipolar symptoms. *Molecular Psychiatry,* 19(4), 462–470. https://doi.org/10.1038/mp.2013.44

Palaniyappan, L., Das, T. K., Winmill, L., Hough, M., & James, A. (2019). Progressive post-onset reorganisation of MRI-derived cortical thickness in adolescents with schizophrenia. *Schizophrenia Research,* 208, 477–478. https://doi.org/10.1016/j.schres.2019.01.041

Pasternak, O., Kelly, S., Sydnor, V. J., & Shenton, M. E. (2018). Advances in microstructural diffusion neuroimaging for psychiatric disorders. *NeuroImage,* 182, 259–282. https://doi.org/10.1016/j.neuroimage.2018.04.051

Pavuluri, M. N., Yang, S., Kamineni, K., Passarotti, A. M., Srinivasan, G., Harral, E. M., Sweeney, J. A., & Zhou, X. J. (2009). Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biological Psychiatry,* 65(7), 586–593. https://doi.org/10.1016/j.biopsych.2008.10.015

Radoeva, P. D., Jenkins, G. A., Schettini, E., Gilbert, A. C., Barthelemy, C. M., DeYoung, L. L. A., Kudinova, A. Y., Kim, K. L., MacPherson, H. A., & Dickstein, D. P. (2020). White matter correlates of cognitive flexibility in youth with bipolar disorder and typically developing children and adolescents. *Psychiatry Research - Neuroimaging*, *305*. https://doi.org/10.1016/j.pscychresns.2020.111169

Rapoport, J. L., Giedd, J. N., Blumenthal, J., Hamburger, S., Jeffries, N., Fernandez, T., Nicolson, R., Bedwell, J., Lenane, M., Zijdenbos, A., Paus, T., & Evans, A. (1999). Progressive cortical change during adolescence in childhood-onset schizophrenia: A longitudinal magnetic resonance imaging study. *Archives of General Psychiatry,* 56(7), 649–654. https://doi.org/10.1001/archpsyc.56.7.649

Rapoport, J. L., & Gogtay, N. (2011). Childhood onset schizophrenia: Support for a progressive neurodevelopmental disorder. *International Journal of Developmental Neuroscience,* 29(3), 251–258. https://doi.org/10.1016/j.ijdevneu.2010.10.003

Ren, S., Chang, M., Yin, Z., Feng, R., Wei, Y., Duan, J., Jiang, X., Wei, S., Tang, Y., Wang, F., & Li, S. (2020). Age-related alterations of white matter integrity in adolescents and young adults with bipolar disorder. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.01010

Rimol, L. M., Hartberg, C. B., Nesvåg, R., Fennema-Notestine, C., Hagler, D. J., Pung, C. J., Jennings, R. G., Haukvik, U. K., Lange, E., Nakstad, P. H., Melle, I., Andreassen, O. A., Dale, A. M., & Agartz, I. (2010). Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biological Psychiatry,* 68(1), 41–50. https://doi.org/10.1016/j.biopsych.2010.03.036

Roberts, G., Wen, W., Frankland, A., Perich, T., Holmes-Preston, E., Levy, F., Lenroot, R. K., Hadzi-Pavlovic, D., Nurnberger, J. I., Breakspear, M., & Mitchell, P. B. (2016). Interhemispheric white matter integrity in young people with bipolar disorder and at high genetic risk. *Psychological Medicine,* 46(11), 2385–2396. https://doi.org/10.1017/S0033291716001161

Sallet, P. C., Elkis, H., Alves, T. M., Oliveira, J. R., Sassi, E., Campi De Castro, C., Busatto, G. F., & Gattaz, W. F. (2003). Reduced cortical folding in schizophrenia: An MRI morphometric study. *American Journal of Psychiatry,* 160(9), 1606–1613. https://doi.org/10.1176/appi.ajp.160.9.1606

Sämann, P. G., Iglesias, J. E., Gutman, B., Grotegerd, D., Leenings, R., Flint, C., Dannlowski, U., Clarke-Rubright, E. K., Morey, R. A., van Erp, T. G. M., Whelan, C. D., Han, L. K. M., van Velzen, L. S., Cao, B., Augustinack, J. C., Thompson, P. M., Jahanshad, N., & Schmaal, L. (2020). FreeSurfer-based segmentation of hippocampal subfields: A review of methods and applications, with a novel quality control procedure for ENIGMA studies and other collaborative efforts. *Human Brain Mapping, 43*, 207−233. https://doi.org/10.1002/hbm.25326

Sanches, M., Sassi, R. B., Axelson, D., Nicoletti, M., Brambilla, P., Hatch, J. P., Keshavan, M. S., Ryan, N. D., Birmaher, B., & Soares, J. C. (2005). Subgenual prefrontal cortex of child and adolescent bipolar patients: A morphometric magnetic resonance imaging study. *Psychiatry Research - Neuroimaging,* 138(1), 43−49. https://doi.org/10.1016/j.pscychresns.2004.11.004

Sassi, R. B., Stanley, J. A., Axelson, D., Brambilla, P., Nicoletti, M. A., Keshavan, M. S., Ramos, R. T., Ryan, N., Birmaher, B., & Soares, J. C. (2005). Reduced NAA levels in the dorsolateral prefrontal cortex of young bipolar patients. *American Journal of Psychiatry,* 162(11), 2109−2115. https://doi.org/10.1176/appi.ajp.162.11.2109

Sgouros, S., Goldin, J. H., Hockley, A. D., Wake, M. J. C., & Natarajan, K. (1999). Intracranial volume change in childhood. *Journal of Neurosurgery,* 91(4), 610−616. https://doi.org/10.3171/jns.1999.91.4.0610

Shonibare, D. O., Patel, R. R., Islam, A. H., Metcalfe, A. W. S., Fiksenbaum, L., Freeman, N., MacIntosh, B. J., Kennedy, J. L., & Goldstein, B. I. (2021). Neurostructural phenotypes of CACNA1C rs1006737 in adolescents with bipolar disorder and healthy controls. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *104*. https://doi.org/10.1016/j.pnpbp.2020.110071

Sultan, A. A., Kennedy, K. G., Fiksenbaum, L., Macintosh, B. J., & Goldstein, B. I. (2021). Neurostructural correlates of cannabis use in adolescent bipolar disorder. *International Journal of Neuropsychopharmacology,* 24(3), 181−190. https://doi.org/10.1093/ijnp/pyaa077

Tamnes, C. K., & Agartz, I. (2016). White matter microstructure in early-onset schizophrenia: A systematic review of diffusion tensor imaging studies. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(4), 269−279. https://doi.org/10.1016/j.jaac.2016.01.004

Tamnes, C. K., Herting, M. M., Goddings, A. L., Meuwese, R., Blakemore, S. J., Dahl, R. E., Güroğlu, B., Raznahan, A., Sowell, E. R., Crone, E. A., & Mills, K. L. (2017). Development of the cerebral cortex across adolescence: A multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. *Journal of Neuroscience,* 37(12), 3402−3412. https://doi.org/10.1523/JNEUROSCI.3302-16.2017

Tamnes, C. K., Roalf, D. R., Goddings, A. L., & Lebel, C. (2018). Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. *Developmental Cognitive Neuroscience,* 33, 161−175. https://doi.org/10.1016/j.dcn.2017.12.002

Tamnes, C. K., Walhovd, K. B., Dale, A. M., Østby, Y., Grydeland, H., Richardson, G., Westlye, L. T., Roddey, J. C., Hagler, D. J., Due-Tønnessen, P., Holland, D., & Fjell, A. M. (2013). Brain development and aging: Overlapping and unique patterns of change. *NeuroImage,* 68, 63−74. https://doi.org/10.1016/j.neuroimage.2012.11.039

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., Toga, A. W., & Rapoport, J. L. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America,* 98(20), 11650−11655. https://doi.org/10.1073/pnas.201243998

Thormodsen, R., Rimol, L. M., Tamnes, C. K., Juuhl-Langseth, M., Holmén, A., Emblem, K. E., Rund, B. R., & Agartz, I. (2013). Age-related cortical thickness differences in adolescents

with early-onset schizophrenia compared with healthy adolescents. *Psychiatry Research - Neuroimaging,* 214(3), 190−196. https://doi.org/10.1016/j.pscychresns.2013.07.003

Tiemeier, H., Lenroot, R. K., Greenstein, D. K., Tran, L., Pierson, R., & Giedd, J. N. (2010). Cerebellum development during childhood and adolescence: A longitudinal morphometric MRI study. *NeuroImage,* 49(1), 63−70. https://doi.org/10.1016/j.neuroimage.2009.08.016

Toma, S., Islam, A. H., Metcalfe, A. W. S., Mitchell, R. H. B., Fiksenbaum, L., Macintosh, B. J., & Goldstein, B. I. (2019). Cortical volume and thickness across bipolar disorder subtypes in adolescents: A preliminary study. *Journal of Child and Adolescent Psychopharmacology,* 29(2), 141−151. https://doi.org/10.1089/cap.2017.0137

Tournier, J. D., Mori, S., & Leemans, A. (2011). Diffusion tensor imaging and beyond. *Magnetic Resonance in Medicine,* 65(6), 1532−1556. https://doi.org/10.1002/mrm.22924

Vijayakumar, N., Op de Macks, Z., Shirtcliff, E. A., & Pfeifer, J. H. (2018). Puberty and the human brain: Insights into adolescent development. *Neuroscience and Biobehavioral Reviews,* 92, 417−436. https://doi.org/10.1016/j.neubiorev.2018.06.004

Vitolo, E., Tatu, M. K., Pignolo, C., Cauda, F., Costa, T., Ando, A., & Zennaro, A. (2017). White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging studies. *Psychiatry Research - Neuroimaging,* 270, 8−21. https://doi.org/10.1016/j.pscychresns.2017.09.014

Voets, N. L., Hough, M. G., Douaud, G., Matthews, P. M., James, A., Winmill, L., Webster, P., & Smith, S. (2008). Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. *NeuroImage,* 43(4), 665−675. https://doi.org/10.1016/j.neuroimage.2008.08.013

Wang, F., Kalmar, J. H., Womer, F. Y., Edmiston, E. E., Chepenik, L. G., Chen, R., Spencer, L., & Blumberg, H. P. (2011). Olfactocentric paralimbic cortex morphology in adolescents with bipolar disorder. *Brain,* 134(7), 2005−2012. https://doi.org/10.1093/brain/awr124

Wang, S. M., Ouyang, W. C., Wu, M. Y., & Kuo, L. C. (2020). Relationship between motor function and psychotic symptomatology in young−adult patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience,* 270(3), 373−382. https://doi.org/10.1007/s00406-019-01004-1

Weathers, J., Lippard, E. T. C., Spencer, L., Pittman, B., Wang, F., & Blumberg, H. P. (2018). Longitudinal diffusion tensor imaging study of adolescents and young adults with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry,* 57(2), 111−117. https://doi.org/10.1016/j.jaac.2017.11.014

White, T., Andreasen, N. C., Nopoulos, P., & Magnotta, V. (2003). Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. *Biological Psychiatry,* 54(4), 418−426. https://doi.org/10.1016/S0006-3223(03)00065-9

Zhang, C., Wang, Q., Ni, P., Deng, W., Li, Y., Zhao, L., Ma, X., Wang, Y., Yu, H., Li, X., Zhang, P., Meng, Y., Liang, S., Li, M., & Li, T. (2017). Differential cortical gray matter deficits in adolescent- and adult-onset first-episode treatment-naïve patients with schizophrenia. *Scientific Reports,* 7(1). https://doi.org/10.1038/s41598-017-10688-1

Zhang, W., Xiao, Y., Sun, H., Patino, L. R., Tallman, M. J., Weber, W. A., Adler, C. M., Klein, C., Strawn, J. R., Nery, F. G., Gong, Q., Sweeney, J. A., Lui, S., & DelBello, M. P. (2018). Discrete patterns of cortical thickness in youth with bipolar disorder differentially predict treatment response to quetiapine but not lithium. *Neuropsychopharmacology,* 43(11), 2256−2263. https://doi.org/10.1038/s41386-018-0120-y

Chapter 9

Functional brain imaging in early-onset psychosis

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Introduction

Schizophrenia and bipolar disorder are often jointly referred to as psychotic disorders because positive psychotic symptoms are shared clinical features (American Psychiatric Association, 2013). Further, genetic and epidemiological studies have demonstrated substantial overlap between these two disorders in terms of genetic architecture and familial segregation (Lee et al., 2013; Lichtenstein et al., 2009). Early-onset psychosis is not a specific diagnostic entity, but an umbrella term commonly used in research to designate individuals with childhood- or adolescent-onset schizophrenia (early-onset schizophrenia; EOS) or bipolar disorder (early-onset bipolar disorder; EOBD). Although the age boundaries vary across studies, the terms childhood-onset typically refer to disease onset prior to the 13th birthday while the terms adolescent-onset typically refer to disease onset between the ages of 13 and 18 years. Because of the rarity of childhood-onset psychosis, affecting one to four in 10,000 individuals (Clemmensen et al., 2012), most studies tend to study mixed child and adolescent samples. In addition, some children and adolescents might be at elevated risk for these disorders by virtue of subsyndromal psychopathology or familial risk or a combination of both. Familial high-risk (FHR) is generally defined by the presence of at least one first-degree relative (commonly a parent) affected with either schizophrenia or bipolar disorder. The concept of clinical high-risk (CHR) was initially developed in the context of schizophrenia using specific criteria about the nature and duration of the subthreshold symptoms that increase the risk of syndromal

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Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00008-1

schizophrenia (Fusar-Poli, 2017). However, the symptoms defined by the CHR concept do not have prognostic specificity for schizophrenia because they can also present in individuals that later develop bipolar disorder (Fusar-Poli, 2017). Taken together, schizophrenia and bipolar disorder in children and adolescents, as well as the familial and clinical high-risk states for these disorders, represent the full spectrum of early-onset psychosis and related conditions. Youth with these conditions are of clinical interest because of their risk of significant and persistent clinical morbidity and social disability (Fusar-Poli, 2017). In parallel, there is much research interest in these conditions because of their potential to offer a window into interactions between evolving disease mechanisms and brain maturational processes.

This chapter provides a critical review of findings from studies on children and adolescents with early-onset psychosis and related conditions that employed functional magnetic resonance imaging (fMRI). Magnetic resonance imaging enables the safe in-vivo study of brain organization and function in health and disease and has had a transformative role in establishing that psychiatric disorders are disorders of the brain. The underlying assumption of fMRI is that blood flow and the oxy-to deoxy-hemoglobin ratio change in response to metabolic demands engendered by neuronal activity and that these changes can be inferred from the blood oxygenation level-dependent (BOLD) signal. The BOLD signal has been used to model the activity and functional connectivity of brain regions at rest or during the execution of directed and effortful mental operations. Resting-state fMRI (rs-fMRI) has been fundamental in uncovering the intrinsic activity of the brain, as inferred from the spontaneous fluctuations in the BOLD signal. By contrast, task-based fMRI (t-fMRI) has been used to study brain activity and connectivity during goal-directed or effortful cognition based on the contrast of the BOLD signal between task-stimulated states and control states; this contrast is used to identify brain regions whose activity or connectivity is differentially affected by task performance.

Systematic literature review

A systematic literature review was undertaken within the digital database PubMed to identify relevant fMRI articles published during the last decade (January 1st, 2011, to March 1st, 2021) with age filters for childhood and adolescent samples. The search included the following terms and their combinations: schizophrenia; schizophrenic; psychosis; bipolar disorder; mania; depression; affective psychosis; nonaffective psychosis; psychotic; prodrome; prodromal; at-risk; clinical high-risk; clinical ultra-high-risk; genetic risk; familial risk; offspring; early-onset; youth; adolescence; adolescent; adolescent-onset; child; pediatric; childhood-onset; fMRI; brain activation; brain activity; functional MRI; resting-state; rs-fMRI; task-fMRI; networks; connectivity; memory; inhibition; attention; language.

Eligible articles (1) were peer-reviewed and published in English; (2) used fMRI techniques to acquire neuroimaging data; (3) involved participants who

were children and/or adolescents at the time of scanning. As there was marked interstudy variability with regard to the upper age boundary of the adolescent samples, studies were included if more than 70% of the study participants were below the age of 18 years as inferred by the mean age and standard deviation of the study sample; and (4) included a healthy comparison group in addition to clinical samples. With respect to the clinical samples, these were required to meet one of the following definitions: (a) children or adolescents with EOS or EOBD according to criteria set by the fourth or fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000, 2013); (b) children or adolescents at clinical high-risk for schizophrenia (CHR-SCZ) or bipolar disorder (CHR-BD) as determined by dedicated scales and instruments; (c) children or adolescents at familial high-risk for schizophrenia (FHR-SCZ) or bipolar disorder (FHR-BD), as determined by having at least one first-degree relative diagnosed with schizophrenia or bipolar disorder. Studies reporting different fMRI investigations on the same sample and longitudinal studies on the same sample were retained. When the same fMRI investigation was applied to significantly overlapping samples but reported in separate articles, only the article with the largest sample size was retained. Articles reporting on treatment interventions were only included if they provided baseline case-control differences prior to treatment initiation. Articles reporting on psychosis in the context of chromosomal or other specific genetic abnormalities (e.g., velocardiofacial syndrome) were excluded.

This literature search yielded 1290 potentially eligible studies on EOS and related high-risk states and 363 articles on EOBD and related high-risk states. Following exclusion of articles that did not meet eligibility criteria, 47 EOS-related studies (t-fMRI = 18; rs-fMRI = 29) and 58 EOBD-related studies (t-fMRI = 43; rs-fMRI = 15) were retained (Fig. 9.1).

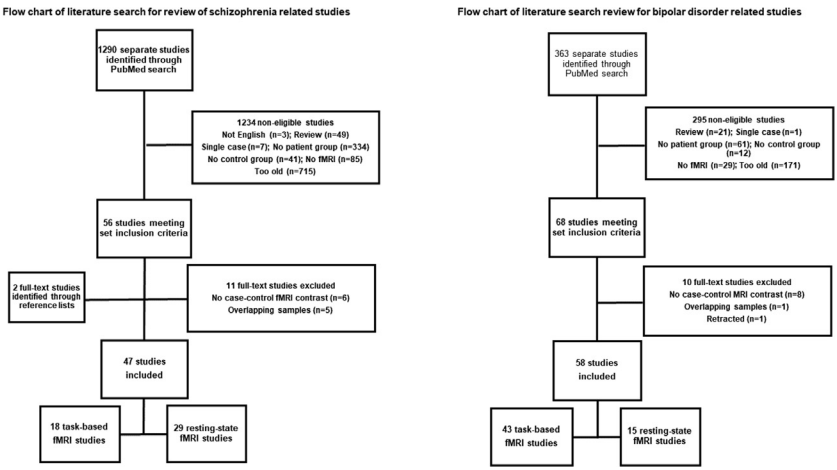

FIGURE 9.1 Flow chart of article selection for the systematic literature review.

Task-related functional magnetic resonance imaging studies

A diverse array of fMRI tasks has been used to investigate task-related brain activity and connectivity in youth with early-onset psychosis. We used the Research Domain Criteria (RDoC) framework (Insel et al., 2010), proposed by the US National Institute of Mental Health (NIMH), to synthesize findings. This framework represents the best available approximation to a criterion approach for the classification of the various fMRI tasks and enables the attribution of study findings to functional changes in clearly defined domains of mental functioning. The RDoC framework comprises six major domains: systems for negative and positive valence, cognitive and sensorimotor systems, systems for social processes, and arousal/regulatory systems. Within each domain, elements representing subordinate processes are further specified as constructs and subconstructs. The t-fMRI studies included in this review are summarized in Tables 9.1 and 9.2 and classified according to the RDoC construct that most closely mapped to the fMRI paradigm used. Unless otherwise specified, all the reported comparisons below use the healthy youth group in each study as the normative reference.

Cognitive systems

In youth with early-onset psychosis, fMRI studies corresponding to the domain of cognitive systems have used tasks that map onto the constructs of cognitive control, declarative memory, and working memory. Across tasks, these constructs are supported by a network which encompasses the dorsolateral, ventrolateral, ventromedial and frontopolar cortex, the anterior cingulate cortex (ACC), the superior and inferior parietal cortex, parts of the occipital and temporal cortices and subcortical regions comprising the caudate, putamen, thalamus, and cerebellum (Niendam et al., 2012). Within this network, the ACC is thought to be involved in performance monitoring. The dorsal frontoparietal regions are postulated to support goal-representation and working memory, while ventrolateral and striatal pathways are primarily engaged in response inhibition and selection.

Cognitive control: response selection, inhibition/suppression, performance monitoring

Tasks mapping to these cognitive control subconstructs include those that require suppression of responses (e.g., the stop-signal and go/no-go tasks) and those that require suppression of learned reactions and selection of alternative responses (e.g., Stroop Color Word Test and the AX version of the Continuous Performance Task). In studies using these paradigms, patients with EOBD showed a pattern of hyperactivation of prefrontal regions despite adequate performance, which has been interpreted as evidence of neural compensation

TABLE 9.1 Schizophrenia-related task-fMRI studies.

Study	PMID	Early-onset		Familial high- risk		Clinical high-risk		fMRI paradigm	Construct
		n	Mean age, years (SD)	n	Mean age, years (SD)	n	Mean age, years (SD)		
Cognitive systems									
Bakshi et al. (2011) [a]	21306732			19	14.3 (3.1)			N-back task	Working memory
Bittner et al. (2015)	24675869	17	17.9					Delayed visual discrimination task	Working memory
Cao et al. (2019)	30215784					155	18.8(4.19)	Paired-associates	Declarative memory
Diwadkar, Pruitt, et al. (2011) [a]	21497490			18	14.0 (3.1)			CPT	Cognitive control
Diwadkar, Segel, et al. (2011) [a]	21729757			19	14.1 (2.85)			N-back task	Working memory
Diwadkar et al. (2012) [a]	22033368			19	14.3			Facial affect N-back task	Working memory
Gisselgård et al. (2018)	29742121					41	16.7 (2.4)	N-back task	Working memory
Hart et al. (2013)	23482245			21	14.4 (2.56)			Oddball task	Attention
Karlsgodt et al. (2014)	24144510					20	16.85 (2.06)	Sternberg memory task	Working memory
Niendam et al. (2014)	24120302	35	18.27 (2.63)			25	16.92 (3.85)	AX CPT	Cognitive control
Rajarethinam et al. (2011) [a]	21684722			15	15.1 (3.4)			Story comprehension	Language

Continued

TABLE 9.1 Schizophrenia-related task-fMRI studies.—cont'd

Study	PMID	Early-onset		Familial high- risk		Clinical high-risk		fMRI paradigm	Construct
		n	Mean age, years (SD)	n	Mean age, years (SD)	n	Mean age, years (SD)		
Sugranyes et al. (2012)	22475381	22	17.1 (1.5)					N-back task	Working memory
Thormodsen et al. (2011)	22079661	15	16.2 (1.3)					N-back task	Working memory
White et al. (2011)	21211946	22	15 (2.8)					Sternberg memory task	Working memory
Wolf et al. (2015)	25785510					260	15.7 (2.7)	N-back task	Working memory
Systems for social processes									
Barbour et al. (2012) [a]	22222174			19	14.71			Facial affect processing	Social communication
Wolf et al. (2015)	25785510					260	15.7 (2.7)	Facial affect processing	Social communication
Positive valence systems									
Fett et al. (2019)	31506672	22	17.57 (1.27)					Social trust task	Reward evaluation
Wagshal et al. (2014)	24162516			10	12.6 (2.32)			Weather prediction task	Reward learning

CPT, continuous performance task; *PMID*, Article ID number in PubMed.
[a]*Studies with overlapping samples.*

TABLE 9.2 Bipolar-related task-fMRI studies.

Study	PMID	Early-onset		Familial high-risk		fMRI paradigm	Construct
		n	Mean age, years (SD)	n	Mean age, years (SD)		
Cognitive systems							
Acuff et al. (2018) [a]	30193355			31	13.87 (2.42)	Facial affect N-back task	Social communication
Adleman et al. (2013)	23541333	29	14.5 (2.7)			Encoding and retrieval	Declarative memory
Deveney et al. (2012)	22008364	32	14.5 (2.5)			Stop-signal task	Cognitive control
Diler, de Almeida et al. (2013) [a]	23607410	10	15.6 (0.9)			Go/no-go task	Cognitive control
Kim et al. (2012)	22024484	28	14.37 (2.63)	13	13.90 (2.02)	Go-change task	Cognitive control
Ladouceur et al. (2013)	23590840			16	14.2 (2.3)	Facial affect N-back task	Working memory
Metcalfe et al. (2016)	27187236	30	16.8 (1.4)			Go/no-go task	Cognitive control
Nery et al. (2021)	32876131			54	13.74 (2)	CPT with emotional distractors	Cognitive control
Pagliaccio et al. (2017)	27837919	24	19.1 (3.77)	29	14.88 (3.47)	Selective attention task	Attention
Passarotti et al. (2011)	21390505	17	14.29 (2.05)			Facial affect N-back task	Working memory

Continued

TABLE 9.2 Bipolar-related task-fMRI studies.—cont'd

Study	PMID	Early-onset		Familial high-risk		fMRI paradigm	Construct
		n	Mean age, years (SD)	n	Mean age, years (SD)		
Pavuluri et al. (2012) [a]	22265362	21	13.6 (2.5)			Facial affect N-back task	Working memory
Schneider et al. (2014)	25035298	11	13.0 (2.2)			CPT	Cognitive control
Schneider et al. (2012)	22801290	23	14.6 (2.2)			CPT	Cognitive control
Tseng et al. (2015)	25172156	27	14.44 (2.82)	13	13.71 (2.28)	Encoding and retrieval	Declarative memory
Weathers et al. (2012) [a]	22581312	16	11.71 (3.65)			Stop-signal task	Cognitive control
Weathers et al. (2013) [a]	23958598	15	11.69 (3.79)			Stop-signal task	Cognitive control
Welge et al. (2016)	27806866	32	15.5 (1)	64	14.85 (3)	CPT	Cognitive control
Systems for social processes							
Brotman, Deveney, et al. (2014) [a]	23930595	36	14.77 (2.55)			Emotion processing task	Social communication
Brotman, Tseng, et al. (2014) [a]	24617738	20	15.6 (2.3)	15	14.5 (2.2)	Parametric faces paradigm	Social communication
Chang et al. (2017)	28667891			50	13.5 (2.9)	Facial expressions task	Social communication
Deveney et al. (2014)	24493839	19	15.7 (2.3)			Emotion processing task	Social communication

Diler, Segreti, et al. (2013) [a]	24080517	10	15.6 (1.1)			Emotional facial expression gender labeling task	Social communication
Garrett et al. (2015)	25283342			12	13.55 (3.4)	Facial expression task	Social communication
Garrett et al. (2012)	22840553	20	15.63 (2.1)			Facial affect processing	Social communication
Hafeman et al. (2014)	25151338	34	13.95 (2.1)			Facial affect processing	Social communication
Systems for social processes							
Kryza-Lacombe et al. (2019)	30851221	24	16.5 (2.4)			Facial affect processing	Social communication
Ladouceur et al. (2011)	22115148	34	13.64 (2.27)			Facial affect processing	Social communication
Nimarko et al. (2019)	31064610			50	13.55 (2.47)	Facial affect processing	Social communication
Olsavsky et al. (2012)	22365465	32	14.7 (2.7)	13	14 (2.4)	Facial affect processing	Social communication
Pavuluri et al. (2011) [a]	21592741	24	12.65 (2.5)			Affective word-color matching	Social communication
Perlman et al. (2013)	24290464	20	13.5 (2.04)			Facial affect processing	Social communication
Wiggins et al. (2017)	27993231	36	17.9 (3.3)	22	15.7 (3.6)	Facial affect processing	Social communication
Yang et al. (2013)	23517886	13	13.25 (2.27)			Affective word-color matching	Social communication

Continued

TABLE 9.2 Bipolar-related task-fMRI studies.—cont'd

Study	PMID	Early-onset		Familial high-risk		fMRI paradigm	Construct
		n	Mean age, years (SD)	n	Mean age, years (SD)		
Positive valence systems							
Acuff et al. (2019) [a]	30755725			32	13.95 (2.43)	Number guessing reward task	Reward learning
Adleman et al. (2011)	22024005	26	14.34 (2.59)			Probabilistic response reversal task	Reward learning
Bitter et al. (2014)	24962329	14	17 (3)			Cue—reactivity task	Reward responsiveness
Manelis et al. (2016)	26373895			29	13.81 (2.45)	Number guessing reward task	Reward learning
Singh, Chang, et al. (2014) [a]	25142103			20	12.74 (2.85)	Monetary incentive delay task	Reward responsiveness
Singh et al. (2013)	23265635	24	15.7 (1.7)			Monetary incentive delay task	Reward responsiveness
Soehner et al. (2016)	27442458			25	14.2 (2.25)	Number guessing reward task	Reward responsiveness

Urošević et al. (2016)	27114896	21	16.33 (1.66)			Monetary incentive delay task	Reward responsiveness
Sensorimotor Systems							
King et al. (2018)	29451300	35	15.7 (1.97)			Finger-tapping task	Motor actions
Arousal and regulatory systems							
Urback et al. (2019)	30422372	25	17.22 (1.14)			Breath hold task	Arousal

CPT, continuous performance Task; *PMID,* Article ID number in PubMed.
[a]*Studies with overlapping samples.*

(Diler, de Almeida, et al., 2013; Metcalfe et al., 2016; Weathers et al., 2013), coupled with ACC hypoactivation during inhibition failures, indicative of dysfunctional performance monitoring (Weathers et al., 2012). A similar pattern of hyperactivation has also been noted in youth at FHR-BD (Kim et al., 2012). Notably, patients with EOS, as well as youth at CHR-SCZ and FHR-SCZ evidenced similar patterns of prefrontal hyperactivation, but these were associated with task underperformance (Diwadkar, Segel, et al., 2011; Niendam et al., 2014; Schneider et al., 2014).

Cognitive control: updating, representation, and maintenance

These cognitive control subconstructs refer to the ability to adhere to rules or goals while excluding highly reflexive or compelling competing influences. The successful neural implementation of these processes is thought to depend on the integrity of frontoparietal regions (Niendam et al., 2012). The relevant tasks typically require participants to maintain goal-directed behavior in the presence of distractor stimuli, which can be either affective or nonaffective in nature. In patients with EOS and youth at FHR-SCZ, dysfunctional activation has been noted in medial and dorsal prefrontal regions when affective words were used as distractors (Pavuluri et al., 2011; Yang et al., 2013) coupled with further abnormalities in "emotion-generating" regions such as the amygdala and pregenual ACC (Hart et al., 2013; Nery et al., 2021; Welge et al., 2016).

Declarative memory

Declarative memory consists of facts and events that can be stored via encoding and consciously recalled or "declared." Memory processing of human faces involves a specialized region of the fusiform gyrus (Natu & O'Toole, 2011). A single study that examined facial encoding and recall in children with EOBD, identified hyperactivation in the fusiform gyrus during correctly recalled faces (Adleman et al., 2013).

Working memory

Working memory is the ability to encode, maintain, and retrieve information in support of ongoing goal-directed behavior (Baddeley, 1992). Working memory tasks require individuals to recall the order or location of stimuli and use this information to fulfill task-response rules. Tasks typically include conditions of increasing difficulty to test neural responses to increasing working memory demands. For example, in the popular n-back task, individuals are shown a series of stimuli (e.g., letters, numbers, objects, or faces) and are asked to respond every time the current stimulus is the same as the one presented one, two, or three trials back.

In patients with EOS and in youth at FHR-SCZ and CHR-SCZ, the pattern of abnormalities within the working memory network varies with task demands. At low task-demands, performance is typically maintained but is associated

with hyperactivation in frontoparietal regions (Thormodsen et al., 2011; White et al., 2011) and the hippocampal formation (Gisselgård et al., 2018). The same pattern has been reported in patients with EOBD and in youth at FHR-BD and FHR-SCZ, when either emotional stimuli or emotional distracters were used (Diwadkar et al., 2012; Ladouceur et al., 2011; Passarotti et al., 2011). At higher levels of difficulty, both task underperformance and widespread hypoactivation within the working memory network have been reported in both patients with EOS and in youth at FHR-SCZ (Bakshi et al., 2011; Diwadkar, Pruitt, et al., 2011; Sugranyes et al., 2012). Working memory studies that distinguished between neural engagement during encoding or retrieval have reported that patients with EOS and youth at CHR-SCZ typically show subtle frontoparietal hypoactivation during encoding and hyperactivation in the same regions during retrieval (Bittner et al., 2015; Cao et al., 2019).

Social processes

Social communication: reception of facial communication

Reception of facial communication engages brain regions associated with the processing of facial features (notably the visual cortex, the fusiform and superior temporal gyri) and brain regions involved in the evaluation of facial affect (notably the posterior superior temporal sulcus, the ventral ACC, the medial prefrontal cortex, and the amygdala) (Dricu & Frühholz, 2016). This network interacts with cognitive control regions that provide inhibitory feedback (Haxby et al., 2000). In patients with EOBD, processing negatively valenced faces has been generally associated with *hyperactivation* in brain regions that support emotional processing, such as the amygdala and ventral ACC, which appears unresponsive to increasing intensity levels of expressed facial emotion (Deveney et al., 2014); and *hypoactivation* in cognitive control regions in the ventral prefrontal cortex and the anterior ACC (Brotman, Tseng, et al., 2014; Garrett et al., 2012; Hafeman et al., 2014; Kim et al., 2012; Kryza-Lacombe et al., 2019; Ladouceur et al., 2011). Youth at FHR-BD evidence the same pattern although hyperactivation in emotional processing regions is more consistently observed than hypoactivation in cognitive control regions (Acuff et al., 2018; Brotman, Deveney, et al., 2014; Chang et al., 2017; Nimarko et al., 2019; Olsavsky et al., 2012; Wiggins et al., 2017).

Positive valence systems

Key regions in the reward processing network include (1) the ventrolateral prefrontal cortex, important for encoding values of choices and decision-making options; (2) the ventromedial prefrontal cortex, important for encoding reward values and comparing values of different options; (3) the ventral striatum, important for anticipation and prediction error; (4) the amygdala, important for stimulus-value associations; and (5) the anterior insula, important for the representation of interoceptive effects rewards (Sescousse et al., 2013).

Reward learning: probabilistic and reinforcement learning

This construct and subconstruct refer to the ability to learn stimulus-outcome associations based on their reward value. Typical tasks require participants to deduce the rules governing stimulus-outcome associations by rewarding correct choices (usually by monetary gains) and punishing wrong responses (usually by monetary losses). Two articles, using an overlapping sample of youth at FHR-BD, reported hyperactivation in the ventromedial and ventrolateral prefrontal cortex (Manelis et al., 2016) and hypoactivation in the posterior insula (Soehner et al., 2016) during reward learning but neither finding was reproducible in an independent sample (Acuff et al., 2019).

Reward responsiveness

This construct refers to neural engagement in anticipation or following receipt of a positive or negative outcome. The monetary incentive delay task is commonly used for this purpose as it includes a delay between stimuli presentation and their associated gain or loss. In patients with EOBD reward anticipation was associated with increased medial frontal activation and reduced subgenual ACC while loss anticipation was associated with decreased activation in the parahippocampal gyrus (Singh et al., 2013). Greater prefrontal activation during reward anticipation has also been reported in youth at FHR-BD who also showed reduced pregenual ACC activation during loss anticipation (Singh, Kelley, et al., 2014). The opposite pattern was found in a separate study of youth with EOBD who showed decreased activation in frontal regions in anticipation of reward (Urošević et al., 2016). A further study assessed activation in the caudate, ACC and prefrontal cortex in patients with EOBD using a reversal learning paradigm that combines cognitive flexibility with reward processing; patients showed lower sensitivity to either positive or negative outcomes as inferred by the reduced difference in caudate and prefrontal activation between correct and incorrect responses compared to healthy youth (Adleman et al., 2011).

Sensorimotor systems: motor actions

A single study examined brain activation during a selfpaced finger tapping task in adolescents with EOBD. The only case−control difference involved ACC hypoactivation in the patient group which is difficult to interpret as the study did not acquire task performance data (King et al., 2018).

Arousal and regulatory systems: arousal

A single study assessed a physiological aspect of arousal in adolescents with EOBD, as inferred from cerebrovascular reactivity (vasodilatory or vasoconstrictive response) using a paradigm that compared 15-second breath-holds to

normal breathing; during breath-holds, patients showed hypoactivation in the posterior cingulate cortex, lingual gyrus, right temporal pole, and supramarginal gyrus (Urback et al., 2019).

Summary of t-fMRI findings

The literature reviewed is dominated by studies on cognitive systems, social processes, and positive valence to the exclusion of all other RDoC domains. Moreover, studies on patients with EOS and in youth at CHR and FHR predominantly use tasks that map onto cognitive systems, while studies in patients with EOBD and youth at FHR-BD mainly use tasks mapping onto social and reward processes. There was marked interstudy variability in the results in terms of the direction and spatial distribution of case−control differences (Fig. 9.2). Arguably, the two most convincing patterns observed, involved: transdiagnostic abnormalities in the activation of frontoparietal regions during cognitive systems' tasks, indicating deficient activation in youth with EOS and EOBD and inefficient activation in those at risk; and hyperactivation in "emotional" processing regions for youth with EOBD and those at risk.

Resting-state functional magnetic resonance imaging studies

Rs-fMRI measures the spontaneous (as opposed to task-induced) fluctuations in the BOLD signal and the spatiotemporal patterns of these fluctuations are

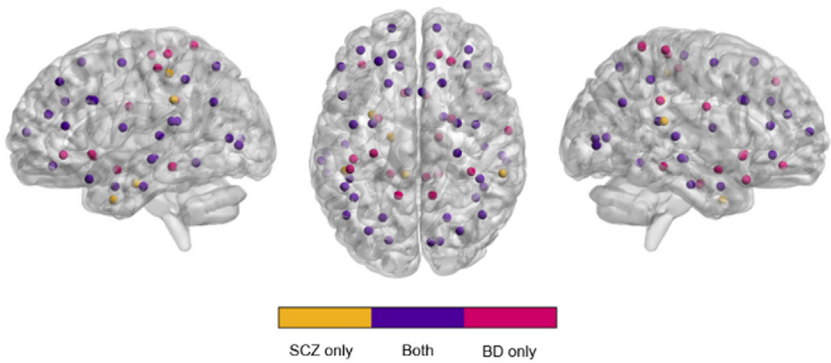

FIGURE 9.2 Spatial distribution of case-control differences in the Task-fMRI studies. Each dot represents regions where case-control findings have been reported in patients with early-onset psychosis and in individuals at clinical or familial high-risk: Yellow: Regions implicated in patients with schizophrenia including early onset, clinical high-risk and familial high-risk samples; Pink: Regions implicated in patients with bipolar disorder including early-onset, clinical high-risk, and familial high-risk samples; Purple: Regions implicated across all groups. Information about directionality has been omitted for ease of visualization. BD: bipolar disorder; SCZ: Schizophrenia. The relevant studies are shown in Tables 9.1 and 9.2.

used to compute resting-state connectivity (Fox & Raichle, 2007). The most common approach relies on the statistical dependency of the BOLD signal time series between different brain elements, either voxels or regions. Functional connectivity at the level of voxels is commonly measured as: voxel-mirrored homotopic connectivity, which is a voxel-wise measure of connectivity between homotypic regions in the two hemispheres; and regional homogeneity, which is a measure of the similarity of the time series of a given voxel to those of its nearest neighbors. Seed-based functional connectivity describes the pattern of correlations of the BOLD signal time series between a specific brain region (the "seed") and that of other brain regions. The temporal covariation of BOLD signals across multiple brain regions has been used to define resting-state networks, which are further characterized in terms of their internal cohesiveness (within-network connectivity) and their integration (between-network connectivity) within the whole-brain functional connectome (Fox & Raichle, 2007). Graph theory is a popular method for the study of the organizational properties of brain networks, such as the importance of different brain regions for information flow (Bullmore & Sporns, 2009). Finally, the amplitude of low-frequency fluctuations (ALFF) is used to capture the intensity of the BOLD signal (Zuo et al., 2010). Details of the rs-fMRI studies reviewed are provided in Table 9.3. Unless otherwise specified, all comparisons reported below use healthy individuals as the normative reference group.

Resting-state connectome architecture and topology

A series of studies were conducted at the NIMH on a small but unique sample of adolescents with childhood-onset schizophrenia and their siblings, who represent youth at FHR-SCZ. Patients differed from their healthy counterparts in the number and modularity (i.e., the extent to which networks could be decomposed in subnetworks) of resting-state networks (Alexander-Bloch et al., 2012, 2013). These changes could be accounted for by a selective reduction in the functional connectivity of neighboring, but not distal, brain regions (Alexander-Bloch et al., 2012, 2013). The asymptomatic siblings in this study did not evidence any such abnormalities (Watsky et al., 2018) which contrasts with findings of reduced long-distance connectivity between brain "hubs" reported in an independent sample of adolescents at FHR-SCZ (Collin et al., 2017).

In a separate sample, adolescent patients with EOS showed preserved efficiency of information transmission across the whole brain connectome (global efficiency) but with local reductions at individual brain regions (nodal efficiency) within the hippocampus, parahippocampus, and precuneus (Li, Becker, et al., 2019). By contrast, no such abnormalities have been detected in adolescents at FHR-BD (Collin et al., 2017) or in youth with psychotic-like experiences from the Philadelphia Neurodevelopmental Cohort, an unselected population sample (Jalbrzikowski et al., 2020).

TABLE 9.3 Resting-state fMRI studies.

Study	PMID	Early-onset		Familial high-risk		Clinical high-risk		Method
		n	Mean age, years (SD)	n	Mean age, years (SD)	n	Mean age, years (SD)	
Schizophrenia-relates studies								
Alexander-Bloch et al. (2012)	22119652	19	18.7 (4.9)					Global functional architecture
Alexander-Bloch et al. (2013)	22275481	19	18.7 (4.9)					Global functional architecture and regional connectivity
Amico et al. (2017)	28125578	20	14.2 (1.28)					RSN connectivity
Anticevic et al. (2015)	26267151					243	18.99 (4.18)	Seed-based connectivity
Bernard et al. (2014)	24464473					32	18.59 (1.85)	Seed-based connectivity
Ilzarbe et al. (2019)	31791005	27	18.1 (1.6)					DMN connectivity
Jacobson-McEwen et al. (2014)	23621452	11	12.48 (0.42)					Seed-based connectivity

Continued

TABLE 9.3 Resting-state fMRI studies.—cont'd

Study	PMID	Early-onset		Familial high-risk		Clinical high-risk		Method
		n	Mean age, years (SD)	n	Mean age, years (SD)	n	Mean age, years (SD)	
Jalbrzikowski et al. (2019) [a]	30654642					162	16 (2.9)	Seed-based connectivity
Jalbrzikowski et al. (2020) [a]	31424081					273	16.1 (2.9)	Global functional architecture
Jiang et al. (2015) [a]	25966366	26	14.51 (1.94)					Regional homogeneity and seed-based connectivity
Li et al. (2015) [a]	25130214	26	14.5 (1.94)					Voxel-mirrored homotopic connectivity and seed-based connectivity
Li, Hu, et al. (2019) [a]	29850901	35	15.5 (1.7)					Global and regional efficiency
Liu, Guo et al. (2018) [a]	29228204	48	15.79 (1.64)					Voxel-mirrored homotopic connectivity
Liu, Zhang, et al. (2018) [a]	28476336	48	15.79 (1.64)					Regional homogeneity
Mennigen et al. (2020) [a]	31219595					129	15 (2.8)	Dynamic RSN connectivity
Satterthwaite et al. (2015) [a]	26033240					188	15.74 (2.9)	RSN connectivity

Solé-Padullés et al. (2017)	28032201	34	15.88 (0.98)			44	15.15 (1.6)	LAN connectivity
Tang et al. (2013)	23923052	32	16.2 (1.2)					DMN connectivity
Wang et al. (2017) [a]	28185094	48	15.79 (1.64)					Global voxel-wise connectivity
Wang, Zhang, et al. (2018) [a]	28823850	48	15.79 (1.64)					Local and distal connectivity
Wang, Zhan, et al., (2018) [a]	28587813	48	15.79 (1.64)					Regional homogeneity
Wang et al. (2019) [a]	30772067	35	15.5 (1.8)					Voxel-wise connectivity strength
Watsky et al. (2018)	29310911	26	19.89 (5.55)	28	17.47 (6.2)			Whole-brain connectivity
Wei et al. (2017)	28287187	45	18.42 (3.84)					Seed-based connectivity
Zhang et al. (2015) [a]	26281967	37	15.5 (1.8)					Seed-based connectivity
Zhang et al. (2020) [a]	31784338	48	15.79 (1.64)					DMN connectivity and homogeneity
Zheng et al. (2016) [a]	27000303	35	15.5 (1.76)					ALFF and seed-based connectivity

Continued

TABLE 9.3 Resting-state fMRI studies.—cont'd

Study	PMID	Early-onset		Familial high-risk		Clinical high-risk		Method
		n	Mean age, years (SD)	n	Mean age, years (SD)	n	Mean age, years (SD)	
Bipolar disorder-related studies								
Gao et al. (2014)	25095790	17	14.4 (1.77)					Regional homogeneity
Hafeman et al. (2019)	30410014			32	14.3 (2.3)			Seed-based connectivity
Hafeman et al. (2020)	32697703			35	11.89 (1.3)			Seed-based connectivity
Lin et al. (2018)	29331931			28	18.04 (5.39)	22	16.64 (7.14)	ALFF, regional homogeneity and seed-based connectivity
Lopez-Larson et al. (2017)	29560889	32	15.1 (2.0)					RSN connectivity
Singh, Kelley, et al. (2014)	24938878			24	12.25 (3.03)			RSN and seed-based connectivity
Singh et al. (2015)	26299298	20	17.21 (1.89)					Seed-based connectivity
Singh et al. (2018)	29168420			31	11.61 (2.70)			Seed-based connectivity

Son et al. (2017)	28264765	22	14.7 (1.2)					RSN and seed-based connectivity
Stoddard et al. (2015)	25544024	14	14.6 (2.5)					Seed-based connectivity
Xiao et al. (2013)	23526961	15	15 (1.7)					Regional homogeneity
Xiao et al. (2019)	31123970	43	15 (1.76)					Regional homogeneity
Zhong et al. (2019)	30515682	55	15 (2.10)					DMN connectivity
Collin et al. (2017)	28734460	SCZ: 28 BD: 60	SCZ: 13.1 (3.1) BD: 14.2 (2.5)					Rich club connectivity
Solé-Padullés et al. (2016)	26885824			SCZ: 27 BD: 39	SCZ: 11.96 (3.41) BD: 13.87 (3.49)			RSN connectivity

BD, bipolar disorder; *DMN*, default mode network; *LAN*, language network; *LFF*, amplitude low frequency fluctuation; *PMID*, Article ID number in PubMed; *RSN*, resting-state networks; *SCZ*, schizophrenia.
[a]*Studies with overlapping samples.*

MR regional homogeneity and amplitude

Findings regarding MR regional homogeneity (that a voxel is temporally similar to its neighbors) (Zang et al., 2004) and ALFF derive from a series of studies conducted on the same sample of adolescent patients with EOS. In this sample, homogeneity was elevated in the superior frontal cortex and decreased in the postcentral and middle occipital cortex (Wang et al., 2017). The two latter regions showed hypo-connectivity with their homotopic and other brain regions (Jiang et al., 2015), while both local and distal connectivity was increased in the prefrontal cortex and decreased in the cuneus and precuneus (Wang, Zhan, et al., 2018). Intriguingly, a re-analysis of the same sample published as a separate article, reported higher homogeneity in patients in the mediodorsal prefrontal cortex; and lower homogeneity in the superior temporal and precentral cortex, and in the inferior parietal and paracentral lobules (Wang, Zhang, et al., 2018). When coherence homogeneity was measured in the same sample, it was reported as lower in frontoparietal, sensorimotor and auditory regions, and in the precuneus (Liu, Zhang, et al., 2018). A further study of the same EOS sample found increased ALFF in the medioventral cortex and decreased ALFF in the precuneus; these regions also evidenced widespread hypo-connectivity (Zheng et al., 2016).

Findings regarding signal homogeneity metrics in adolescent patients with EOBD are based on a series of studies that include overlapping patient samples where homogeneity was examined during mania, depression, and euthymia. Depressive states were associated with decreased homogeneity in the medial and dorsolateral prefrontal cortex, the lateral mid-temporal cortex, and the putamen (Gao et al., 2014). In manic states, homogeneity was higher in the ACC, the hippocampus/parahippocampus, and the caudate; and lower in the dorsolateral and ventrolateral prefrontal cortex, the superior parietal lobule and superior temporal cortex, the precentral cortex, and the precuneus (Xiao et al., 2013). However, in a subsequent study on manic states by the same authors, results were replicated only for the superior parietal lobule, and the superior temporal and precentral cortex, while additional homogeneity reductions were noted in the insula and cerebellum (Xiao et al., 2019). Homogeneity reductions in the superior parietal lobule and the superior temporal cortex were also present in remitted patients with EOBD (Xiao et al., 2019).

A single study examined regional homogeneity and amplitude (ALFF) in the amygdala, the inferior frontal gyrus, the putamen, the parahippocampus and hippocampus, in youth at FHR-BD without and with subsyndromal mood symptoms. No abnormalities were reported in homogeneity, but the asymptomatic youth showed decreased ALFF in the putamen and motor cortex while those who were symptomatic showed higher ALFF in the pars orbitalis, the primary visual cortex, and the cerebellum (Lin et al., 2018).

Resting-state networks

Resting-state networks are defined by the statistical dependencies of the spontaneous fluctuations in the BOLD signal time-series of multiple brain regions. The most consistent resting-state networks can be divided into those supporting internally guided, higher order mental functions, which include the default-mode (DMN), central executive (CEN), language (LAN) and salience (SAL) networks and those supporting specialized sensory and motor processing, which include the visual (VIS), sensorimotor (SMN) and basal ganglia (BGN) networks (Biswal et al., 2010; Smith et al., 2009).

A study that focused specifically on the LAN reported connectivity reductions in patients with EOS and in youth at FHR-SCZ and CHR-SCZ although the decrements in the at-risk groups were not statistically significant (Solé-Padullés et al., 2017). Studies specifically targeting the DMN in patients with EOS have reported reduced connectivity but also increased homogeneity in the anterior DMN (involving medial prefrontal regions) (Ilzarbe et al., 2019; Tang et al., 2013; Zhang et al., 2020) and lower homogeneity in the posterior DMN (involving the posterior cingulate gyrus and the precuneus) (Zhang et al., 2020). Lower connectivity of the anterior DMN in youth with EOBD appears to be linked to the presence of psychosis as it has only been reported in patients who experience psychotic features (Zhong et al., 2019). A further study which examined patients with EOS with prominent auditory hallucinations, found general reductions in the connectivity of the DMN, CEN, and SAL and the auditory cortices while the connectivity of the gyrus rectus and dorsolateral prefrontal cortex was increased (Amico et al., 2017). Adolescents at FHR-BD or FHR-SCZ showed no abnormalities in the DMN, CEN, or SAL (Solé-Padullés et al., 2016). In the same study, reduced BGN connectivity was noted in youth at FHR-SCZ but not in those at FHR-BD (Solé-Padullés et al., 2016).

A series of studies have examined resting-state network connectivity in youth with psychotic-like experiences from the Philadelphia Neurodevelopmental Cohort. In this sample, the overall structure of the resting-state networks was preserved but there was hyper-connectivity between DMN regions and hypo-connectivity between SAL regions (Satterthwaite et al., 2015). The same sample also evidenced persistent abnormalities in the dynamic connectivity (i.e., changes in network connectivity over the duration of the scan) of the SMN and VIS while dynamic dysconnectivity of the DMN, SAL, and CEN occurred only sporadically (Mennigen et al., 2020).

Examination of the DMN and CEN in adolescents at FHR-BD found increased CEN connectivity, particularly involving ventrolateral prefrontal regions (Singh, Chang, et al., 2014). When resting-state networks were extracted through k-means clustering of voxel-wise connectivity, adolescent patients with EOBD were found to have reduced connectivity in two clusters. One cluster comprised the putamen, insula, the dorsolateral and ventrolateral prefrontal

cortex, sensorimotor areas and the inferior parietal lobules, and the other cluster comprised temporal and visual cortical regions (Stoddard et al., 2015).

Seed-based resting-state connectivity

Amygdala

The centromedial and basolateral divisions of the amygdaloid complex are cytoarcitectonically and functionally distinct. The basolateral division is involved in assessing the emotional valence of afferent sensory information, while efferent projections originating from the centromedial division support salience-related allocation of attentional resources (Bzdok et al., 2013). Several studies have therefore defined "seeds" of the whole amygdaloid complex or its subdivisions to assess their resting-state connectivity with the entire brain or with specific regions or networks.

A single study examined age-related changes in the functional connectivity of the centromedial division in the Philadelphia Neurodevelopmental Cohort (Jalbrzikowski et al., 2019). In this study, data from healthy participants were used to generate normative growth curves. Compared to the normative values, younger participants with psychotic-like experiences exhibited reduced connectivity between the centromedial division and the ventrolateral prefrontal and occipital cortex, the thalamus, the caudate, and the putamen (Jalbrzikowski et al., 2019). They also exhibited elevated connectivity between the centromedial division and the dorsolateral prefrontal cortex. The pattern was different in older participants with psychotic-like experiences who had higher connectivity of the centromedial division to the ventrolateral prefrontal and the occipital cortex and the putamen. In a separate sample, adolescent patients with EOS were reported to have decreased whole-amygdala connectivity with the dorsolateral prefrontal cortex and the dorsal ACC (Wei et al., 2017).

In patients with EOBD, the basolateral division of the amygdala evidenced reduced connectivity with the hippocampus and precentral gyrus and increased connectivity with the precuneus (Singh et al., 2015). Two studies examined the connectivity of the whole amygdala in adolescents at FHR-BD. One study found hypo-connectivity between the pregenual ACC and the amygdala (Singh, Chang, et al., 2014) in these youth while the other found that the connectivity of the amygdala with medial temporal regions (parahippocampus and hippocampus) was reduced in those who were asymptomatic and increased in those with mood symptoms (Lin et al., 2018).

Thalamus

A single study in adolescents at CHR-SCZ used the thalamus as the "seed" and reported that thalamic connectivity was increased with sensorimotor regions and decreased with the cerebellum, the dorsolateral and dorsomedial prefrontal cortex and the dorsal ACC. These findings were more pronounced in those youth

that later converted to full-blown schizophrenia (Anticevic et al., 2015). A further study highlighted reduced whole-brain thalamic connectivity in adolescents with childhood-onset schizophrenia from the NIMH sample but increased thalamic connectivity in their asymptomatic siblings (Watsky et al., 2018).

Cerebellum

A single study examined cortico-cerebellar connectivity in adolescents at CHR-SCZ by placing "seeds" in the vermis and lobules I−VI, Crus I and II, Lobules VIIb-X, Vermis VI, Vermis Crus II, and Vermis VIIb-X (Bernard et al., 2014). The study found that adolescents at CHR-SCZ had reduced connectivity between lobules I−VII and VIIB and the dorsolateral prefrontal cortex, as well as the superior and inferior parietal lobules (Bernard et al., 2014).

Prefrontal regions

Although prefrontal regions have been implicated in youth with early-onset psychosis in many studies, only a few have used prefrontal regions as connectivity "seeds". In a very small sample of non−help-seeking individuals with psychotic experiences, seeds were defined in prefrontal and in multiple other cortical and striatal regions based on their association with activation abnormalities during tasks of inhibitory control. In this study, the resting-state connectivity of the ACC and ventrolateral prefrontal regions were reduced in the symptomatic group (Jacobson Mcewen et al., 2014). Another study found reduced connectivity between a ventrolateral prefrontal seed and the caudate in adolescents at FHR-BD (Singh, Chang, et al., 2014).

Interhemispheric connectivity

Voxel-mirrored homotopic connectivity, which measures interhemispheric synchronization between any pair of symmetric (homotopic) brain regions, was assessed in two studies of patients with EOS. In one sample, the patients had globally reduced interhemispheric homotopic synchronization, while additional regional decrements and widespread dysconnectivity were noted in the posterior temporal and ventral postcentral cortices (Li et al., 2015). In the other sample, patients showed reduced homotopic synchronization only in the superior temporal gyrus/insula, the precentral and fusiform gyri and the precuneus (Liu, Guo, et al., 2018).

Summary of rs-fMRI findings

Arguably, the most significant observation from the rs-fMRI literature reviewed is the marked interstudy variability in methods and the low interstudy consistency in the findings reported. Nevertheless, two patterns seem to emerge: the global architecture of the functional connectome appears

preserved in youth with early-onset psychosis while connectivity changes were noted at the level of individual brain region; and connectivity changes in youth with early-onset psychosis appear very widespread and implicate nearly all brain regions if all studies are considered together. Accordingly, the data support the notion of dysconnectivity in patients with early-onset psychosis as well as in those at clinical or familial risk, but its precise nature remains elusive.

Conclusions and future directions

As noted above, available studies have yielded a variety of results with minimal interstudy consistency. Inconsistencies are often attributed to the "heterogeneity" of psychosis, which may be the case, but methodological considerations should be considered first. As shown in Tables 9.1–9.3, the sample sizes across all studies are remarkably small (median $n = 26$) raising the possibility that the results reported may often reflect false positive or chance findings. Several studies have reported associations with symptoms, which were not summarized here as their interstudy inconsistency was striking. Medication effects were considered only in a few studies and were generally minimally associated with case–control differences. However, this observation needs to be considered cautiously because all studies were underpowered for detecting such effects. These limitations prevent any meaningful conclusions to be drawn with the comparable literature in adult-onset cases; at a very general level the findings summarized here are aligned with observations in adult-onset samples (Janiri et al., 2020; Li, Becker, et al., 2019; McTeague et al., 2017; Syan et al., 2018). Further, nearly none of the studies summarized addressed the issue of potential interactions between disease mechanisms and development. A notable exception is the study by Jalbrzikowski et al. (2019) who referenced amygdala connectivity changes in youth with psychotic-like experiences to the normative range using growth curves. This design is recommended for future studies and is also timely as large-scale normative data in youth are increasingly available. Longitudinal studies would also be informative with respect to developmental pathways, and their general absence from the current literature is regrettable. The t-fMRI literature is also very limited in terms of the constructs examined. Comprehensive characterization of the same sample of individuals with early-onset psychosis or youth at risk of psychosis would be an invaluable contribution to the literature as it would enable detection of task-related circuits that maybe differentially affected. The effect of psychotropic medications on the developing brain remains largely unknown and represents an important issue to address in future studies aiming to inform on the optimal treatment of youth with early-onset psychosis.

References

Acuff, H., Versace, A., Bertocci, M., Ladouceur, C., Manelis, A., Monk, K., Bonar, L., McCaffrey, A., Goldstein, B., Sakolsky, D., Axelson, D., Birmaher, B., & Phillips, M. (2018). Longitudinal assessment of manic symptoms (LAMS) consortium. Association of neuroimaging measures of emotion processing and regulation neural circuitries with symptoms of bipolar disorder in offspring at risk for bipolar disorder. *JAMA Psychiatry, 75*(12), 1241−1251. https://doi.org/10.1001/jamapsychiatry.2018.2318. PMID: 30193355; PMCID: PMC6528787.

Acuff, H. E., Versace, A., Bertocci, M. A., Ladouceur, C. D., Hanford, L. C., Manelis, A., Monk, K., Bonar, L., McCaffrey, A., Goldstein, B. I., Goldstein, T. R., Sakolsky, D., Axelson, D., Birmaher, B., & Phillips, M. L. (2019). Baseline and follow-up activity and functional connectivity in reward neural circuitries in offspring at risk for bipolar disorder. *Neuropsychopharmacology, 44*(9), 1570−1578. https://doi.org/10.1038/s41386-019-0339-2

Adleman, N. E., Kayser, R., Dickstein, D., Blair, R. J. R., Pine, D., & Leibenluft, E. (2011). Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(11), 1173−1185. https://doi.org/10.1016/j.jaac.2011.07.011

Adleman, N. E., Kayser, R. R., Olsavsky, A. K., Bones, B. L., Muhrer, E. J., Fromm, S. J., Pine, D. S., Zarate, C., Leibenluft, E., & Brotman, M. A. (2013). Abnormal fusiform activation during emotional-face encoding assessed with functional magnetic resonance imaging. *Psychiatry Research: Neuroimaging, 212*(2), 161−163. https://doi.org/10.1016/j.pscychresns.2013.01.006

Alexander-Bloch, A. F., Lambiotte, R., Roberts, B., Giedd, J., Gogtay, N., & Bullmore, E. (2012). The discovery of population differences in network community structure: New methods and applications to brain functional networks in schizophrenia. *NeuroImage, 59*(4), 3889−3900. https://doi.org/10.1016/j.neuroimage.2011.11.035

Alexander-Bloch, A. F., Vértes, P. E., Stidd, R., Lalonde, F., Clasen, L., Rapoport, J., Giedd, J., Bullmore, E. T., & Gogtay, N. (2013). The anatomical distance of functional connections predicts brain network topology in health and schizophrenia. *Cerebral Cortex, 23*(1), 127−138. https://doi.org/10.1093/cercor/bhr388

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders, text revision* (4th ed.). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

Amico, F., O'Hanlon, E., Kraft, D., Oertel-Knöchel, V., Clarke, M., Kelleher, I., Higgins, N., Coughlan, H., Creegan, D., Heneghan, M., Power, E., Power, L., Ryan, J., Frodl, T., Cannon, M., & van Amelsvoort, T. (2017). Functional connectivity Anomalies in adolescents with psychotic symptoms. *PLOS ONE, 12*(1). https://doi.org/10.1371/journal.pone.0169364. e0169364.

Anticevic, A., Haut, K., Murray, J. D., Repovs, G., Yang, G. J., Diehl, C., McEwen, S. C., Bearden, C. E., Addington, J., Goodyear, B., Cadenhead, K. S., Mirzakhanian, H., Cornblatt, B. A., Olvet, D., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Belger, A., Seidman, L. J., … Cannon, T. D. (2015). Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. *JAMA Psychiatry, 72*(9), 882−891. https://doi.org/10.1001/jamapsychiatry.2015.0566

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556−559. https://doi.org/10.1126/science.1736359

Bakshi, N., Pruitt, P., Radwan, J., Keshavan, M. S., Rajan, U., Zajac-Benitez, C., & Diwadkar, V. A. (2011). Inefficiently increased anterior cingulate modulation of cortical systems during working memory in young offspring of schizophrenia patients. *Journal of Psychiatric Research, 45*(8), 1067−1076. https://doi.org/10.1016/j.jpsychires.2011.01.002

Barbour, T., Pruitt, P., & Diwadkar, V. A. (2012). FMRI responses to emotional faces in children and adolescents at genetic risk for psychiatric illness share some of the features of depression. *Journal of Affective Disorders, 136*(3), 276−285. https://doi.org/10.1016/j.jad.2011.11.036

Bernard, J. A., Dean, D. J., Kent, J. S., Orr, J. M., Pelletier-Baldelli, A., Lunsford-Avery, J. R., Gupta, T., & Mittal, V. A. (2014). Cerebellar networks in individuals at ultra high-risk of psychosis: Impact on postural sway and symptom severity. *Human Brain Mapping, 35*(8), 4064−4078. https://doi.org/10.1002/hbm.22458

Biswal, B. B., Mennes, M., Zuo, X.-N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A.-M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kotter, R., Li, S.-J., … Milham, M. P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences, 107*(10), 4734−4739. https://doi.org/10.1073/pnas.0911855107

Bitter, S. M., Adler, C. M., Eliassen, J. C., Weber, W. A., Welge, J. A., Burciaga, J., Shear, P. K., Strakowski, S. M., & Delbello, M. P. (2014). Neurofunctional changes in adolescent cannabis users with and without bipolar disorder. *Addiction, 109*(11), 1901−1909. https://doi.org/10.1111/add.12668

Bittner, R. A., Linden, D. E. J., Roebroeck, A., Härtling, F., Rotarska-Jagiela, A., Maurer, K., Goebel, R., Singer, W., & Haenschel, C. (2015). The when and where of working memory dysfunction in early-onset schizophrenia - a functional magnetic resonance imaging study. *Cerebral Cortex, 25*(9), 2494−2506. https://doi.org/10.1093/cercor/bhu050

Brotman, M. A., Deveney, C. M., Thomas, L. A., Hinton, K. E., Yi, J. Y., Pine, D. S., & Leibenluft, E. (2014). Parametric modulation of neural activity during face emotion processing in unaffected youth at familial risk for bipolar disorder. *Bipolar Disorders, 16*(7), 756−763. https://doi.org/10.1111/bdi.12193

Brotman, M. A., Tseng, W. L., Olsavsky, A. K., Fromm, S. J., Muhrer, E. J., Rutenberg, J. G., Deveney, C. M., Adleman, N. E., Zarate, C. A., Pine, D. S., & Leibenluft, E. (2014). Fronto-limbic-striatal dysfunction in pediatric and adult patients with bipolar disorder: Impact of face emotion and attentional demands. *Psychological Medicine, 44*(8), 1639−1651. https://doi.org/10.1017/S003329171300202X

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience, 10*(3), 186−198. https://doi.org/10.1038/nrn2575

Bzdok, D., Laird, A. R., Zilles, K., Fox, P. T., & Eickhoff, S. B. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Human Brain Mapping, 34*(12), 3247−3266. https://doi.org/10.1002/hbm.22138

Cao, H., McEwen, S. C., Chung, Y., Chén, O. Y., Bearden, C. E., Addington, J., Goodyear, B., Cadenhead, K. S., Mirzakhanian, H., Cornblatt, B. A., Carrión, R. E., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Belger, A., Seidman, L. J., Thermenos, H., Tsuang, M. T., Van Erp, T. G. M., … Cannon, T. D. (2019). Altered brain activation during memory retrieval precedes and predicts conversion to psychosis in individuals at clinical high risk. *Schizophrenia Bulletin, 45*(4), 924−933. https://doi.org/10.1093/schbul/sby122

Chang, K., Garrett, A., Kelley, R., Howe, M., Sanders, E. M., Acquaye, T., Bararpour, L., Li, S., Singh, M., Jo, B., Hallmayer, J., & Reiss, A. (2017). Anomalous prefrontal-limbic activation and connectivity in youth at high-risk for bipolar disorder. *Journal of Affective Disorders, 222*, 7−13. https://doi.org/10.1016/j.jad.2017.05.051

Clemmensen, L., Vernal, D. L., & Steinhausen, H. C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry, 12*. https://doi.org/10.1186/1471-244X-12-150

Collin, G., Scholtens, L. H., Kahn, R. S., Hillegers, M. H. J., & van den Heuvel, M. P. (2017). Affected anatomical Rich Club and structural−functional coupling in young offspring of schizophrenia and bipolar disorder patients. *Biological Psychiatry, 82*(10), 746−755. https://doi.org/10.1016/j.biopsych.2017.06.013

Deveney, C. M., Brotman, M. A., Thomas, L. A., Hinton, K. E., Muhrer, E. M., Reynolds, R. C., Adleman, N. E., Zarate, C. A., Pine, D. S., & Leibenluft, E. (2014). Neural response during explicit and implicit face processing varies developmentally in bipolar disorder. *Social Cognitive and Affective Neuroscience, 9*(12), 1984−1992. https://doi.org/10.1093/scan/nsu014

Deveney, C. M., Connolly, M. E., Jenkins, S. E., Kim, P., Fromm, S. J., Pine, D. S., & Leibenluft, E. (2012). Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biological Psychology, 89*(1), 148−155. https://doi.org/10.1016/j.biopsycho.2011.10.003

Diler, R. S., de Almeida, J. R. C., Ladouceur, C., Birmaher, B., Axelson, D., & Phillips, M. (2013). Neural activity to intense positive versus negative stimuli can help differentiate bipolar disorder from unipolar major depressive disorder in depressed adolescents: A pilot fMRI study. *Psychiatry Research: Neuroimaging, 214*(3), 277−284. https://doi.org/10.1016/j.pscychresns.2013.06.013

Diler, R. S., Segreti, A. M., Ladouceur, C. D., Almeida, J. R., Birmaher, B., Axelson, D. A., Phillips, M. L., & Pan, L. (2013). Neural correlates of treatment in adolescents with bipolar depression during response inhibition. *Journal of Child and Adolescent Psychopharmacology, 23*(3), 214−221. https://doi.org/10.1089/cap.2012.0054

Diwadkar, V. A., Pruitt, P., Goradia, D., Murphy, E., Bakshi, N., Keshavan, M. S., Rajan, U., Reid, A., & Zajac-Benitez, C. (2011). Fronto-parietal hypo-activation during working memory independent of structural abnormalities: Conjoint fMRI and sMRI analyses in adolescent offspring of schizophrenia patients. *NeuroImage, 58*(1), 234−241. https://doi.org/10.1016/j.neuroimage.2011.06.033

Diwadkar, V. A., Pruitt, P., Zhang, A., Radwan, J., Keshavan, M. S., Murphy, E., Rajan, U., & Zajac-Benitez, C. (2012). The neural correlates of performance in adolescents at risk for schizophrenia: Inefficiently increased cortico-striatal responses measured with fMRI. *Journal of Psychiatric Research, 46*(1), 12−21. https://doi.org/10.1016/j.jpsychires.2011.09.016

Diwadkar, V. A., Segel, J., Pruitt, P., Murphy, E. R., Keshavan, M. S., Radwan, J., Rajan, U., & Zajac-Benitez, C. (2011). Hypo-activation in the executive core of the sustained attention network in adolescent offspring of schizophrenia patients mediated by premorbid functional deficits. *Psychiatry Research: Neuroimaging, 192*(2), 91−99. https://doi.org/10.1016/j.pscychresns.2010.12.005

Dricu, M., & Frühholz, S. (2016). Perceiving emotional expressions in others: Activation likelihood estimation meta-analyses of explicit evaluation, passive perception and incidental perception of emotions. *Neuroscience and Biobehavioral Reviews, 71*, 810−828. https://doi.org/10.1016/j.neubiorev.2016.10.020

Fett, A. K. J., Mouchlianitis, E., Gromann, P. M., Vanes, L., Shergill, S. S., & Krabbendam, L. (2019). The neural mechanisms of social reward in early psychosis. *Social Cognitive and Affective Neuroscience, 14*(8), 861−870. https://doi.org/10.1093/scan/nsz058

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*(9), 700−711. https://doi.org/10.1038/nrn2201

Fusar-Poli, P. (2017). The clinical high-risk state for psychosis (CHR-P), Version II. *Schizophrenia Bulletin, 43*(1), 44−47. https://doi.org/10.1093/schbul/sbw158

Gao, W., Jiao, Q., Lu, S., Zhong, Y., Qi, R., Lu, D., Xiao, Q., Yang, F., Lu, G., & Su, L. (2014). Alterations of regional homogeneity in pediatric bipolar depression: A resting-state fMRI study. *BMC Psychiatry, 14*(1). https://doi.org/10.1186/s12888-014-0222-y

Garrett, A. S., Miklowitz, D. J., Howe, M. E., Singh, M. K., Acquaye, T. K., Hawkey, C. G., Glover, G. H., Reiss, A. L., & Chang, K. D. (2015). Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 56*, 215−220. https://doi.org/10.1016/j.pnpbp.2014.09.007

Garrett, A. S., Reiss, A. L., Howe, M. E., Kelley, R. G., Singh, M. K., Adleman, N. E., Karchemskiy, A., & Chang, K. D. (2012). Abnormal amygdala and prefrontal cortex activation to facial expressions in pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(8), 821−831. https://doi.org/10.1016/j.jaac.2012.06.005

Gisselgård, J., Lebedev, A. V., Dæhli Kurz, K., Joa, I., Johannessen, J. O., Brønnick, K., & van Amelsvoort, T. (2018). Structural and functional alterations in the brain during working memory in medication-naïve patients at clinical high-risk for psychosis. *PLOS ONE, 13*(5). https://doi.org/10.1371/journal.pone.0196289. e0196289.

Hafeman, D. M., Bebko, G., Bertocci, M. A., Fournier, J. C., Bonar, L., Perlman, S. B., Travis, M., Gill, M. K., Diwadkar, V. A., Sunshine, J. L., Holland, S. K., Kowatch, R. A., Birmaher, B., Axelson, D., Horwitz, S. M., Arnold, L. E., Fristad, M. A., Frazier, T. W., Youngstrom, E. A., … Phillips, M. L. (2014). Abnormal deactivation of the inferior frontal gyrus during implicit emotion processing in youth with bipolar disorder: Attenuated by medication. *Journal of Psychiatric Research, 58*, 129−136. https://doi.org/10.1016/j.jpsychires.2014.07.023

Hafeman, D. M., Chase, H. W., Monk, K., Bonar, L., Hickey, M. B., McCaffrey, A., Graur, S., Manelis, A., Ladouceur, C. D., Merranko, J., Axelson, D. A., Goldstein, B. I., Goldstein, T. R., Birmaher, B., & Phillips, M. L. (2019). Intrinsic functional connectivity correlates of person-level risk for bipolar disorder in offspring of affected parents. *Neuropsychopharmacology, 44*(3), 629−634. https://doi.org/10.1038/s41386-018-0264-9

Hafeman, D. M., Ostroff, A. N., Feldman, J., Hickey, M. B., Phillips, M. L., Creswell, D., Birmaher, B., & Goldstein, T. R. (2020). Mindfulness-based intervention to decrease mood lability in at-risk youth: Preliminary evidence for changes in resting state functional connectivity. *Journal of Affective Disorders, 276*, 23−29. https://doi.org/10.1016/j.jad.2020.06.042

Hart, S. J., Bizzell, J., McMahon, M. A., Gu, H., Perkins, D. O., & Belger, A. (2013). Altered fronto-limbic activity in children and adolescents with familial high risk for schizophrenia. *Psychiatry Research: Neuroimaging, 212*(1), 19−27. https://doi.org/10.1016/j.pscychresns.2012.12.003

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*(6), 223−233. https://doi.org/10.1016/S1364-6613(00)01482-0

Ilzarbe, D., de la Serna, E., Baeza, I., Rosa, M., Puig, O., Calvo, A., Masias, M., Borras, R., Pariente, J. C., Castro-Fornieles, J., & Sugranyes, G. (2019). The relationship between performance in a theory of mind task and intrinsic functional connectivity in youth with early onset psychosis. *Developmental Cognitive Neuroscience, 40*, 100726. https://doi.org/10.1016/j.dcn.2019.100726

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748−751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jacobson Mcewen, S. C., Connolly, C. G., Kelly, A. M. C., Kelleher, I., O'Hanlon, E., Clarke, M., Blanchard, M., Mcnamara, S., Connor, D., Sheehan, E., Donohoe, G., Cannon, M., & Garavan, H. (2014). Resting-state connectivity deficits associated with impaired inhibitory control in non-treatment-seeking adolescents with psychotic symptoms. *Acta Psychiatrica Scandinavica, 129*(2), 134–142. https://doi.org/10.1111/acps.12141

Jalbrzikowski, M., Liu, F., Foran, W., Roeder, K., Devlin, B., & Luna, B. (2020). Resting-state functional network organization is stable across adolescent development for typical and psychosis spectrum youth. *Schizophrenia Bulletin, 46*(2), 395–407. https://doi.org/10.1093/schbul/sbz053

Jalbrzikowski, M., Murty, V. P., Tervo-Clemmens, B., Foran, W., & Luna, B. (2019). Age-associated deviations of amygdala functional connectivity in youths with psychosis spectrum disorders: Relevance to psychotic symptoms. *American Journal of Psychiatry, 176*(3), 196–207. https://doi.org/10.1176/appi.ajp.2018.18040443

Janiri, D., Moser, D. A., Doucet, G. E., Luber, M. J., Rasgon, A., Lee, W. H., Murrough, J. W., Sani, G., Eickhoff, S. B., & Frangou, S. (2020). Shared neural phenotypes for mood and anxiety disorders: A meta-analysis of 226 task-related functional imaging studies. *JAMA Psychiatry, 77*(2), 172–179. https://doi.org/10.1001/jamapsychiatry.2019.3351

Jiang, L., Xu, Y., Zhu, X. T., Yang, Z., Li, H. J., & Zuo, X. N. (2015). Local-to-remote cortical connectivity in early-and adulthood-onset schizophrenia. *Translational Psychiatry, 5*(5). https://doi.org/10.1038/tp.2015.59

Karlsgodt, K. H., van Erp, T. G. M., Bearden, C. E., & Cannon, T. D. (2014). Altered relationships between age and functional brain activation in adolescents at clinical high risk for psychosis. *Psychiatry Research: Neuroimaging, 221*(1), 21–29. https://doi.org/10.1016/j.pscychresns.2013.08.004

Kim, P., Jenkins, S. E., Connolly, M. E., Deveney, C. M., Fromm, S. J., Brotman, M. A., Nelson, E. E., Pine, D. S., & Leibenluft, E. (2012). Neural correlates of cognitive flexibility in children at risk for bipolar disorder. *Journal of Psychiatric Research, 46*(1), 22–30. https://doi.org/10.1016/j.jpsychires.2011.09.015

King, J. B., Anderson, J. S., Yurgelun-Todd, D. A., Subramaniam, P., Ehrler, M. R., & Lopez-Larson, M. P. (2018). Decreased anterior cingulate activation in a motor task in youths with bipolar disorder. *Journal of Child Psychology and Psychiatry, 59*(8), 900–907. https://doi.org/10.1111/jcpp.12875

Kryza-Lacombe, M., Brotman, M. A., Reynolds, R. C., Towbin, K., Pine, D. S., Leibenluft, E., & Wiggins, J. L. (2019). Neural mechanisms of face emotion processing in youths and adults with bipolar disorder. *Bipolar Disorders, 21*(4), 309–320. https://doi.org/10.1111/bdi.12768

Ladouceur, C. D., Diwadkar, V. A., White, R., Bass, J., Birmaher, B., Axelson, D. A., & Phillips, M. L. (2013). Fronto-limbic function in unaffected offspring at familial risk for bipolar disorder during an emotional working memory paradigm. *Developmental Cognitive Neuroscience, 5*, 185–196. https://doi.org/10.1016/j.dcn.2013.03.004

Ladouceur, C. D., Farchione, T., Diwadkar, V., Pruitt, P., Radwan, J., Axelson, D. A., Birmaher, B., & Phillips, M. L. (2011). Differential patterns of abnormal activity and connectivity in the amygdala–prefrontal circuitry in bipolar-I and bipolar-NOS youth. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(12), 1275–1289. https://doi.org/10.1016/j.jaac.2011.09.023. e2.

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H., Mowry, B. J., Thapar, A., Goddard, M. E., Witte, J. S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O. A., Anjorin, A., Anney, R., Anttila, V., Arking, D. E., … Wray, N. R. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics, 45*(9), 984–994. https://doi.org/10.1038/ng.2711

Li, M., Becker, B., Zheng, J., Zhang, Y., Chen, H., Liao, W., Duan, X., Liu, H., Zhao, J., & Chen, H. (2019). Dysregulated maturation of the functional connectome in antipsychotic-naïve, first-episode patients with adolescent-onset schizophrenia. *Schizophrenia Bulletin, 45*(3), 689−697. https://doi.org/10.1093/schbul/sby063

Lichtenstein, P., Yip, B. H., Björk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *The Lancet, 373*(9659), 234−239. https://doi.org/10.1016/S0140-6736(09)60072-6

Li, S., Hu, N., Zhang, W., Tao, B., Dai, J., Gong, Y., Tan, Y., Cai, D., & Lui, S. (2019). Dysconnectivity of multiple brain networks in schizophrenia: A meta-analysis of resting-state functional connectivity. *Frontiers in Psychiatry, 10*(482), 1−11. https://doi.org/10.3389/fpsyt.2019.00482

Lin, K., Shao, R., Lu, R., Chen, K., Lu, W., Li, T., Kong, J., So, K. F., & Xu, G. (2018). Resting-state fMRI signals in offspring of parents with bipolar disorder at the high-risk and ultra-high-risk stages and their relations with cognitive function. *Journal of Psychiatric Research, 98*, 99−106. https://doi.org/10.1016/j.jpsychires.2018.01.001

Liu, Y., Guo, W., Zhang, Y., Lv, L., Hu, F., Wu, R., & Zhao, J. (2018). Decreased resting-state interhemispheric functional connectivity correlated with neurocognitive deficits in drug-naive first-episode adolescent-onset schizophrenia. *International Journal of Neuropsychopharmacology, 21*(1), 33−41. https://doi.org/10.1093/ijnp/pyx095

Liu, Y., Zhang, Y., Lv, L., Wu, R., Zhao, J., & Guo, W. (2018). Abnormal neural activity as a potential biomarker for drug-naive first-episode adolescent-onset schizophrenia with coherence regional homogeneity and support vector machine analyses. *Schizophrenia Research, 192*, 408−415. https://doi.org/10.1016/j.schres.2017.04.028

Li, H. J., Xu, Y., Zhang, K.-R., Hoptman, M. J., & Zuo, X.-N. (2015). Homotopic connectivity in drug-naïve, first-episode, early-onset schizophrenia. *Journal of Child Psychology and Psychiatry, 56*(4), 432−443. https://doi.org/10.1111/jcpp.12307

Lopez-Larson, M. P., Shah, L. M., Weeks, H. R., King, J. B., Mallik, A. K., Yurgelun-Todd, D. A., & Anderson, J. S. (2017). Abnormal functional connectivity between default and salience networks in pediatric bipolar disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2*(1), 85−93. https://doi.org/10.1016/j.bpsc.2016.10.001

Manelis, A., Ladouceur, C. D., Graur, S., Monk, K., Bonar, L. K., Hickey, M. B., Dwojak, A. C., Axelson, D., Goldstein, B. I., Goldstein, T. R., Bebko, G., Bertocci, M. A., Gill, M. K., Birmaher, B., & Phillips, M. L. (2016). Altered functioning of reward circuitry in youth offspring of parents with bipolar disorder. *Psychological Medicine, 46*(1), 197−208. https://doi.org/10.1017/S003329171500166X

McTeague, L. M., Huemer, J., Carreon, D. M., Jiang, Y., Eickhoff, S. B., & Etkin, A. (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *American Journal of Psychiatry, 174*(7), 676−685. https://doi.org/10.1176/appi.ajp.2017.16040400

Mennigen, E., Jolles, D. D., Hegarty, C. E., Gupta, M., Jalbrzikowski, M., Olde Loohuis, L. M., Ophoff, R. A., Karlsgodt, K. H., & Bearden, C. E. (2020). State-dependent functional dysconnectivity in youth with psychosis spectrum symptoms. *Schizophrenia Bulletin, 46*(2), 408−421. https://doi.org/10.1093/schbul/sbz052

Metcalfe, A. W. S., MacIntosh, B. J., Scavone, A., Ou, X., Korczak, D., & Goldstein, B. I. (2016). Effects of acute aerobic exercise on neural correlates of attention and inhibition in adolescents with bipolar disorder. *Translational Psychiatry, 6*(5), e814. https://doi.org/10.1038/tp.2016.85

Natu, V., & O'Toole, A. J. (2011). The neural processing of familiar and unfamiliar faces: A review and synopsis. *British Journal of Psychology, 102*(4), 726–747. https://doi.org/10.1111/j.2044-8295.2011.02053.x

Nery, F. G., Masifi, S. L., Strawn, J. R., Duran, L. R., Weber, W. A., Welge, J. A., Adler, C. M., Strakowski, S. M., & Delbello, M. P. (2021). Association between poor tolerability of antidepressant treatment and brain functional activation in youth at risk for bipolar disorder. *Brazilian Journal of Psychiatry, 43*(1), 70–74. https://doi.org/10.1590/1516-4446-2019-0803

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective and Behavioral Neuroscience, 12*(2), 241–268. https://doi.org/10.3758/s13415-011-0083-5

Niendam, T. A., Lesh, T. A., Yoon, J., Westphal, A. J., Hutchison, N., Daniel Ragland, J., Solomon, M., Minzenberg, M., & Carter, C. S. (2014). Impaired context processing as a potential marker of psychosis risk state. *Psychiatry Research: Neuroimaging, 221*(1), 13–20. https://doi.org/10.1016/j.pscychresns.2013.09.001

Nimarko, A. F., Garrett, A. S., Carlson, G. A., & Singh, M. K. (2019). Neural correlates of emotion processing predict resilience in youth at familial risk for mood disorders. *Development and Psychopathology, 31*(3), 1037–1052. https://doi.org/10.1017/S0954579419000579

Olsavsky, A. K., Brotman, M. A., Rutenberg, J. G., Muhrer, E. J., Deveney, C. M., Fromm, S. J., Towbin, K., Pine, D. S., & Leibenluft, E. (2012). Amygdala hyperactivation during face emotion processing in unaffected youth at risk for bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(3), 294–303. https://doi.org/10.1016/j.jaac.2011.12.008

Pagliaccio, D., Wiggins, J. L., Adleman, N. E., Harkins, E., Curhan, A., Towbin, K. E., Brotman, M. A., Pine, D. S., & Leibenluft, E. (2017). Behavioral and neural sustained attention deficits in bipolar disorder and familial risk of bipolar disorder. *Biological Psychiatry, 82*(9), 669–678. https://doi.org/10.1016/j.biopsych.2016.09.006

Passarotti, A. M., Sweeney, J. A., & Pavuluri, M. N. (2011). Fronto-limbic dysfunction in mania pre-treatment and persistent amygdala over-activity post-treatment in pediatric bipolar disorder. *Psychopharmacology, 216*(4), 485–499. https://doi.org/10.1007/s00213-011-2243-2

Pavuluri, M. N., Passarotti, A. M., Fitzgerald, J. M., Wegbreit, E., & Sweeney, J. A. (2012). Risperidone and divalproex differentially engage the fronto-striato- temporal circuitry in pediatric mania: A pharmacological functional magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(2), 157–170. https://doi.org/10.1016/j.jaac.2011.10.019. e5.

Pavuluri, M. N., Passarotti, A. M., Lu, L. H., Carbray, J. A., & Sweeney, J. A. (2011). Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder: fMRI outcomes. *Psychiatry Research: Neuroimaging, 193*(1), 28–37. https://doi.org/10.1016/j.pscychresns.2011.01.005

Perlman, S. B., Fournier, J. C., Bebko, G., Bertocci, M. A., Hinze, A. K., Bonar, L., Almeida, J. R. C., Versace, A., Schirda, C., Travis, M., Gill, M. K., Demeter, C., Diwadkar, V. A., Sunshine, J. L., Holland, S. K., Kowatch, R. A., Birmaher, B., Axelson, D., Horwitz, S. M., … Phillips, M. L. (2013). Emotional face processing in pediatric bipolar disorder: Evidence for functional impairments in the fusiform gyrus. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(12), 1314–e3. https://doi.org/10.1016/j.jaac.2013.09.004

Rajarethinam, R., Venkatesh, B. K., Peethala, R., Phan, K. L., & Keshavan, M. (2011). Reduced activation of superior temporal gyrus during auditory comprehension in young offspring of patients with schizophrenia. *Schizophrenia Research, 130*(1–3), 101–105. https://doi.org/10.1016/j.schres.2011.05.025

Satterthwaite, T. D., Vandekar, S. N., Wolf, D. H., Bassett, D. S., Ruparel, K., Shehzad, Z., Craddock, R. C., Shinohara, R. T., Moore, T. M., Gennatas, E. D., Jackson, C., Roalf, D. R., Milham, M. P., Calkins, M. E., Hakonarson, H., Gur, R. C., & Gur, R. E. (2015). Connectome-wide network analysis of youth with Psychosis-Spectrum symptoms. *Molecular Psychiatry, 20*(12), 1508−1515. https://doi.org/10.1038/mp.2015.66

Schneider, M. R., Adler, C. M., Whitsel, R., Weber, W., Mills, N. P., Bitter, S. M., Eliassen, J., Strakowski, S. M., & DelBello, M. P. (2012). The effects of ziprasidone on prefrontal and amygdalar activation in manic youth with bipolar disorder. *Israel Journal of Psychiatry and Related Sciences, 49*(2), 112−121. https://ijp.doctorsonly.co.il/.

Schneider, M. R., Klein, C. C., Weber, W., Bitter, S. M., Elliott, K. B., Strakowski, S. M., Adler, C. M., & DelBello, M. P. (2014). The effects of carbamazepine on prefrontal activation in manic youth with bipolar disorder. *Psychiatry Research: Neuroimaging, 223*(3), 268−270. https://doi.org/10.1016/j.pscychresns.2014.04.011

Sescousse, G., Caldú, X., Segura, B., & Dreher, J. C. (2013). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 37*(4), 681−696. https://doi.org/10.1016/j.neubiorev.2013.02.002

Singh, M. K., Chang, K. D., Kelley, R. G., Cui, X., Sherdell, L., Howe, M. E., Gotlib, I. H., & Reiss, A. L. (2013). Reward processing in adolescents with bipolar i disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(1), 68−83. https://doi.org/10.1016/j.jaac.2012.10.004

Singh, M. K., Chang, K. D., Kelley, R. G., Saggar, M., Reiss, A. L., & Gotlib, I. H. (2014). Early signs of anomalous neural functional connectivity in healthy offspring of parents with bipolar disorder. *Bipolar Disorders, 16*(7), 678−689. https://doi.org/10.1111/bdi.12221

Singh, M. K., Kelley, R. G., Chang, K. D., & Gotlib, I. H. (2015). Intrinsic amygdala functional connectivity in youth with bipolar i disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 54*(9), 763−770. https://doi.org/10.1016/j.jaac.2015.06.016

Singh, M. K., Kelley, R. G., Howe, M. E., Reiss, A. L., Gotlib, I. H., & Chang, K. D. (2014). Reward processing in healthy offspring of parents with bipolar disorder. *JAMA Psychiatry, 71*(10), 1148−1156. https://doi.org/10.1001/jamapsychiatry.2014.1031

Singh, M. K., Leslie, S. M., Bhattacharjee, K., Gross, M., Weisman, E. F., Soudi, L. M., Phillips, O. R., & Onopa, A. (2018). Vulnerabilities in sequencing and task switching in healthy youth offspring of parents with mood disorders. *Journal of Clinical and Experimental Neuropsychology, 40*(6), 606−618. https://doi.org/10.1080/13803395.2017.1401597

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences, 106*(31), 13040−13045. https://doi.org/10.1073/pnas.0905267106

Soehner, A. M., Bertocci, M. A., Manelis, A., Bebko, G., Ladouceur, C. D., Graur, S., Monk, K., Bonar, L. K., Hickey, M. B., Axelson, D., Goldstein, B. I., Goldstein, T. R., Birmaher, B., & Phillips, M. L. (2016). Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder. *Journal of Affective Disorders, 205*, 144−153. https://doi.org/10.1016/j.jad.2016.03.074

Solé-Padullés, C., Castro-Fornieles, J., de la Serna, E., Romero, S., Calvo, A., Sánchez-Gistau, V., Padrós-Fornieles, M., Baeza, I., Bargalló, N., Frangou, S., Sugranyes, G., & Abulseoud, O. A. (2016). Altered cortico-striatal connectivity in offspring of schizophrenia patients relative to offspring of bipolar patients and controls. *PLOS ONE, 11*(2), e0148045. https://doi.org/10.1371/journal.pone.0148045

Solé-Padullés, C., Castro-Fornieles, J., de la Serna, E., Sánchez-Gistau, V., Romero, S., Puig, O., Calvo, A., Bargalló, N., Baeza, I., & Sugranyes, G. (2017). Intrinsic functional connectivity of fronto-temporal networks in adolescents with early psychosis. *European Child and Adolescent Psychiatry, 26*(6), 669–679. https://doi.org/10.1007/s00787-016-0931-5

Son, Y. D., Han, D. H., Kim, S. M., Min, K. J., & Renshaw, P. F. (2017). A functional connectivity comparison between attention deficit hyperactivity disorder and bipolar disorder in medication-naïve adolescents with mood fluctuation and attention problems. *Psychiatry Research: Neuroimaging, 263*, 1–7. https://doi.org/10.1016/j.pscychresns.2017.02.006

Stoddard, J., Hsu, D., Reynolds, R. C., Brotman, M. A., Ernst, M., Pine, D. S., Leibenluft, E., & Dickstein, D. P. (2015). Aberrant amygdala intrinsic functional connectivity distinguishes youths with bipolar disorder from those with severe mood dysregulation. *Psychiatry Research: Neuroimaging, 231*(2), 120–125. https://doi.org/10.1016/j.pscychresns.2014.11.006

Sugranyes, G., Kyriakopoulos, M., Dima, D., O'Muircheartaigh, J., Corrigall, R., Pendelbury, G., Hayes, D., Calhoun, V. D., & Frangou, S. (2012). Multimodal analyses identify linked functional and white matter abnormalities within the working memory network in schizophrenia. *Schizophrenia Research, 138*(2–3), 136–142. https://doi.org/10.1016/j.schres.2012.03.011

Syan, S. K., Smith, M., Frey, B. N., Remtulla, R., Kapczinski, F., Hall, G. B. C., & Minuzzi, L. (2018). Resting-state functional connectivity in individuals with bipolar disorder during clinical remission: A systematic review. *Journal of Psychiatry and Neuroscience, 43*(5), 298–316. https://doi.org/10.1503/jpn.170175

Tang, J., Liao, Y., Song, M., Gao, J.-H., Zhou, B., Tan, C., Liu, T., Tang, Y., Chen, J., Chen, X., & Zhan, W. (2013). Aberrant default mode functional connectivity in early onset schizophrenia. *PLOS ONE, 8*(7). https://doi.org/10.1371/journal.pone.0071061. e71061.

Thormodsen, R., Jensen, J., Holmèn, A., Juuhl-Langseth, M., Emblem, K. E., Andreassen, O. A., & Rund, B. R. (2011). Prefrontal hyperactivation during a working memory task in early-onset schizophrenia spectrum disorders: An fMRI study. *Psychiatry Research: Neuroimaging, 194*(3), 257–262. https://doi.org/10.1016/j.pscychresns.2011.05.011

Tseng, W. L., Bones, B. L., Kayser, R. R., Olsavsky, A. K., Fromm, S. J., Pine, D. S., Leibenluft, E., & Brotman, M. A. (2015). An fMRI study of emotional face encoding in youth at risk for bipolar disorder. *European Psychiatry, 30*(1), 94–98. https://doi.org/10.1016/j.eurpsy.2014.05.004

Urback, A. L., Metcalfe, A. W. S., Korczak, D. J., MacIntosh, B. J., & Goldstein, B. I. (2019). Reduced cerebrovascular reactivity among adolescents with bipolar disorder. *Bipolar Disorders, 21*(2), 124–131. https://doi.org/10.1111/bdi.12719

Urošević, S., Luciana, M., Jensen, J. B., Youngstrom, E. A., & Thomas, K. M. (2016). Age associations with neural processing of reward anticipation in adolescents with bipolar disorders. *NeuroImage: Clinical, 11*, 476–485. https://doi.org/10.1016/j.nicl.2016.03.013

Wagshal, D., Knowlton, B. J., Suthana, N. A., Cohen, J. R., Poldrack, R. A., Bookheimer, S. Y., Bilder, R. M., & Asarnow, R. F. (2014). Evidence for corticostriatal dysfunction during cognitive skill learning in adolescent siblings of patients with childhood-onset schizophrenia. *Schizophrenia Bulletin, 40*(5), 1030–1039. https://doi.org/10.1093/schbul/sbt147

Wang, X., Liao, W., Han, S., Li, J., Zhang, Y., Zhao, J., & Chen, H. (2019). Altered dynamic global signal topography in antipsychotic-naive adolescents with early-onset schizophrenia. *Schizophrenia Research, 208*, 308–316. https://doi.org/10.1016/j.schres.2019.01.035

Wang, S., Zhang, Y., Lv, L., Wu, R., Fan, X., Zhao, J., & Guo, W. (2018). Abnormal regional homogeneity as a potential imaging biomarker for adolescent-onset schizophrenia: A resting-state fMRI study and support vector machine analysis. *Schizophrenia Research, 192*, 179–184. https://doi.org/10.1016/j.schres.2017.05.038

Wang, S., Zhan, Y., Zhang, Y., Lv, L., Wu, R., Zhao, J., & Guo, W. (2017). Abnormal functional connectivity strength in patients with adolescent-onset schizophrenia: A resting-state fMRI study. *European Child and Adolescent Psychiatry, 26*(7), 839–845. https://doi.org/10.1007/s00787-017-0958-2

Wang, S., Zhan, Y., Zhang, Y., Lyu, L., Lyu, H., Wang, G., Wu, R., Zhao, J., & Guo, W. (2018). Abnormal long- and short-range functional connectivity in adolescent-onset schizophrenia patients: A resting-state fMRI study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 81*, 445–451. https://doi.org/10.1016/j.pnpbp.2017.08.012

Watsky, R. E., Gotts, S. J., Berman, R. A., McAdams, H. M., Zhou, X., Greenstein, D., Lalonde, F. M., Gochman, P., Clasen, L. S., Shora, L., Ordóñez, A. E., Gogtay, N., Martin, A., Barch, D. M., Rapoport, J. L., & Liu, S. (2018). Attenuated resting-state functional connectivity in patients with childhood- and adult-onset schizophrenia. *Schizophrenia Research, 197*, 219–225. https://doi.org/10.1016/j.schres.2018.01.003

Weathers, J., Brotman, M. A., Deveney, C. M., Kim, P., Zarate, C., Fromm, S., Pine, D., & Leibenluft, E. (2013). A developmental study on the neural circuitry mediating response flexibility in bipolar disorder. *Psychiatry Research: Neuroimaging, 214*(1), 56–65. https://doi.org/10.1016/j.pscychresns.2013.05.002

Weathers, J. D., Stringaris, A., Deveney, C. M., Brotman, M. A., Zarate, C. A., Connolly, M. E., Fromm, S. J., LeBourdais, S. B., Pine, D. S., & Leibenluft, E. (2012). A developmental study of the neural circuitry mediating motor inhibition in bipolar disorder. *American Journal of Psychiatry, 169*(6), 633–641. https://doi.org/10.1176/appi.ajp.2012.11081244

Wei, S., Womer, F., Geng, H., Jiang, X., Zhou, Q., Chang, M., Zhou, Y., Tang, Y., & Wang, F. (2017). Similarities and differences of functional connectivity in drug-naïve, first-episode adolescent and young adult with major depressive disorder and schizophrenia. *Scientific Reports, 7*. https://doi.org/10.1038/srep44316

Welge, J. A., Saliba, L. J., Strawn, J. R., Eliassen, J. C., Patino, L. R., Adler, C. M., Weber, W., Schneider, M. R., Barzman, D. H., Strakowski, S. M., DelBello, M. P., & McNamara, R. K. (2016). Neurofunctional differences among youth with and at varying risk for developing mania. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(11), 980–989. https://doi.org/10.1016/j.jaac.2016.08.006

White, T., Hongwanishkul, D., & Schmidt, M. (2011). Increased anterior cingulate and temporal lobe activity during visuospatial working memory in children and adolescents with schizophrenia. *Schizophrenia Research, 125*(2–3), 118–128. https://doi.org/10.1016/j.schres.2010.11.014

Wiggins, J. L., Brotman, M. A., Adleman, N. E., Kim, P., Wambach, C. G., Reynolds, R. C., Chen, G., Towbin, K., Pine, D. S., & Leibenluft, E. (2017). Neural markers in pediatric bipolar disorder and familial risk for bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(1), 67–78. https://doi.org/10.1016/j.jaac.2016.10.009

Wolf, D. H., Satterthwaite, T. D., Calkins, M. E., Ruparel, K., Elliott, M. A., Hopson, R. D., Jackson, C. T., Prabhakaran, K., Bilker, W. B., Hakonarson, H., Gur, R. C., & Gur, R. E. (2015). Functional neuroimaging abnormalities in youth with psychosis spectrum symptoms. *JAMA Psychiatry, 72*(5), 456–465. https://doi.org/10.1001/jamapsychiatry.2014.3169

Xiao, Q., Cui, D., Jiao, Q., Zhong, Y., Cao, W., Lu, G., & Su, L. (2019). Altered regional homogeneity in pediatric bipolar disorder during manic and euthymic state: A resting-state fMRI study. *Brain Imaging and Behavior, 13*(6), 1789–1798. https://doi.org/10.1007/s11682-019-00117-4

Xiao, Q., Zhong, Y., Lu, D., Gao, W., Jiao, Q., Lu, G., Su, L., & Zang, Y.-F. (2013). Altered regional homogeneity in pediatric bipolar disorder during manic state: A resting-state fMRI study. *PLOS ONE, 8*(3). https://doi.org/10.1371/journal.pone.0057978. e57978.

Yang, H., Lu, L. H., Wu, M., Stevens, M., Wegbreit, E., Fitzgerald, J., Levitan, B., Shankman, S., & Pavuluri, M. N. (2013). Time course of recovery showing initial prefrontal cortex changes at 16 weeks, extending to subcortical changes by 3 years in pediatric bipolar disorder. *Journal of Affective Disorders, 150*(2), 571−577. https://doi.org/10.1016/j.jad.2013.02.007

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage, 22*(1), 394−400. https://doi.org/10.1016/j.neuroimage.2003.12.030

Zhang, S., Yang, G., Ou, Y., Guo, W., Peng, Y., Hao, K., Zhao, J., Yang, Y., Li, W., Zhang, Y., & Lv, L. (2020). Abnormal default-mode network homogeneity and its correlations with neurocognitive deficits in drug-naive first-episode adolescent-onset schizophrenia. *Schizophrenia Research, 215*, 140−147. https://doi.org/10.1016/j.schres.2019.10.056

Zhang, Y., Zheng, J., Fan, X., Guo, X., Guo, W., Yang, G., Chen, H., Zhao, J., & Lv, L. (2015). Dysfunctional resting-state connectivities of brain regions with structural deficits in drug-naive first-episode schizophrenia adolescents. *Schizophrenia Research, 168*(1−2), 353−359. https://doi.org/10.1016/j.schres.2015.07.031

Zheng, J., Zhang, Y., Guo, X., Duan, X., Zhang, J., Zhao, J., & Chen, H. (2016). Disrupted amplitude of low-frequency fluctuations in antipsychotic-naïve adolescents with early-onset schizophrenia. *Psychiatry Research: Neuroimaging, 249*, 20−26. https://doi.org/10.1016/j.pscychresns.2015.11.006

Zhong, Y., Wang, C., Gao, W., Xiao, Q., Lu, D., Jiao, Q., Su, L., & Lu, G. (2019). Aberrant resting-state functional connectivity in the default mode network in pediatric bipolar disorder patients with and without psychotic symptoms. *Neuroscience Bulletin, 35*(4), 581−590. https://doi.org/10.1007/s12264-018-0315-6

Zuo, X. N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., & Milham, M. P. (2010). The oscillating brain: Complex and reliable. *NeuroImage, 49*(2), 1432−1445. https://doi.org/10.1016/j.neuroimage.2009.09.037

Chapter 10

Adolescence as a vulnerable period for psychosis development

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Introduction

Puberty and adolescence refer to two complementary concepts: gonadal maturation (puberty), and an emergence of adult-like social and cognitive behaviors (adolescence). Here I review some of the key aspects of social behavior during adolescence as related to both sexual maturation and stress and provide a brief overview of the hypothalamus–pituitary–adrenal (HPA) (stress) and hypothalamus–pituitary–gonadal (HPG) (sexual maturation) axes. In the following three sections, I discuss how the two axes shape structure and function of the adolescent brain. The final section outlines some of the future directions that could enhance our understanding of the factors in our social environment and genes that may modulate the risk of developing psychosis in youth.

In primates, social communication and behavior are of critical importance for establishing and maintaining bonds between individuals, cooperation in groups and for reproduction (Liebal et al., 2014). Adolescence represents a unique period of development when sexual maturation becomes one of the key factors influencing social dynamics among conspecifics. As observed in nonhuman primates in the wild, this may manifest itself in the establishment of social hierarchies within a group (female adolescents) or by social distancing and eventual dispersal from the natal group (male adolescents) (Onyango et al., 2013). In humans, the interplay between sexual maturation and social behavior is, of course, more subtle. It plays out over an extended period of time ($\sim$10 years) and takes place mostly among peers.

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00012-3

Social behavior during adolescence

As reviewed in detail elsewhere, peer relationships become highly salient during adolescence (Brown & Larson, 2009). Compared with childhood, the complexity of social relationships increases during this period of human development for a couple of reasons. First, in the transitions from elementary to middle school, and from middle school to high school, adolescents must navigate new, and often more extensive, social environments. In high school, this task is made even more challenging by an educational structure in which the adolescent often joins different groups of peers in different classes to complete various school subjects offered in a given grade. Second, romantic relationships[1], arguably a hallmark of adolescence (Collins et al., 2009), become a dominant type of dyadic peer–peer interactions (Laursen & Williams, 1997). Based on data collected in the National Longitudinal Study of Adolescent to Adult Health (USA), the percentage of adolescents reporting a romantic relationship (in the last 18 months) increased from 36% (age 13 years) through 53% (age 15 years) to 70% (age 17 years) (Carver et al., 2003).

Both friendships and romantic relationships represent important context for the development of autonomous reasoning when interacting with individuals who are close to each other. Using an experimental approach embedded in a longitudinal study of youth (13, 18 and 21 years of age), Oudekerk and colleagues examined developmental cascades shaping inter-individual variations in the ability to balance autonomy and relatedness during disagreements (Oudekerk et al., 2015). Autonomy and relatedness with a close friend at 13 years of age cascaded to the dynamics of a romantic relationship at 18 that, in turn, predicted autonomy and relatedness with both a close friend and a romantic partner at 21 years of age (Oudekerk et al., 2015). Putting aside possible reasons for individual differences in this ability (e.g., parental psychological control, as examined in the study), this work illustrates the possibilities for investigating the likely bidirectional nature of brain–behavior relationships (and cascades) during adolescent development. For example, certain perceptual abilities (e.g., face and voice processing) or cognitive skills (e.g., conflict resolution (Ljungberg et al., 1999)), and related neural circuits developed and shaped during childhood, may influence the probability of engaging more or less in social interactions during adolescence. In turn, these interactions continue to shape relevant neural circuits.

1. Romantic relationships typically refer to "mutually acknowledged ongoing voluntary interactions, commonly marked by expression of affection and perhaps current or anticipated sexual behavior". These are distinct from romantic experiences defined as "varied behavioral, cognitive and emotional phenomena with romantic content; may or may not include direct experiences with a romantic partner" (Collins, W. A., Welsh, D. P., & Furman, W. (2009). Adolescent romantic relationships. Annual Review of Psychology, 60, 631–652. https://doi.org/10.1146/annurev.psych.60.110707.163459).

The Oudekerk study also raises an important methodological issue: the need for behavioral data (in addition to self-reports) to understand the variations in social dynamics during adolescence. In their study, each dyad (two close friends or two romantic partners) participated in an 8-min videotaped interaction during which they tried to resolve a series of disagreements (Oudekerk et al., 2015). Of course, this quasi-ethological approach (observations in a laboratory) is highly demanding both for participants and researchers, limiting its application in large population-based studies (Paus, 2010b, 2013). Could we envisage the use of a truly ethological approach, namely observing the behavior of large numbers of adolescents in their natural environments, in future research? I will come back to this question in the last part of this chapter.

Social interactions can be rewarding and stressful

If we conceptualize stress as "a cognitive perception of uncontrollability and/or unpredictability" (Koolhaas et al., 2011), the stressful nature of social interactions becomes particularly salient during adolescence. The dynamics of social relationships during this developmental period are considerable, limiting predictability and controllability of peer-peer interactions. Romantic relationships change over a short period of time. In the National Longitudinal Study of Adolescent to Adult Health, only 18% of adolescents (11−18 years of age) were in "steady dating" relationships at two time points, 1 year apart, while 28% changed their relationship over the same period (e.g., from no relationship to one casual/multiple partners, or from one casual relationship to no relationship) (Meier & Allen, 2009). Nonromantic peer−peer relationships (friendships) are also fluid. Even over a short period of 3 weeks, the chance of maintaining a mutual friendship (i.e., nominating each other as "best friends" again) varies between 0.32 (Grade 4) and 0.46 (Grade 7) (Cairns et al., 1995). School transitions, as well as large numbers of permutations in a group membership while attending various classes in high school, place additional demands on establishing one's position in the existing (or emerging) social hierarchy. In nonhuman primates, the order in which a female is introduced to a small group of unrelated females predicts strongly her dominance rank (Snyder-Mackler, Kohn, et al., 2016), and changing the dominance rank experimentally affects behavior, related physiology, as well as immune functions (Kohn et al., 2016; Snyder-Mackler, Sanz, et al., 2016). Overall, the uncontrollability (e.g., break ups with romantic partners) and unpredictability (e.g., new classmates during school transitions) of social relationships during adolescence are high and, as such, place considerable demands on regulatory mechanisms in the adolescent brain and body.

Stress represents a well-known risk factor for psychiatric disorders and has been studied extensively in the context of both mood disorders and schizophrenia (Beards et al., 2013; Girshkin et al., 2014; Matheson et al., 2013).

Several reviews have identified an exposure to stressors during childhood and adolescence as a possible pathway leading to the emergence of these (and other) disorders (Grant et al., 2003; Turner & Lloyd, 2004; Varese et al., 2012). As pointed out above, social stressors play a particularly important role during adolescence, a period when peers come to dominate an adolescent's social structure (McCormick et al., 2015; Susman et al., 1988). It has also been suggested that stress reactivity is higher during adolescence when compared with adulthood (Dahl & Gunnar, 2009; Eiland & Romeo, 2013; McCormick et al., 2010). Stress involves a complex and intertwined set of physiological responses to a stressor (Selye, 1950; Tsigos & Chrousos, 2002). As described below, the stress response begins with an activation of the HPA axis and sympathetic adrenomedullary system, followed by a number of other downstream effects such as the production of proinflammatory cytokines (e.g., TNFα (Koolhaas et al., 2011)), and metabolic consequences (e.g., hyperglycemia (Reagan et al., 2008)). Both cortisol and cytokines may influence cytoskeletal proteins and axonal transport (see the Section on white matter later in the Chapter).

In the next three subsections, I will review the basics about the HPA and HPG axes, and their interactions.

Hypothalamus–pituitary–adrenal axis

The HPA axis is the main regulator of the production, by adrenal glands, of glucocorticoid hormones, cortisol in primates, and corticosterone in rodents. High glucocorticoids do not equate to high stress, however. As shown in Fig. 10.1, glucocorticoids are produced under many conditions, both appetitive (e.g., sexual behavior) and aversive (e.g., social defeat). For this reason, a mere increase in plasma cortisol should not be viewed as a biological marker of stress (Koolhaas et al., 2011).

Neurons in the paraventricular nucleus (PVN) of the hypothalamus produce corticotropin releasing hormone (CRH) that, in turn, stimulates release of adrenocorticotropic hormone (ACTH) from the pituitary (its anterior lobe). ACTH enters peripheral circulation and, in the zona fasciculata of the adrenal cortex, stimulates production of glucocorticoids (Melmed et al., 2015). Glucocorticoid production is also under the control of the sympathetic nervous system (via splanchnic nerve). This pathway begins in the suprachiasmatic nucleus (SCN) of the hypothalamus. Activity of SCN neurons is under the influence of retinohypothalamic projections that, in turn, drive circadian fluctuations in glucocorticoid levels (Leliavski et al., 2015). This 24-hour diurnal cycle is superimposed on burst-like spikes of ACTH, and slightly delayed spikes of cortisol. It is possible that this ultradian rhythm reflects feedforward and feedback interactions between the pituitary gland and adrenal cortex (Lightman & Conway-Campbell, 2010). In the feedback loop, cortisol inhibits production of CRH (hypothalamus) and ACTH (pituitary) by

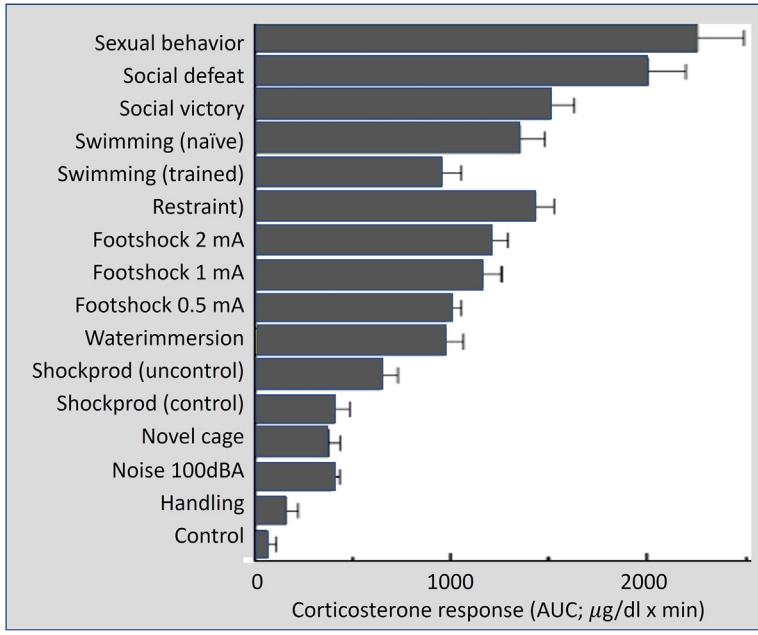

FIGURE 10.1 **Corticosterone response in different test conditions in rodents.** *Reprinted from Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wöhr, M., & Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept.* Neuroscience and Biobehavioral Reviews, 35*(5), 1291–1301. https://doi.org/10.1016/j.neubiorev.2011.02.003. Reprinted with permission.*

repressing, respectively, transcription of *CRH* and proopiomelanocortin (*POMC)* (an ACTH precursor)[2].

In addition to the above regulatory mechanisms, a number of neural pathways converge on the hypothalamus, including inputs from subcortical structures, such as the amygdala, hippocampus, the bed nucleus of the stria terminalis and the nucleus of the solitary tract, as well as in several regions of the cerebral cortex, such as the medial prefrontal cortex and the anterior cingulate cortex (Herman et al., 2003). As mentioned above, the adrenal cortex also receives projections from the sympathetic branch of the autonomic nervous system. This innervation (via the splanchnic nerve) influences the release

2. The combined dexamethasone/CRH test is used to test the activational effectiveness of this negative feedback loop in various conditions, such as in individuals with a personal history of early life trauma, current major depression, or a family history of depression (Holsboer, F., & Ising, M. (2010). Stress hormone regulation: Biological role and translation into therapy. Annual Review of Psychology, 61, 81–109. https://doi.org/10.1146/annurev.psych.093008.100321).

of hormones from both the adrenal medulla (catecholamines) and the adrenal cortex (corticosteroids) (Edwards & Jones, 1993; Ehrhart-Bornstem et al., 1995). In an elegant study of multisynaptic innervation of the adrenal medulla, Dum and colleagues described two broad networks originating in the monkey cerebral cortex, one involving a set of motor (e.g., supplementary motor area, cingulate motor areas) and somatosensory regions, and another located in the pregenual and subgenual cingulate cortex (Dum et al., 2016). Overall, it is likely that the above brain regions provide context-dependent modulation of the HPA axis that reflects the individual's history (e.g., learning and memory), evaluation of environmental cues regarding their controllability and predictability (see the above definition of "stress"), as well as the preparation of appropriate actions (Paus, 2001).

Hypothalamus–pituitary–gonadal axis

The HPG axis is the main regulator of the production of gonadal hormones, namely estrogens, progesterone, and androgens. As the name implies, these hormones are produced mainly by gonads (ovaries, testes) but some quantities of androgens are also synthesized in the adrenal cortex (zona reticularis). Neurons in the arcuate nucleus of the hypothalamus produce gonadotropin releasing hormone (GnRH) that, in turn, stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary. LH and FSH enter peripheral circulation and stimulate production of estradiol and progesterone in the ovaries, and testosterone in the testes (LH). Although all axons of the GnRH-positive neurons converge onto the median eminence (where they release GnRH into the hypophyseal portal vein (Miyata, 2017)), their cell bodies are found not only in the arcuate nucleus but also in other parts of the hypothalamus and the basal forebrain (septum and the diagonal band of Broca), especially in rodents (Campbell, 2007) (Sisk, personal communication). The rather scattered distribution of GnRH neurons in the rodent brain made it difficult to study their afferent inputs with classical anatomical approaches. This was overcome by the availability of tracers capable of visualizing cells, and their connections, expressing particular molecules, such as GnRH. Using this approach (infection of GnRH neurons by pseudorabies virus, and its retrograde trans-synaptic spread), Yoon and colleagues showed an extensive network of afferent inputs to the mouse GnRH neurons (Yoon et al., 2005). Besides the expected local hypothalamic connections, the strongest inputs appeared to come from the olfactory system: olfactory sensory neurons, the primary olfactory cortex and the amygdala (basolateral and posterolateral cortical amygdaloid nucleus) (Yoon et al., 2005). Additional multisynaptic inputs included several cortical regions (somatosensory and motor cortex), basal ganglia (caudate-putamen, globus pallidus, substantia nigra), the hippocampus (CA1, CA3, subiculum), and the brainstem (VGA and PAG) (Yoon et al., 2005). The above neural circuitry

demonstrates the richness of information reaching GnRH neurons, the key regulators of the HPG axis.

Interactions between the HPA and HPG axes

As shown in experimental studies carried out with rodents, stress modulates the HPG axis. In rodents, restraint stress inhibits the release of gonadotropins (Blake, 1975; Krulich et al., 1974; Rivier et al., 1986; Tilbrook et al., 1999; Yonetani et al., 1974) and delays ovulation (Yonetani et al., 1974). Exposure to intermittent electroshocks inhibits the release of LH and lowers LH plasma concentrations in (castrated) males (Rivier et al., 1986). Forced immobilization also lowers levels of LH and delays ovulation in females (Yonetani et al., 1974). Direct administration of "stress" hormones also influences the HPG axis. Thus, administration of exogenous CRH in the third or lateral ventricles of the brain of ovariectomized females inhibits the secretion of GnRH and LH (Ono et al., 1984; Rivier et al., 1986). Similarly, administration of ACTH in ovariectomized rats reduces LH serum concentrations (Ogle, 1977). Administration of dexamethasone, a synthetic glucocorticoid, inhibits release of LH and blocks ovulation in cycling females (Baldwin & Sawyer, 1974).

The HPA-HPG interactions are bidirectional, with an HPG activation also influencing the HPA axis. Thus, testosterone levels correlate negatively with an HPA response to restraint in both intact rodents and testosterone-replaced gonadectomized rodents (Viau & Meaney, 1996). Also, reflecting the inhibitory influence of testosterone on stress reactivity, gonadectomy of male rats results in elevated stress-induced secretion of ACTH and corticosterone; this effect appears to be reversible with testosterone treatment (Handa et al., 1994; Viau & Meaney, 1996). In addition to rodents, androgen treatment also inhibits reactivity of the HPA axis in monkeys and humans (Rubinow et al., 2005; Toufexis & Wilson, 2012). There seems to be a difference, however, between the effects of male and female sex hormones. Thus, infusion of estradiol into the PVN of the hypothalamus increases corticosterone responses to stress in rats (Liu et al., 2012; Lund et al., 2006) while ovariectomy reduces stress-induced ACTH and corticosterone secretion, an effect reversed by estradiol treatment (Burgess & Handa, 1992; Serova et al., 2010). Implants of a specific estrogen receptor antagonist also reduce levels of corticosterone following restraint stress (Isgor et al., 2003).

The relationship between the HPA and HPG axes has been more mixed in studies carried out in humans, in that coactivation, suppression, and independent effects have been observed (Buchanan et al., 1992; Romeo, 2010; Susman et al., 2017). Some studies suggest that the relationship between the HPA and HPG axes is dependent on the age, sex, pubertal stage, and stress exposure of the individual. Thus, Matchock and colleagues (Matchock et al., 2007) observed a negative relationship between cortisol and testosterone in adolescents at an advanced pubertal stage (Tanner stage 5) but not at earlier

pubertal stages (Tanner stages 2–4) [3]. Ruttle and colleagues (Ruttle et al., 2015) found that the relationship between cortisol and testosterone is positive in young adolescents aged 11 years, but it becomes negative in older adolescents from 13 through 15 years of age; these relationships may be moderated by early life stress, especially in girls (as described in the next paragraph).

Early life stress can influence the interactions between the HPA and HPG axes during development. Exposure to early life stress (especially parental depression and parental conflict and anger) leads to the early development of the "adult-like" negative relationship between cortisol and testosterone in female adolescents (Ruttle et al., 2015). At age 11, positive cortisol–testosterone correlations were found in both stress-exposed and nonexposed girls. In mid-puberty, the correlation switched into a negative one but this happened earlier in the stress-exposed (vs. nonexposed) girls (13 vs. 15 years of age) (Ruttle et al., 2015). Simmons and colleagues (Simmons et al., 2015) found that the direction of cortisol-testosterone relationship varied as a function of the level of "aggressive" parenting. These studies demonstrate the moderating influence of adversity on cortisol and testosterone covariation in adolescents.

After this brief introduction of the endocrine systems involved in puberty and stress, let us now review some of the findings relating these systems to the maturation of the adolescent brain.

White matter during adolescence

The human brain contains 176,000 km of axons (Marner & Pakkenberg, 2003), most of which are short (<3 mm) intracortical axons supporting cortico-cortical connectivity within the same cerebral hemisphere (Schüz, 2002). Axonal cytoskeleton is built of neurofilaments that provide structural support for microtubules, the latter serving as "roads" on which motor proteins shuttle their cargoes between the cell body and the synapse (Paus, 2010a; Paus et al., 2014). The majority of axons in the (adult) human brain are covered by a myelin sheath generated by oligodendrocytes. The myelin sheath facilitates the so-called saltatory conduction of electrical impulses from one node of Ranvier to another, thus speeding up the conduction of action potentials. Oligodendrocytes and neurons communicate with each other in a local manner whereby myelin-derived signals influence axonal cytoskeleton (Garcia et al., 2003) (Fig. 10.2).

3. In most studies, Tanner stages refer to the following five categories of pubertal status: (1) pre-pubertal, (2) beginning pubertal, (3) mid-pubertal, (4) advanced pubertal, (5) post-pubertal (e.g., the Puberty Development Scale; Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. Journal of Youth and Adolescence, 17(2), 117–133. https://doi.org/10.1007/BF01537962).

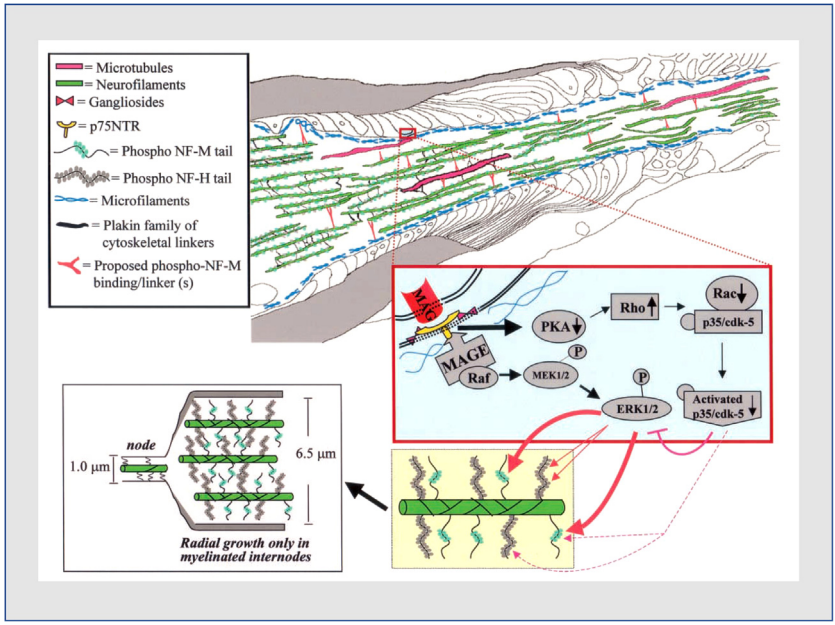

FIGURE 10.2 Model of myelin-dependent outside-in signaling cascade that controls radial axonal Growth In normal axons, axoplasmic organization is dependent upon myelinating cells. Signal cascades (blue Box) originating from MAG in the membrane of myelinating cells utilize the low affinity nerve growth factor receptor ($p75^{NTR}$) in combination with neuronal gangliosides to transduce the myelin-dependent signal into the axoplasm. Upon association of MAG with $p75^{NTR}$, members of the melanoma antigen (MAGE) gene family associate with an intracellular domain of $p75^{NTR}$, providing an intracellular scaffold for activation of ERK1/2 cascade, resulting in phosphorylation of NF-M (orange arrows) and NF−H (purple arrows) tail domains. MAG-dependent inactivation of p35/cdk-5 may reduce cdk-5 phosphorylation of NF-M and NF−H as well as prevent cdk-5−dependent inhibition of ERK1/2, allowing for near stoichiometric phosphorylation of NF−H and NF-M (yellow box). NF-M phosphorylation is required for establishing a volume-determining three-dimensional array (pink box) by a series of linkages that span between adjacent neurofilaments (green) and between neurofilaments and microtubules (pink) or cortical actin (blue) filaments. Neurofilaments, microtubules, and cortical actin are interlinked by plakin family members of cytoskeletal linkers (blue). Axonal volume is, in part, established by a new class of linking protein that associates with neurofilaments in an NF-M tail phosphorylation−dependent manner to assist in long-range interactions that are necessary for the more than fivefold increase in axonal volume associated with radial growth. *Reprinted from Garcia, M. L., Lobsiger, C. S., Shah, S. B., Deerinck, T. J., Crum, J., Young, D., Ward, C. M., Crawford, T. O., Gotow, T., Uchiyama, Y., Ellisman, M. H., Calcutt, N. A., & Cleveland, D. W. (2003). NF-M is an essential target for the myelin-directed "outside-in" signaling cascade that mediates radial axonal growth.* Journal of Cell Biology, 163*(5), 1011−1020. https://doi.org/10.1083/jcb.200308159. Reprinted with permission.*

Activation of the HPG axis at the beginning of puberty, and the related increase in circulating gonadal hormones, shapes structural properties of white matter. In one of our initial studies of the adolescent brain, we found that the volume of white matter increased steeply with age in males, a change driven in

part by age-related increases in plasma levels of testosterone (Perrin et al., 2008). The testosterone−white-matter relationship was stronger in male adolescents with a more efficient version of the androgen receptor gene. We proposed that this increase in white matter volume could be explained by the radial growth of axons (rather than myelination) (Perrin et al., 2008). We confirmed this hypothesis in subsequent experimental studies (Pesaresi et al., 2015). Thus, we demonstrated that castration of male rats shortly after weaning results in a much smaller axonal diameter in young adulthood, as compared with intact male rats (Pesaresi et al., 2015). In an in vitro study, we showed that adding synthetic testosterone to a culture of sympathetic neurons increases axon diameter and changes the rate of (anterograde) axonal transport in a time-dependent manner (Pesaresi et al., 2015). In an in vivo study (unpublished), we used manganese (Mn^{2+}) imaging to measure the rate of axonal transport in the olfactory system (Smith et al., 2007), and observed slightly lower rates of the transport in male mice castrated after weaning (Fig. 10.3).

In the latter study, we have not measured axon diameter in these mice and, therefore, can only speculate that the observed difference in the rate of axonal transport between the castrated and intact males is due to differences in the axon diameter (as observed in our previous study (Pesaresi et al., 2015)). Nonetheless, this possibility is supported by a study carried out in monkeys in which the rate of Mn^{2+} ions from the eye to the lateral geniculate nucleus was

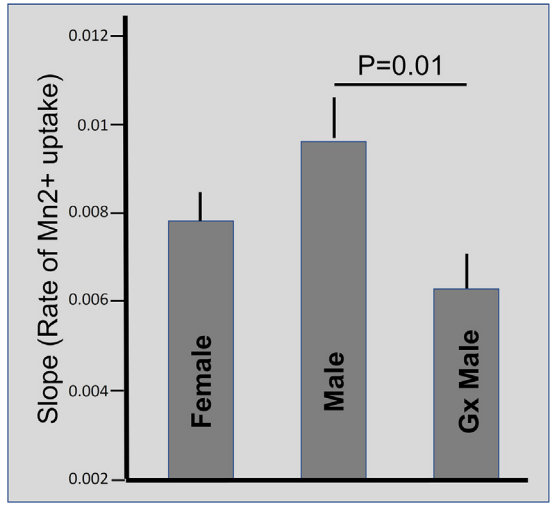

FIGURE 10.3 **Rate of manganese transport in Mice** Gonadectomized (Gx) male mice were castrated after weaning and scanned at 2 months of age. The bars show group means with the corresponding standard deviations of the rate of manganese transport from the olfactory epithelium (after nasal lavage) to the olfactory bulb (via olfactory sensory neurons). The number of mice was as follows: 15 females, 13 males, and 13 gonadectomized males. *Adapted from Pesaresi, M., Spring, S., Cahill, L., Sled, J., Pautler, R.G., and Paus, T. (unpublished observations, 2014).*

greater in the large-axon (magnocellular) versus small-axon (parvocellular) pathway (Murayama et al., 2006). It is also consistent with the fact that the number of microtubules is greater in axons with larger diameters (Chatzopoulou et al., 2008), thus providing a potentially greater axonal-transport capacity.

Stress-related activation of the HPA axis is also likely to shape structural properties of white matter. Using longitudinal data on stress exposure across multiple developmental periods, we showed that stress during adolescence is associated with variations in magnetization transfer ratio (MTR) in the genu of the human corpus callosum, as assessed in young adulthood (Fig. 10.4) (Jensen et al., 2018). Given the known interregional variations in the fiber composition of the corpus callosum (Aboitiz et al., 1992), and related spatial profiles of

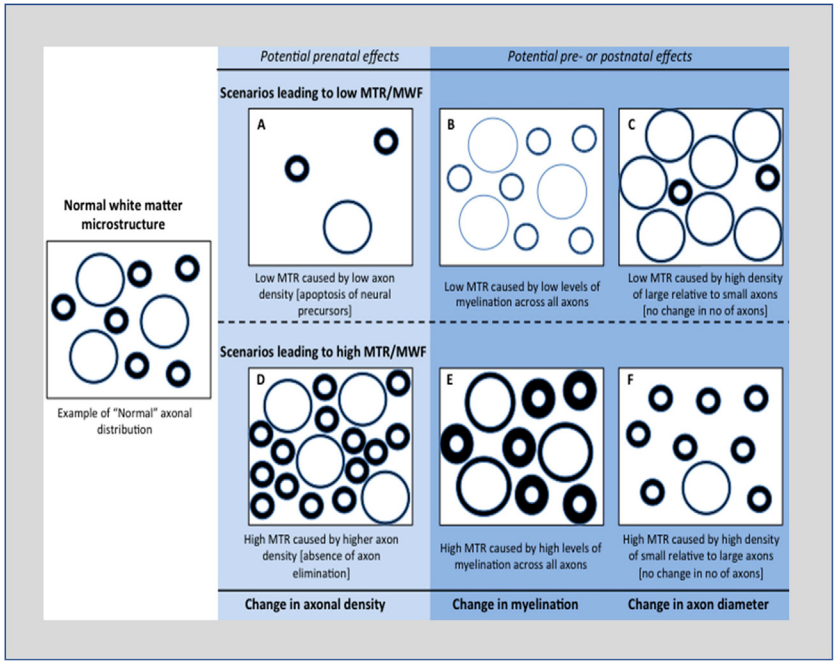

FIGURE 10.4 **Hypothesized microstructural changes driving variation in the magnetization transfer ratio (MTR) and myelin water fraction (MWF) signal** Illustration of suggested potential drivers of changes in white matter properties associated with prenatal, childhood, and adolescent stress. Scenarios on the light shaded background represent effects that may relate to prenatal or early postnatal experiences only, that is, variations in the number/density of axons. Scenarios on the darker shaded background represent effects that can be either pre- or postnatal, that is, variations in the thickness of the myelin sheath and variations in the radial size (diameter) of the axons. MTR, magnetization transfer ratio; MWF, myelin water fraction. *Reprinted from Jensen, S. K. G., Pangelinan, M., Björnholm, L., Klasnja, A., Leemans, A., Drakesmith, M., Evans, C. J., Barker, E. D., & Paus, T. (2018). Associations between prenatal, childhood, and adolescent stress and variations in white-matter properties in young men.* NeuroImage, 182*, 389–397. https://doi.org/10.1016/j.neuroimage.2017.10.033. Reprinted with permission.*

multiple magnetic resonance imaging (MRI) metrics (Björnholm et al., 2017), we speculated that this stress−structure relationship might be due to a shift from large-to small-diameter axons or due to differences in myelination.

A number of previous studies reported differences in various MRI metrics as a function of prenatal and postnatal stress (Lautarescu et al., 2020; Lim et al., 2020). But the complexity of both the "exposures" (timing and nature of stressful events, their assessments) and "outcomes" (different MRI-derived characteristics of white matter), together with relatively small sample sizes, make it difficult to gain insight into their underlying mechanisms and, most importantly, to draw any conclusions about causality and directionality of these relationships. When studying "effects" of stress on the brain, we should also keep in mind that there is a possibility of the opposite directionality, namely from brain variations to stress "sensitivity." The latter point was well illustrated by an observation that posttraumatic stress disorder is more likely to develop after an exposure to combat trauma in soldiers whose monozygotic cotwins, not exposed to combat, have a smaller hippocampus (Gilbertson et al., 2002). Keeping the limitations of observational studies in mind, the above examples illustrate the possibility that variations in the activity of the HPG and HPA axes, and their interactions (see above), may shape structural properties of white matter and, in turn, brain functioning.

As pointed out, white matter can be seen not only as a network of "electrical wires" but also as one of "roads and highways." The latter metaphor is meant to highlight the importance of axonal transport for both the maintenance of axonal cytoskeleton (the building blocks of neurofilaments and microtubules synthesized in the cell nucleus and transported anterogradely by motor proteins), and the transport of a multitude of organelles (e.g., mitochondria), vesicles, proteins, and other components essential for neurotransmission, metabolism, and trophic functions (Mandelkow & Mandelkow, 2002). As illustrated schematically in Fig. 10.5, during adolescence, axonal transport can

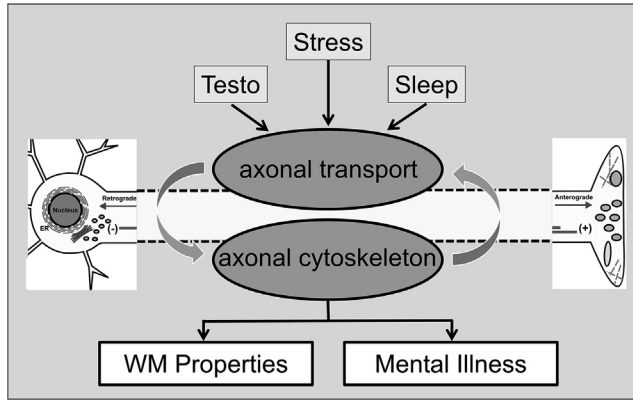

FIGURE 10.5 **Hypothetical pathway of instability leading to psychosis. WM, white matter.**

be influenced by a number of processes involving the HPG and HPA axes, with possible consequences on the risk of developing psychosis. Theoretically, both upregulation and downregulation of axonal transport may cause instability in neuronal networks, a mismatch between the expected (as experienced previously) and actual (as experienced presently) neuronal representation of an input (e.g., hearing one owns voice) and, in turn, emergence of psychotic symptoms (e.g., auditory hallucinations ["hearing voices"]).

As we reviewed above, variations in plasma levels of testosterone, over hours, days, or weeks, may be one such a source of instability in axonal transport. Similarly, stress-related release of cortisol and cytokines may influence cytoskeletal proteins and axonal transport and contribute to the overall instability of the transport system. Thus, chronic exposure to stress (in rats) increased phosphorylation of tau protein in neuronal culture (Zhang et al., 2012), affecting neurite morphology (Liu et al., 2006). These changes were accompanied by an increased axonal transport of mitochondria and reversed by a treatment with lithium (Zhang et al., 2012). In cultured neurons, TNFα reduced axonal transport of mitochondria by inducing phosphorylation of kinesin-1 by c-Jun N-terminal kinase, and dissociation of this motor protein from microtubules (Stagi et al., 2006). Another major driver of daily and weekly fluctuations in the adolescent physiology is sleep deprivation. Accumulation of sleep debt and its partial recovery during a weekend are typical of the adolescent period (Keyes et al., 2015; Matthews et al., 2014; Owens et al., 2014). Sleep deprivation has a multitude of effects on the brain and body, including variations in proinflammatory cytokines, such as TNFα, and various indices of cellular stress (Cirelli, 2006, 2013; Elliott et al., 2014; McEwen & Karatsoreos, 2015; Vgontzas et al., 2004). Axonal transport may be one of the downstream effects of these changes in extracellular and cellular environments. In cultured hippocampal neurons, hydrogen peroxide (a reactive oxygen species released by microglia) inhibited axonal transport of mitochondria and vesicles (Fang et al., 2012). As assessed in vivo with Mn^{2+} imaging, oxidative stress induced by hyperglycemia impaired axonal transport in mice, an effect associated with increased phosphorylation of tau protein (Sharma et al., 2010).

Altogether, the instability of hormonal and social environments typical of the adolescent period may lead to instabilities in the flow of cargoes along the 176,000-km long network of axons and, in turn, might increase the risk of developing psychosis by putting high demands on the maintenance of stable neuronal representations of the external world.

Cerebral cortex during adolescence

The majority of symptoms of mental illness, including hallucinations and delusions in psychosis, are rooted in disturbances of perceptual, cognitive and affective processes implemented by the cerebral cortex. The human cerebral

cortex is a highly folded sheath of tissue containing about 12 billion neurons and 17 billion nonneuronal cells (Azevedo et al., 2009). Using standard T1-weighted MR images, one can characterize individual differences in two macroscale metrics of the cerebral cortex: its surface area and its thickness. There are striking differences in the developmental timetable of the two features. While surface area undergoes dramatic growth prenatally and in the first few years of postnatal life (Gilmore et al., 2018), cortical thickness continues to change throughout the lifespan (Fjell et al., 2015). During adolescence, we see no age-related changes in surface area while there is a robust age-related decrease in cortical thickness, which is more pronounced in male (thickness by age: $r^2 = 0.28$) versus female ($r^2 = 0.10$) adolescents. In the text below, I will touch on the possible contributions of sex and stress hormones in shaping cortical thickness during adolescence and outline possible neurobiological underpinnings of these influences.

In our initial studies, we simply asked whether plasma levels of testosterone were related (in a cross-sectional manner) to cortical thickness in male adolescents. This was clearly the case, especially in males with a more efficient version of the androgen receptor gene (Paus et al., 2010). In subsequent studies, we took a different approach. Instead of examining the relationship between a particular hormone and cortical thickness across individuals, we asked whether we could explain regional differences in cortical thickness observed in a group of individuals through differences in the expression of certain genes across the same set of regions (French & Paus, 2015). Regional levels of gene expression are derived from the Allen Human Brain Atlas (Hawrylycz et al., 2012), and mapped into the Desikan-Killiany parcellation of the human cerebral cortex (French & Paus, 2015). Calculating such spatial correlations between gene expression and MRI-derived metrics allows us to test specific hypotheses about the implication of a particular molecular process in the observed MRI phenotype (e.g., using *CNR1* in a study of cannabis-related variations in cortical thickness (French et al., 2015)), and to gain insights into cellular underpinnings of the studied phenotype through "virtual histology" (Shin et al., 2018) (see section on Virtual Histology below for details).

In the first study using this approach, we observed strong spatial correlations between age-related thinning of the cerebral cortex in adolescents and the expression of both the androgen receptor gene (*AR*) and glucocorticoid receptor gene (*NR3C1*) (Wong et al., 2018). In both male and female adolescents, regions with high *AR* and *NR3C1* expression had showed stronger negative correlation between age and cortical thickness, that is, greater cortical "thinning." The interregional profiles of gene expression explained between 10% (*AR* expression in females) and 46% (*NR3C1* expression in males) of variance in the interregional profiles of cortical thinning (Wong et al., 2018). Furthermore, we showed that the relationship between the *NR3C1* expression was particularly strong in regions with low *AR* expression, and almost absent in regions with high AR expression (Fig. 10.6). This latter finding might be a

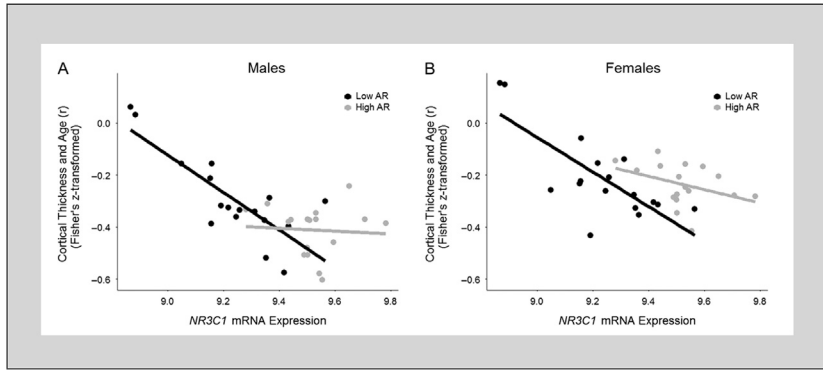

FIGURE 10.6 **Interaction of glucocorticoid receptor (NR3C1) and androgen receptor (AR) mRNA expression Levels** There was a significant *NR3C1* and *AR* interaction in males and in females. In both males and females, interregional age-related cortical thinning varied as a function of interregional *NR3C1* mRNA expression levels in the low *AR* mRNA expression group (in black), but not the high *AR* mRNA expression group (in gray). Note: Within each plot, each point represents one of the 34 cortical regions. *Reprinted from Wong, A. P. Y., French, L., Leonard, G., Perron, M., Pike, G. B., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2018). Inter-regional variations in gene expression and age-related cortical thinning in the adolescent brain.* Cerebral Cortex (New York, N.Y.: 1991), 28*(4), 1272−1281. https://doi.org/10.1093/cercor/bhx040. Reprinted with permission.*

manifestation, at the tissue level, of the kind of interactions between the HPG and HPA axes observed previously at the systems level (see above).

At this point, if we were conducting experimental studies, we would ask: which cells are being influenced by the (nuclear) action of the two receptors, mediating, in turn, age-related decreases in cortical thickness during adolescence? To answer, albeit indirectly, this question, we now turn to virtual histology.

Virtual histology

In virtual histology, we start by estimating the mean values of gene expression, reported in the Allen Human Brain Atlas (Hawrylycz et al., 2012), for each of 34 cortical regions segmented by FreeSurfer per hemisphere (French & Paus, 2015). Given the limited number of donor brains, we use only a subset of genes ($n = 2511$) identified as having "consistent" interregional profiles of their expression. This is done using a two-stage procedure based on: (1) similarity of individual profiles across donors included in the Allen Human Brain Atlas; and (2) similarity of average profiles derived from two independent atlases of gene expression in the human cerebral cortex (i.e., the Allen Human Brain Atlas [6 donors] and the BrainSpan Atlas (Miller et al., 2014) [11 donors of relevant age]). Note that *AR* and *NR3C1* discussed above are among these 2511 consistent genes. The next step involves selecting markers

of the main types of neuronal and glial cells found in the cerebral cortex, namely pyramidal neurons, interneurons, astrocytes, microglia, oligodendrocytes, ependymal, endothelial, and mural (pericytes and vascular smooth muscle cells) cells; these cell-specific marker-genes were identified by others using single-cell transcriptomes for 3005 cells extracted from the somatosensory cortex and hippocampus of mice (Zeisel et al., 2015). The intersection of the "consistent" genes with the "marker" genes yields the "virtual histology" panels: there are between 25 (mural cells) and 103 (CA1 pyramidal cells) genes in each panel (Shin et al., 2018). Finally, *across* the 34 FreeSurfer regions of the left hemisphere, we relate interregional profiles of the expression of these cell-specific marker genes to interregional profiles of MRI-derived metrics. Fig. 10.7 illustrates this approach by showing interregional variations in cortical thickness (left) and expression of *FARP1*, one of 54 markers of astrocytes (middle), and their correlation across the 34 cortical regions (right).

Let us now come back to our questions. First, which cells explain inter-individual variations in cortical thickness and/or cortical thinning? Using MRI data from the Saguenay Youth Study (Pausova et al., 2016), we determined that the interregional profile of cortical thinning during adolescence is related, in both sexes, to the expression profiles of 4 cell types, namely astrocytes, microglia and two types of pyramidal neurons. The 4 cell types explained about 72% (males) and 36% (females) of variance in interregional differences in cortical thinning (Shin et al., 2018). Regions with higher expressions of genes specific to astrocytes, microglia and CA1 pyramidal cells showed less

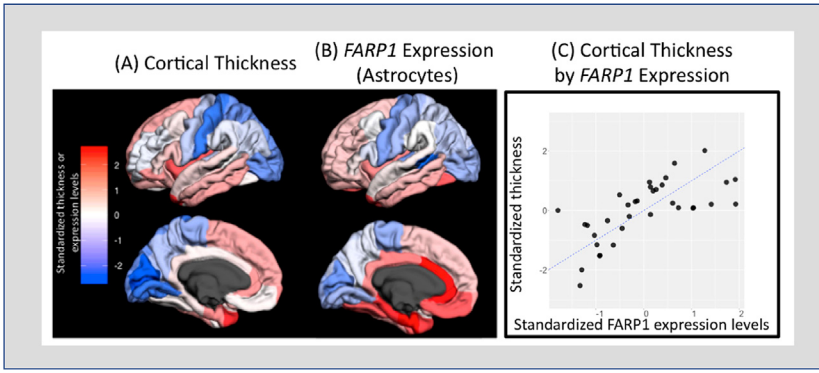

FIGURE 10.7 **Virtual Histology** (A) distribution of the standardized average cortical thickness measurements across the 34 cortical regions obtained from 981 SYS adolescents; (B) distribution of the standardized median gene-expression level for *FARP1* (obtained from the allen human brain atlas; (C) cortical thickness in the 34 cortical regions plotted as a function of *FARP1* expression in the same regions. The ranges of the standardized thickness values and expression levels are indicated by the color-scale bar on the left. *Peprinted from Paus, T. (2018). Imaging microstructure in the living human brain: A viewpoint.* NeuroImage, 182, 3–7. *https://doi.org/10.1016/j.neuroimage.2017.10.013. Reprinted with permission.*

cortical thinning (the opposite is true about S1 pyramidal cells). We have replicated these findings in another sample (Vidal-Pineiro et al., 2020). It is of interest to note that variations in cortical thinning during aging show the opposite pattern: regions with high expression of the same cell-specific gene markers show more thinning after ~65 years of age (Vidal-Pineiro et al., 2020). Similarly to the pattern found during aging, group differences in cortical thickness between patients with six different psychiatric disorders, namely attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder and schizophrenia, were also greater in these regions (Patel et al., 2021). We interpret these observations as telling us that while the neurobiological underpinnings of cortical thickness are the same across different conditions (i.e., variations in the number of astrocytes, microglia, and pyramidal cells), molecular pathways that target these cells are different during brain maturation, aging, and psychopathology.

Coming back to the above observations of the strong relations between interregional profiles of cortical thinning and those of *AR* and *NR3C1* expression, we ask the second question: which cell types might be targeted by the activation of the two receptors? Our tentative answer is based on the coexpression analysis of the two genes (*AR*, *NR3C1*) with cell-specific marker genes used in virtual histology. This analysis shows that both genes are coexpressed (negatively) with genes specific to astrocytes, microglia, and CA1 pyramidal cells (Parker et al., 2020 for *NR3C1*; unpublished observation for *AR*). Thus, it appears that both sex (*AR*) and stress (*NR3C1*) pathways may influence cortical thinning by acting on both neuronal (pyramidal cells) and glial (astrocytes, microglia) cell populations. Cortical regions with high expression of the 3 cell types appear to have low expression of *AR* and *NR3C1*, and show less cortical thinning during adolescence. At the same time, these regions appear to be more vulnerable to aging (Vidal-Pineiro et al., 2020), and show larger differences between healthy individuals and those with schizophrenia and other psychiatric disorders (Patel et al., 2021). It is possible that this somewhat counterintuitive finding (more "pathological" thinning in regions with low *NR3C1* expression) might be related to an absence of the protective effects of testosterone vis-à-vis stress (see the Section on HPA-HPG interactions earlier in the Chapter) in these regions.

Let us conclude the section on cortical gray-matter by asking whether an overall exposure to testosterone during puberty, and its timing, leave a long-term structural trace in the (male) cerebral cortex. To answer this question, we characterized structural properties of the human cerebral cortex using a number of metrics assayed with multi-modal MRI in a community-based sample of young males (19 years of age), and related these to testosterone levels sampled repeatedly at 9, 11, 13, 15, and 17 years of age in these individuals, members of a birth cohort (Liao, Patel, et al., 2021). We found that early, but less so late, surges of testosterone during puberty showed a strong

correlation with multiple MRI-derived measures of structural properties, especially with T1 relaxation time (Liao, Patel, et al., 2021). Based on the virtual-histology results, we interpreted these findings as indicating possible effects of testosterone on the radial growth of intracortical axons, a similar mechanism described above in the case of white matter. If correct, this interpretation implies that males with relatively high exposure to testosterone early in puberty might be at risk of experiencing fluctuations in axonal transport during this developmental period and, in turn, ensuing instability in their neuronal representations of the outside world (see Fig. 10.5).

Brain response to faces: organizational and activational effects of testosterone

Human faces are extremely rich sources of information about people, their identities, intentions, and emotions. Given the importance of faces in social communication, it is not surprising that face processing plays an important role during adolescence (Scherf et al., 2012). Neuronal networks supporting different aspects of face processing in the human brain are well-known. Fig. 10.8 shows a probabilistic map of the brain's response to faces (video

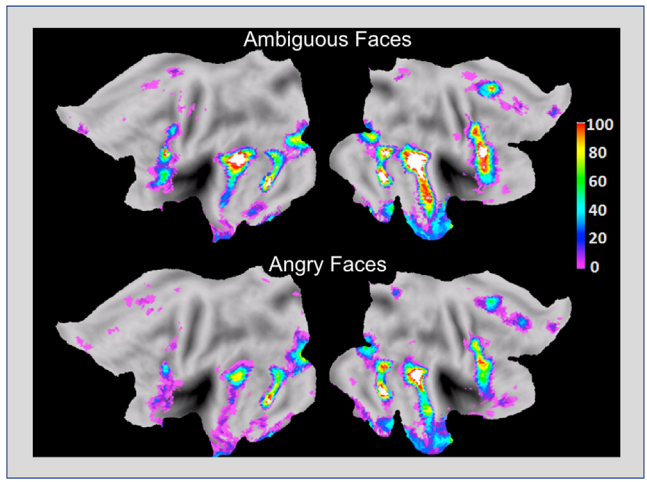

FIGURE 10.8 Probability maps of the ambiguous (a) and angry (b) contrasts between the face and control stimuli displayed of the flatten cerebral ccortex Left and right hemispheres are displayed on the left and right, respectively. *Reprinted from Tahmasebi, A. M., Artiges, E., Banaschewski, T., Barker, G. J., Bruehl, R., Büchel, C., Conrod, P. J., Flor, H., Garavan, H., Gallinat, J., Heinz, A., Ittermann, B., Loth, E., Mareckova, K., Martinot, J. L., Poline, J. B., Rietschel, M., Smolka, M. N., Ströhle, A., … Paus, T. (2012). Creating probabilistic maps of the face network in the adolescent brain: A multicentre functional MRI study.* Human Brain Mapping, *33(4), 938–957. https://doi.org/10.1002/hbm.21261. Reprinted with permission.*

clips showing dynamic faces with ambiguous angry expressions) obtained in over 1000 typically developing adolescents (Tahmasebi et al., 2012). Brain regions with a high probability (>50%) of responding to faces in this sample included members of both the "core" (e.g., fusiform face area, regions along the superior temporal sulcus) and "extended" (e.g., amygdala, prefrontal cortex) systems (Haxby et al., 2000).

We have explored the possibility that testosterone exerts organization effects during puberty, as suggested by previous experimental studies (Schulz et al., 2009), and therefore, might modulate the activational effects of testosterone in adulthood. This claim is based on the known, albeit subtle, sex differences in face processing (Thompson & Voyer, 2014), as well as theories of the possible role of the organizational (prenatal) effects of testosterone on communication skills and/or disorders (Knickmeyer & Baron-Cohen, 2006). Using functional MRI, we measured brain response to faces in a group of young males for whom we assayed levels of testosterone during their puberty ("pubertal T"), and on the day of scanning ("current T″) (Liao, Tilley, et al., 2021). The activational effect of testosterone was present only in young males who experienced low exposure to testosterone during their puberty; this was true for both the brain response and "functional connectivity," as indexed by the node strength (Liao, Tilley, et al., 2021). Based on additional analyses and existing literature, we speculated that "pubertal testosterone modulates the relationship between current testosterone, brain response to social cues carried by the eyes, and the signaling of a potential threat" (page 2990) (Liao, Tilley, et al., 2021). Such interindividual differences in the sensitivity to social cues, especially those signaling threat, might be of particular importance when constructing representations of the social world around us and interpreting the intentions of others. It remains to be seen whether males with relatively low exposure to testosterone during puberty might be at a high risk of developing psychosis, as suggested by a few previous reports (Ramanathan et al., 2015; Van Rijn et al., 2011).

Conclusions and future directions

In this chapter, I have reviewed the current knowledge of ways in which "sex" and "stress" may shape the adolescent brain. I have focused on human studies carried out in typically developing adolescents, thus providing a framework for asking and answering questions specific to adolescents with psychotic disorders and its antecedents. When considering structural properties of the adolescent brain, I have pointed to *axonal transport* as a possible mechanistic pathway linking fluctuations in stress and sex hormones with variations in brain structure and function, and to *pyramidal cells, astrocytes, and microglia* as the cellular substrate of such hormonal influences on the cerebral cortex. For brain function, I have provided an example of testosterone's organizational effects on its activational effects vis-à-vis brain response to faces. Such

"priming" mechanisms may play an important role in social dynamics during adolescence, both in healthy individuals and those at risk of mental illness.

There are, of course, many different ways we should continue building foundational knowledge of the factors that shape the adolescent brain. First of all, most of the work described above is of observational nature. Thus, there is a pressing need to test for causality of the observed relationships using experimental manipulations in in vivo and in vitro models, or to take advantage of special populations exposed to relevant substances (e.g., users of anabolic-androgenic steroids (Bjørnebekk et al., 2017)). Using results of large-scale Genome Wide Association Studies, one can also start addressing the question of directionality of certain relationships using so-called Mendelian randomization (Davey Smith & Hemani, 2014). For example, using this approach, we showed that the relationship between plasma levels of testosterone and body mass index in adults is best explained by the effect of body mass index on testosterone and not vice versa (Liao et al. 2022).

Second, as mentioned above, the ubiquity of digital communications opens new opportunities for studying social behavior in an ethological manner, and on a large scale. This is made possible by integrating data from social media and/or mobile devices either at aggregate or individual levels (Paus, 2016). As an example, one can use activity in a mobile-phone network to study dyadic relationships. This was done by Palchykov and colleagues (Palchykov et al., 2012) who used data from 3.2 million subscribers (1.95 billion calls, 489 million text messages) to study sex differences in social relationships over the lifespan. Despite the rather limited nature of this dataset (age and sex of subscribers and their relative frequency of calling/messaging each other), Palchykov and colleagues were able to extract interesting patterns of dyadic relationships in the two sexes. For instance, they found that the preference for an opposite-sex "best friend" (likely a romantic partner) emerged earlier in females (~18 years of age) compared with males (~22 years of age), and peaked at different ages in the two sexes (females: 27 years; males: 32 years) (Palchykov et al., 2012). This study illustrates the power of using electronic "footprints" as objective markers of our social behavior. Whether used at an individual or aggregate (e.g., neighborhood) level, such "digital ethology" may provide new insights into social behavior of adolescents at risk of developing psychosis, as well as social factors (e.g., psychosocial stress, social buffering) in their neighborhood that may moderate such a risk.

Third, it may be helpful to extend the binary concept of sex (female/male) to a continuum, possibly treated as a poly-phenotypic trait. We have done so recently and showed that the degree of "femaleness/maleness" within each sex predicts certain psychological traits in the same manner (Vosberg et al., 2021). This approach may provide new insights into interindividual variations in resilience or vulnerability to sex-biased psychiatric disorders, including psychosis, within each sex.

References

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Fiber composition of the human corpus callosum. *Brain Research,* 598(1−2), 143−153. https://doi.org/10.1016/0006-8993(92)90178-C

Azevedo, F. A. C., Carvalho, L. R. B., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., Filho, W. J., Lent, R., & Herculano-Houzel, S. (2009). Equal numbers of neuronal and non-neuronal cells make the human brain an isometrically scaled-up primate brain. *The Journal of Comparative Neurology,* 513(5), 532−541. https://doi.org/10.1002/cne.21974

Baldwin, D. M., & Sawyer, C. H. (1974). Effects of dexamethasone on LH release and ovulation in the cyclic rat. *Endocrinology,* 94(5), 1397−1403. https://doi.org/10.1210/endo-94-5-1397

Beards, S., Gayer-Anderson, C., Borges, S., Dewey, M. E., Fisher, H. L., & Morgan, C. (2013). Life events and psychosis: A review and meta-analysis. *Schizophrenia Bulletin,* 39(4), 740−747. https://doi.org/10.1093/schbul/sbt065

Bjørnebekk, A., Walhovd, K. B., Jørstad, M. L., Due-Tønnessen, P., Hullstein, I. R., & Fjell, A. M. (2017). Structural brain imaging of long-term anabolic-androgenic steroid users and nonusing weightlifters. *Biological Psychiatry,* 82(4), 294−302. https://doi.org/10.1016/j.biopsych.2016.06.017

Björnholm, L., Nikkinen, J., Kiviniemi, V., Nordström, T., Niemelä, S., Drakesmith, M., Evans, J. C., Pike, G. B., Veijola, J., & Paus, T. (2017). Structural properties of the human corpus callosum: Multimodal assessment and sex differences. *NeuroImage,* 152, 108−118. https://doi.org/10.1016/j.neuroimage.2017.02.056

Blake, C. A. (1975). Effects of "stress" on pulsatile luteinizing hormone release in ovariectomized rats. *Proceedings of the Society for Experimental Biology and Medicine,* 148(3), 813−815. https://doi.org/10.3181/00379727-148-38638

Brown, B. B., & Larson, J. (2009). In R. M. Lerner, & L. Steinberg (Eds.), *Peer relationships in adolescence* (pp. 74−103). John Wiley & Sons.

Buchanan, C. M., Eccles, J. S., & Becker, J. B. (1992). Are adolescents the victims of raging hormones? Evidence for activational effects of hormones on moods and behavior at adolescence. *Psychological Bulletin,* 111(1), 62−107. https://doi.org/10.1037/0033-2909.111.1.62

Burgess, L. H., & Handa, R. J. (1992). Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. *Endocrinology,* 131(3), 1261−1269. https://doi.org/10.1210/endo.131.3.1324155

Cairns, R. B., Leung, M., Buchanan, L., & Cairns, B. D. (1995). Friendships and social networks in childhood and adolescence: Fluidity, reliability, and interrelations. *Child Development,* 66(5), 1330−1345. https://doi.org/10.1111/j.1467-8624.1995.tb00938.x

Campbell, R. E. (2007). Defining the gonadotrophin-releasing hormone neuronal network: Transgenic approaches to understanding neurocircuitry. *Journal of Neuroendocrinology,* 19(7), 561−573. https://doi.org/10.1111/j.1365-2826.2007.01561.x

Carver, K., Joyner, K., & Udry, J. R. (2003). National estimates of adolescent romantic relationships. In *Adolescent romantic relations and sexual behavior: Theory, research, and practical implications* (pp. 23−56). Lawrence Erlbaum Associates. https://doi.org/10.4324/9781410607782

Chatzopoulou, E., Miguez, A., Savvaki, M., Levasseur, G., Muzerelle, A., Muriel, M. P., Goureau, O., Watanabe, K., Goutebroze, L., Gaspar, P., Zalc, B., Karagogeos, D., & Thomas, J. L. (2008). Structural requirement of TAG-1 for retinal ganglion cell axons and myelin in the mouse optic nerve. *Journal of Neuroscience,* 28(30), 7624−7636. https://doi.org/10.1523/JNEUROSCI.1103-08.2008

Cirelli, C. (2006). Cellular consequences of sleep deprivation in the brain. *Sleep Medicine Reviews,* 10(5), 307−321. https://doi.org/10.1016/j.smrv.2006.04.001

Cirelli, C. (2013). Sleep and synaptic changes. *Current Opinion in Neurobiology,* 23(5), 841−846. https://doi.org/10.1016/j.conb.2013.04.001

Collins, W. A., Welsh, D. P., & Furman, W. (2009). Adolescent romantic relationships. *Annual Review of Psychology,* 60, 631−652. https://doi.org/10.1146/annurev.psych.60.110707.163459

Dahl, R. E., & Gunnar, M. R. (2009). Heightened stress responsiveness and emotional reactivity during pubertal maturation: Implications for psychopathology. *Development and Psychopathology,* 21(1), 1−6. https://doi.org/10.1017/S0954579409000017

Davey Smith, G., & Hemani, G. (2014). Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics,* 23(R1), R89−R98. https://doi.org/10.1093/hmg/ddu328

Dum, R. P., Levinthal, D. J., & Strick, P. L. (2016). Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. *Proceedings of the National Academy of Sciences of the United States of America,* 113(35), 9922−9927. https://doi.org/10.1073/pnas.1605044113

Edwards, A. V., & Jones, C. T. (1993). Autonomic control of adrenal function. In , *Vol 183*. *Journal of anatomy* (pp. 291−307).

Ehrhart-Bornstem, M., Bornstein, S. R., González-Hernández, J., Holst, J. J., Waterman, M. R., & Scherbaum, W. A. (1995). Sympathoadrenal regulation of adrenocortical steroidogenesis. *Endocrine Research,* 21(1−2), 13−24. https://doi.org/10.3109/07435809509030417

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain. *Neuroscience,* 249, 162−171. https://doi.org/10.1016/j.neuroscience.2012.10.048

Elliott, A. S., Huber, J. D., O'Callaghan, J. P., Rosen, C. L., & Miller, D. B. (2014). A review of sleep deprivation studies evaluating the brain transcriptome. *SpringerPlus,* 3(1). https://doi.org/10.1186/2193-1801-3-728

Fang, C., Bourdette, D., & Banker, G. (2012). Oxidative stress inhibits axonal transport: Implications for neurodegenerative diseases. *Molecular Neurodegeneration,* 7(1). https://doi.org/10.1186/1750-1326-7-29

Fjell, A. M., Grydeland, H., Krogsrud, S. K., Amlien, I., Rohani, D. A., Ferschmann, L., Storsve, A. B., Tamnes, C. K., Sala-Llonch, R., Due-Tønnessen, P., Bjørnerud, A., Sølsnes, A. E., Håberg, A. K., Skranes, J., Bartsch, H., Chen, C.-H., Thompson, W. K., Panizzon, M. S., Kremen, W. S., … Walhovd, K. B. (2015). Development and aging of cortical thickness correspond to genetic organization patterns. *Proceedings of the National Academy of Sciences,* 112(50), 15462−15467. https://doi.org/10.1073/pnas.1508831112

French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., Séguin, J. R., Veillette, S., Evans, C. J., Artiges, E., Banaschewski, T., Bokde, A. W. L., Bromberg, U., Bruehl, R., Buchel, C., Cattrell, A., Conrod, P. J., Flor, H., Frouin, V., … Paus, T. (2015). Early cannabis use, polygenic risk score for schizophrenia, and brain maturation in adolescence. *JAMA Psychiatry,* 72(10), 1002−1011. https://doi.org/10.1001/jamapsychiatry.2015.1131

French, L., & Paus, T. (2015). A FreeSurfer view of the cortical transcriptome generated from the allen human brain atlas. *Frontiers in Neuroscience*, *9*. https://doi.org/10.3389/fnins.2015.00323

Garcia, M. L., Lobsiger, C. S., Shah, S. B., Deerinck, T. J., Crum, J., Young, D., Ward, C. M., Crawford, T. O., Gotow, T., Uchiyama, Y., Ellisman, M. H., Calcutt, N. A., & Cleveland, D. W. (2003). NF-M is an essential target for the myelin-directed "outside-in" signaling cascade that mediates radial axonal growth. *Journal of Cell Biology,* 163(5), 1011−1020. https://doi.org/10.1083/jcb.200308159

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience,* 5(11), 1242−1247. https://doi.org/10.1038/nn958

Gilmore, J. H., Knickmeyer, R. C., & Gao, W. (2018). Imaging structural and functional brain development in early childhood. *Nature Reviews Neuroscience,* 19(3), 123−137. https://doi.org/10.1038/nrn.2018.1

Girshkin, L., Matheson, S. L., Shepherd, A. M., & Green, M. J. (2014). Morning cortisol levels in schizophrenia and bipolar disorder: A meta-analysis. *Psychoneuroendocrinology,* 49(1), 187−206. https://doi.org/10.1016/j.psyneuen.2014.07.013

Grant, K. E., Compas, B. E., Stuhlmacher, A. F., Thurm, A. E., McMahon, S. D., & Halpert, J. A. (2003). Stressors and child and adolescent psychopathology: Moving from markers to mechanisms of risk. *Psychological Bulletin,* 129(3), 447−466. https://doi.org/10.1037/0033-2909.129.3.447

Handa, R. J., Nunley, K. M., Lorens, S. A., Louie, J. P., McGivern, R. F., & Bollnow, M. R. (1994). Androgen regulation of adrenocorticotropin and corticosterone secretion in the male rat following novelty and foot shock stressors. *Physiology and Behavior,* 55(1), 117−124. https://doi.org/10.1016/0031-9384(94)90018-3

Hawrylycz, M. J., Lein, E. S., Guillozet-Bongaarts, A. L., Shen, E. H., Ng, L., Miller, J. A., Van De Lagemaat, L. N., Smith, K. A., Ebbert, A., Riley, Z. L., Abajian, C., Beckmann, C. F., Bernard, A., Bertagnolli, D., Boe, A. F., Cartagena, P. M., Mallar Chakravarty, M., Chapin, M., Chong, J., … Jones, A. R. (2012). An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature,* 489(7416), 391−399. https://doi.org/10.1038/nature11405

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences,* 4(6), 223−233. https://doi.org/10.1016/S1364-6613(00)01482-0

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Frontiers in Neuroendocrinology,* 24(3), 151−180. https://doi.org/10.1016/j.yfrne.2003.07.001

Isgor, C., Cecchi, M., Kabbaj, M., Akil, H., & Watson, S. J. (2003). Estrogen receptor β in the paraventricular nucleus of hypothalamus regulates the neuroendocrine response to stress and is regulated by corticosterone. *Neuroscience,* 121(4), 837−845. https://doi.org/10.1016/S0306-4522(03)00561-X

Jensen, S. K. G., Pangelinan, M., Björnholm, L., Klasnja, A., Leemans, A., Drakesmith, M., Evans, C. J., Barker, E. D., & Paus, T. (2018). Associations between prenatal, childhood, and adolescent stress and variations in white-matter properties in young men. *NeuroImage,* 182, 389−397. https://doi.org/10.1016/j.neuroimage.2017.10.033

Keyes, K. M., Maslowsky, J., Hamilton, A., & Schulenberg, J. (2015). The great sleep recession: Changes in sleep duration among US adolescents, 1991−2012. *Pediatrics,* 135(3), 460−468. https://doi.org/10.1542/peds.2014-2707

Knickmeyer, R. C., & Baron-Cohen, S. (2006). Fetal testosterone and sex differences in typical social development and in autism. *Journal of Child Neurology,* 21(10), 825−845. https://doi.org/10.1177/08830738060210101601

Kohn, J. N., Snyder-Mackler, N., Barreiro, L. B., Johnson, Z. P., Tung, J., & Wilson, M. E. (2016). Dominance rank causally affects personality and glucocorticoid regulation in female rhesus macaques. *Psychoneuroendocrinology,* 74, 179−188. https://doi.org/10.1016/j.psyneuen.2016.09.005

Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wöhr, M., & Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. *Neuroscience and Biobehavioral Reviews,* 35(5), 1291−1301. https://doi.org/10.1016/j.neubiorev.2011.02.003

Krulich, L., Hefco, E., Illner, P., & Read, C. B. (1974). The effects of acute stress on the secretion of LH, FSH, prolactin and GH in the normal male rat, with comments on their statistical evaluation. *Neuroendocrinology,* 16(5−6), 293−311. https://doi.org/10.1159/000122576

Laursen, B., & Williams, V. A. (1997). Perceptions of interdependence and closeness in family and peer relationships among adolescents with and without romantic partners. *New Directions for Child Development,* 78, 3−20. https://doi.org/10.1002/cd.23219977803

Lautarescu, A., Craig, M. C., & Glover, V. (2020). Prenatal stress: Effects on fetal and child brain development. In , *Vol 150. International review of neurobiology* (pp. 17−40). Academic Press Inc. https://doi.org/10.1016/bs.irn.2019.11.002

Leliavski, A., Dumbell, R., Ott, V., & Oster, H. (2015). Adrenal clocks and the role of adrenal hormones in the regulation of circadian physiology. *Journal of Biological Rhythms,* 30(1), 20−34. https://doi.org/10.1177/0748730414553971

Liao, Z., Patel, Y., Khairullah, A., Parker, N., & Paus, T. (2021). Pubertal testosterone and the structure of the cerebral cortex in young men. *Cerebral Cortex,* 31(6), 2812−2821. https://doi.org/10.1093/cercor/bhaa389

Liao, Z., Tilley, S., Mouraviev, A., Khairullah, A., & Paus, T. (2021). Pubertal testosterone and brain response to faces in young adulthood: An interplay between organizational and activational effects in young men. *Journal of Neuroscience,* 41(13), 2990−2999. https://doi.org/10.1523/JNEUROSCI.0190-20.2021

Liebal, K., Waller, B., Slocombe, K., & Burrows, A. M. (2014). *Primate communication: A multimodal approach*. Cambridge University Press.

Liao, Z., Vosberg, D. E., Pausova, Z., & Paus, T. (2022). A shifting relationship between sex hormone-binding globulin and total testosterone across puberty in boys. *The Journal of Clinical Endocrinology and Metabolism*, dgac484. https://doi.org/10.1210/clinem/dgac484. PMID: 35965384.

Lightman, S. L., & Conway-Campbell, B. L. (2010). The crucial role of pulsatile activity of the HPA axis for continuous dynamic equilibration. *Nature Reviews Neuroscience,* 11(10), 710−718. https://doi.org/10.1038/nrn2914

Lim, L., Howells, H., Radua, J., & Rubia, K. (2020). Aberrant structural connectivity in childhood maltreatment: A meta-analysis. *Neuroscience and Biobehavioral Reviews,* 116, 406−414. https://doi.org/10.1016/j.neubiorev.2020.07.004

Liu, J., Bisschop, P. H., Eggels, L., Foppen, E., Fliers, E., Zhou, J. N., & Kalsbeek, A. (2012). Intrahypothalamic estradiol modulates hypothalamus-pituitary-adrenal-axis activity in female rats. *Endocrinology,* 153(7), 3337−3344. https://doi.org/10.1210/en.2011-2176

Liu, H. H., Payne, H. R., Wang, B., & Brady, S. T. (2006). Gender differences in response of hippocampus to chronic glucocorticoid stress: Role of glutamate receptors. *Journal of Neuroscience Research,* 83(5), 775−786. https://doi.org/10.1002/jnr.20782

Ljungberg, T., Westlund, K., & Lindqvist Forsberg, A. J. (1999). Conflict resolution in 5-year-old boys: Does postconflict affiliative behaviour have a reconciliatory role? *Animal Behaviour,* 58(5), 1007−1016. https://doi.org/10.1006/anbe.1999.1236

Lund, T. D., Hinds, L. R., & Handa, R. J. (2006). The androgen 5α-dihydrotestosterone and its metabolite 5α-androstan-3β,17β-diol inhibit the hypothalamo-pituitary- adrenal response to stress by acting through estrogen receptor β-expressing neurons in the hypothalamus. *Journal of Neuroscience,* 26(5), 1448−1456. https://doi.org/10.1523/JNEUROSCI.3777-05.2006

Mandelkow, E., & Mandelkow, E. M. (2002). Kinesin motors and disease. *Trends in Cell Biology,* 12(12), 585–591. https://doi.org/10.1016/S0962-8924(02)02400-5

Marner, L., & Pakkenberg, B. (2003). Total length of nerve fibers in prefrontal and global white matter of chronic schizophrenics. *Journal of Psychiatric Research,* 37(6), 539–547. https://doi.org/10.1016/S0022-3956(03)00069-4

Matchock, R. L., Dorn, L. D., & Susman, E. J. (2007). Diurnal and seasonal cortisol, testosterone, and DHEA rhythms in boys and girls during puberty. *Chronobiology International,* 24(5), 969–990. https://doi.org/10.1080/07420520701649471

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J. (2013). Childhood adversity in schizophrenia: A systematic meta-analysis. *Psychological Medicine,* 43(2), 225–238. https://doi.org/10.1017/S0033291712000785

Matthews, K. A., Hall, M., & Dahl, R. E. (2014). Sleep in healthy black and white adolescents. *Pediatrics,* 133(5), e1189–e1196. https://doi.org/10.1542/peds.2013-2399

McCormick, C. M., Hodges, T. E., & Simone, J. J. (2015). Peer pressures: Social instability stress in adolescence and social deficits in adulthood in a rodent model. *Developmental Cognitive Neuroscience,* 11, 2–11. https://doi.org/10.1016/j.dcn.2014.04.002

McCormick, C. M., Mathews, I. Z., Thomas, C., & Waters, P. (2010). Investigations of HPA function and the enduring consequences of stressors in adolescence in animal models. *Brain and Cognition,* 72(1), 73–85. https://doi.org/10.1016/j.bandc.2009.06.003

McEwen, B. S., & Karatsoreos, I. N. (2015). Sleep deprivation and circadian disruption: Stress, allostasis, and allostatic load. *Sleep Medicine Clinics,* 10(1), 1–10. https://doi.org/10.1016/j.jsmc.2014.11.007

Meier, A., & Allen, G. (2009). Romantic relationships from adolescence to young adulthood: Evidence from the national longitudinal study of adolescent health. *Sociological Quarterly,* 50(2), 308–335. https://doi.org/10.1111/j.1533-8525.2009.01142.x

Melmed, S., Polonsky, K., Larsen, P., & Kronenberg, H. M. (2015). *Williams textbook of endocrinology* (13th ed.). Elsevier Health Sciences.

Miller, J. A., Ding, S. L., Sunkin, S. M., Smith, K. A., Ng, L., Szafer, A., Ebbert, A., Riley, Z. L., Royall, J. J., Aiona, K., Arnold, J. M., Bennet, C., Bertagnolli, D., Brouner, K., Butler, S., Caldejon, S., Carey, A., Cuhaciyan, C., Dalley, R. A., … Lein, E. S. (2014). Transcriptional landscape of the prenatal human brain. *Nature,* 508(7495), 199–206. https://doi.org/10.1038/nature13185

Miyata, S. (2017). Advances in understanding of structural reorganization in the hypothalamic neurosecretory system. *Frontiers in Endocrinology*, *8*. https://doi.org/10.3389/fendo.2017.00275

Murayama, Y., Weber, B., Saleem, K. S., Augath, M., & Logothetis, N. K. (2006). Tracing neural circuits in vivo with Mn-enhanced MRI. *Magnetic Resonance Imaging,* 24(4), 349–358. https://doi.org/10.1016/j.mri.2005.12.031

Ogle, T. F. (1977). Modification of serum luteinizing hormone and prolactin concentrations by corticotropin and adrenalectomy in ovariectomized rats. *Endocrinology,* 101(2), 494–497. https://doi.org/10.1210/endo-101-2-494

Ono, N., Lumpkin, M. D., Samson, W. K., McDonald, J. K., & McCann, S. M. (1984). Intrahypothalamic action of corticotrophin-releasing factor (CRF) to inhibit growth hormone and LH release in the rat. *Life Sciences,* 35(10), 1117–1123. https://doi.org/10.1016/0024-3205(84)90077-8

Onyango, P. O., Gesquiere, L. R., Altmann, J., & Alberts, S. C. (2013). Puberty and dispersal in a wild primate population. *Hormones and Behavior,* 64(2), 240–249. https://doi.org/10.1016/j.yhbeh.2013.02.014

Oudekerk, B. A., Allen, J. P., Hessel, E. T., & Molloy, L. E. (2015). The cascading development of autonomy and relatedness from adolescence to adulthood. *Child Development,* 86(2), 472−485. https://doi.org/10.1111/cdev.12313

Owens, J., Au, R., Carskadon, M., Millman, R., Wolfson, A., Braverman, P. K., Adelman, W. P., Breuner, C. C., Levine, D. A., Marcell, A. V., Murray, P. J., & O'Brien, R. F. (2014). Insufficient sleep in adolescents and young adults: An update on causes and consequences. *Pediatrics,* 134(3), e921−e932. https://doi.org/10.1542/peds.2014-1696

Palchykov, V., Kaski, K., Kertész, J., Barabási, A. L., & Dunbar, R. I. M. (2012). Sex differences in intimate relationships. *Scientific Reports*, 2. https://doi.org/10.1038/srep00370

Parker, N., Vidal-Pineiro, D., French, L., Shin, J., Adams, H. H. H., Brodaty, H., Cox, S. R., Deary, I. J., Fjell, A. M., Frenzel, S., Grabe, H., Hosten, N., Ikram, M. A., Jiang, J., Knol, M. J., Mazoyer, B., Mishra, A., Sachdev, P. S., Salum, G., … Paus, T. (2020). Corticosteroids and regional variations in thickness of the human cerebral cortex across the lifespan. *Cerebral Cortex,* 30(2), 575−586. https://doi.org/10.1093/cercor/bhz108

Patel, Y., Parker, N., Shin, J., Howard, D., French, L., Thomopoulos, S. I., Pozzi, E., Abe, Y., Abé, C., Anticevic, A., Alda, M., Aleman, A., Alloza, C., Alonso-Lana, S., Ameis, S. H., Anagnostou, E., McIntosh, A. A., Arango, C., Arnold, P. D., … Paus, T. (2021). Virtual histology of cortical thickness and shared neurobiology in 6 psychiatric disorders. *JAMA Psychiatry,* 78(1), 47−63. https://doi.org/10.1001/jamapsychiatry.2020.2694

Paus, T. (2001). Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience,* 2(6), 417−424. https://doi.org/10.1038/35077500

Paus, T. (2010a). Growth of white matter in the adolescent brain: Myelin or axon? *Brain and Cognition,* 72(1), 26−35. https://doi.org/10.1016/j.bandc.2009.06.002

Paus, T. (2010b). Population neuroscience: Why and how. *Human Brain Mapping,* 31(6), 891−903. https://doi.org/10.1002/hbm.21069

Paus, T. (2013). Population neuroscience. In *Population neuroscience* (pp. 1−184). Springer-Verlag Berlin Heidelberg. https://doi.org/10.1007/978-3-642-36450-1

Paus, T. (2016). Population neuroscience. In *, Vol 138. Handbook of clinical neurology* (pp. 17−37). Elsevier B.V. https://doi.org/10.1016/B978-0-12-802973-2.00002-1

Paus, T., Nawaz-Khan, I., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., Richer, L., Susman, E., Veillette, S., & Pausova, Z. (2010). Sexual dimorphism in the adolescent brain: Role of testosterone and androgen receptor in global and local volumes of grey and white matter. *Hormones and Behavior,* 57(1), 63−75. https://doi.org/10.1016/j.yhbeh.2009.08.004

Pausova, Z., Paus, T., Abrahamowicz, M., Bernard, M., Gaudet, D., Leonard, G., Peron, M., Pike, G. B., Richer, L., Séguin, J. R., & Veillette, S. (2016). Cohort profile: The Saguenay youth study (SYS). *International Journal of Epidemiology,* 46(2). https://doi.org/10.1093/ije/dyw023. dyw023.

Paus, T., Pesaresi, M., & French, L. (2014). White matter as a transport system. *Neuroscience,* 276, 117−125. https://doi.org/10.1016/j.neuroscience.2014.01.055

Perrin, J. S., Herve, P.-Y., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2008). Growth of white matter in the adolescent brain: Role of testosterone and androgen receptor. *Journal of Neuroscience,* 28(38), 9519−9524. https://doi.org/10.1523/jneurosci.1212-08.2008

Pesaresi, M., Soon-Shiong, R., French, L., Kaplan, D. R., Miller, F. D., & Paus, T. (2015). Axon diameter and axonal transport: In vivo and in vitro effects of androgens. *NeuroImage,* 115, 191−201. https://doi.org/10.1016/j.neuroimage.2015.04.048

Ramanathan, S., Miewald, J., Montrose, D., & Keshavan, M. S. (2015). Can age at sexual maturity act as a predictive biomarker for prodromal negative symptoms? *Schizophrenia Research,* 164(1−3), 35−39. https://doi.org/10.1016/j.schres.2015.02.019

Reagan, L. P., Grillo, C. A., & Piroli, G. G. (2008). The as and Ds of stress: Metabolic, morphological and behavioral consequences. *European Journal of Pharmacology,* 585(1), 64–75. https://doi.org/10.1016/j.ejphar.2008.02.050

Rivier, C., Rivier, J., & Vale, W. (1986). Stress-induced inhibition of reproductive functions: Role of endogenous corticotropin-releasing factor. *Science,* 231(4738), 607–609. https://doi.org/10.1126/science.3003907

Romeo, R. D. (2010). Pubertal maturation and programming of hypothalamic-pituitary-adrenal reactivity. *Frontiers in Neuroendocrinology,* 31(2), 232–240. https://doi.org/10.1016/j.yfrne.2010.02.004

Rubinow, D. R., Roca, C. A., Schmidt, P. J., Danaceau, M. A., Putnam, K., Cizza, G., Chrousos, G., & Nieman, L. (2005). Testosterone suppression of CRH-stimulated cortisol in men. *Neuropsychopharmacology,* 30(10), 1906–1912. https://doi.org/10.1038/sj.npp.1300742

Ruttle, P. L., Shirtcliff, E. A., Armstrong, J. M., Klein, M. H., & Essex, M. J. (2015). Neuroendocrine coupling across adolescence and the longitudinal influence of early life stress. *Developmental Psychobiology,* 57(6), 688–704. https://doi.org/10.1002/dev.21138

Scherf, K. S., Behrmann, M., & Dahl, R. E. (2012). Facing changes and changing faces in adolescence: A new model for investigating adolescent-specific interactions between pubertal, brain and behavioral development. *Developmental Cognitive Neuroscience,* 2(2), 199–219. https://doi.org/10.1016/j.dcn.2011.07.016

Schulz, K. M., Zehr, J. L., Salas-Ramirez, K. Y., & Sisk, C. L. (2009). Testosterone programs adult social behavior before and during, but not after, adolescence. *Endocrinology,* 150(8), 3690–3698. https://doi.org/10.1210/en.2008-1708

Schüz, A. (2002). *The human cortical white matter: Quantitative aspects of cortico-cortical long-range connectivity.* Taylor & Francis.

Selye, H. (1950). Stress and the general adaptation syndrome. *British Medical Journal,* 1(4667), 1383–1392. https://doi.org/10.1136/bmj.1.4667.1383

Serova, L. I., Harris, H. A., Maharjan, S., & Sabban, E. L. (2010). Modulation of responses to stress by estradiol benzoate and selective estrogen receptor agonists. *Journal of Endocrinology,* 205(3), 253–262. https://doi.org/10.1677/JOE-10-0029

Sharma, R., Buras, E., Terashima, T., Serrano, F., Massaad, C. A., Hu, L., Bitner, B., Inoue, T., Chan, L., Pautler, R. G., & Wang, Y. (2010). Hyperglycemia induces oxidative stress and impairs axonal transport rates in mice. *PLoS ONE,* 5(10), e13463. https://doi.org/10.1371/journal.pone.0013463

Shin, J., French, L., Xu, T., Leonard, G., Perron, M., Pike, G. B., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2018). Cell-specific gene-expression profiles and cortical thickness in the human brain. *Cerebral Cortex,* 28(9), 3267–3277. https://doi.org/10.1093/cercor/bhx197

Simmons, J. G., Byrne, M. L., Schwartz, O. S., Whittle, S. L., Sheeber, L., Kaess, M., Youssef, G. J., & Allen, N. B. (2015). Dual-axis hormonal covariation in adolescence and the moderating influence of prior trauma and aversive maternal parenting. *Developmental Psychobiology,* 57(6), 670–687. https://doi.org/10.1002/dev.21275

Smith, K. D. B., Kallhoff, V., Zheng, H., & Pautler, R. G. (2007). In vivo axonal transport rates decrease in a mouse model of Alzheimer's disease. *NeuroImage,* 35(4), 1401–1408. https://doi.org/10.1016/j.neuroimage.2007.01.046

Snyder-Mackler, N., Kohn, J. N., Barreiro, L. B., Johnson, Z. P., Wilson, M. E., & Tung, J. (2016). Social status drives social relationships in groups of unrelated female rhesus macaques. *Animal Behaviour,* 111, 307–317. https://doi.org/10.1016/j.anbehav.2015.10.033

Snyder-Mackler, N., Sanz, J., Kohn, J. N., Brinkworth, J. F., Morrow, S., Shaver, A. O., Grenier, J. C., Pique-Regi, R., Johnson, Z. P., Wilson, M. E., Barreiro, L. B., & Tung, J. (2016). Social status alters immune regulation and response to infection in macaques. *Science,* 354(6315), 1041–1045. https://doi.org/10.1126/science.aah3580

Stagi, M., Gorlovoy, P., Larionov, S., Takahashi, K., Neumann, H., Stagi, M., Gorlovoy, P., Larionov, S., Takahashi, K., & Neumann, H. (2006). Unloading kinesin transported cargoes from the tubulin track via the inflammatory c-Jun N-terminal kinase pathway. *The FASEB Journal,* 20(14), 2573−2575. https://doi.org/10.1096/fj.06-6679fje

Susman, E. J., Nottelmann, E. D., Dorn, L. D., Inoff-Germain, G., & Chrousos, G. P. (1988). Physiological and behavioral aspects of stress in adolescence. *Advances in Experimental Medicine and Biology,* 245, 341−352. https://doi.org/10.1007/978-1-4899-2064-5_27

Susman, E. J., Peckins, M. K., Bowes, J. L., & Dorn, L. D. (2017). Longitudinal synergies between cortisol reactivity and diurnal testosterone and antisocial behavior in young adolescents. *Development and Psychopathology,* 29(4), 1353−1369. https://doi.org/10.1017/S0954579416001334

Tahmasebi, A. M., Artiges, E., Banaschewski, T., Barker, G. J., Bruehl, R., Büchel, C., Conrod, P. J., Flor, H., Garavan, H., Gallinat, J., Heinz, A., Ittermann, B., Loth, E., Mareckova, K., Martinot, J. L., Poline, J. B., Rietschel, M., Smolka, M. N., Ströhle, A., … Paus, T. (2012). Creating probabilistic maps of the face network in the adolescent brain: A multicentre functional MRI study. *Human Brain Mapping,* 33(4), 938−957. https://doi.org/10.1002/hbm.21261

Thompson, A. E., & Voyer, D. (2014). Sex differences in the ability to recognise non-verbal displays of emotion: A meta-analysis. *Cognition and Emotion,* 28(7), 1164−1195. https://doi.org/10.1080/02699931.2013.875889

Tilbrook, A. J., Canny, B. J., Serapiglia, M. D., Ambrose, T. J., & Clarke I, J. (1999). Suppression of the secretion of luteinizing hormone due to isolation/restraint stress in gonadectomised rams and ewes is influenced by sex steroids. *Journal of Endocrinology,* 160(3), 469−481. https://doi.org/10.1677/joe.0.1600469

Toufexis, D. J., & Wilson, M. E. (2012). Dihydrotestosterone differentially modulates the cortisol response of the hypothalamic-pituitary-adrenal axis in male and female rhesus macaques, and restores circadian secretion of cortisol in females. *Brain Research,* 1429, 43−51. https://doi.org/10.1016/j.brainres.2011.10.024

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. In *, Vol 53. Journal of psychosomatic research* (pp. 865−871).

Turner, R. J., & Lloyd, D. A. (2004). Stress burden and the lifetime incidence of psychiatric disorder in young adults: Racial and ethnic Contrasts. *Archives of General Psychiatry,* 61(5), 481−488. https://doi.org/10.1001/archpsyc.61.5.481

Van Rijn, S., Aleman, A., De Sonneville, L., Sprong, M., Ziermans, T., Schothorst, P., Van Engeland, H., & Swaab, H. (2011). Neuroendocrine markers of high risk for psychosis: Salivary testosterone in adolescent boys with prodromal symptoms. *Psychological Medicine,* 41(9), 1815−1822. https://doi.org/10.1017/S0033291710002576

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., Van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin,* 38(4), 661−671. https://doi.org/10.1093/schbul/sbs050

Vgontzas, A. N., Zoumakis, E., Bixler, E. O., Lin, H. M., Follett, H., Kales, A., & Chrousos, G. P. (2004). Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *Journal of Clinical Endocrinology and Metabolism,* 89(5), 2119−2126. https://doi.org/10.1210/jc.2003-031562

Viau, V., & Meaney, M. J. (1996). The inhibitory effect of testosterone on hypothalamic-pituitary-adrenal responses to stress is mediated by the medial preoptic area. *Journal of Neuroscience,* 16(5), 1866−1876. https://doi.org/10.1523/jneurosci.16-05-01866.1996

Vidal-Pineiro, D., Parker, N., Shin, J., French, L., Grydeland, H., Jackowski, A. P., Mowinckel, A. M., Patel, Y., Pausova, Z., Salum, G., Sørensen, Ø., Walhovd, K. B., Paus, T., & Fjell, A. M. (2020). Cellular correlates of cortical thinning throughout the lifespan. *Scientific Reports,* 10(1). https://doi.org/10.1038/s41598-020-78471-3

Vosberg, D. E., Syme, C., Parker, N., Richer, L., Pausova, Z., & Paus, T. (2021). Sex continuum in the brain and body during adolescence and psychological traits. *Nature Human Behaviour,* 5(2), 265−272. https://doi.org/10.1038/s41562-020-00968-8

Wong, A. P. Y., French, L., Leonard, G., Perron, M., Pike, G. B., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2018). Inter-regional variations in gene expression and age-related cortical thinning in the adolescent brain. *Cerebral Cortex (New York, N.Y.: 1991),* 28(4), 1272−1281. https://doi.org/10.1093/cercor/bhx040

Yonetani, S., Jojima, M., & Suzuki, Y. (1974). Blockade of ovulation in rats by forced immobilization for surgical treatment. *Endocrinologia Japonica,* 21(1), 61−68. https://doi.org/10.1507/endocrj1954.21.61

Yoon, H., Enquist, L. W., & Dulac, C. (2005). Olfactory inputs to hypothalamic neurons controlling reproduction and fertility. *Cell,* 123(4), 669−682. https://doi.org/10.1016/j.cell.2005.08.039

Zeisel, A., Munoz-Manchado, A. B., Codeluppi, S., Lönnerberg, P., Manno, G. L., Juréus, A., Marques, S., Munguba, H., He, L., Betsholtz, C., Rolny, C., Castelo-Branco, G., Hjerling-Leffler, J., & Linnarsson, S. (2015). Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science,* 347(6226), 1138−1142. https://doi.org/10.1126/science.aaa1934

Zhang, L.-F., Shi, L., Liu, H., Meng, F.-T., Liu, Y.-J., Wu, H.-M., Du, X., & Zhou, J.-N. (2012). Increased hippocampal tau phosphorylation and axonal mitochondrial transport in a mouse model of chronic stress. *The International Journal of Neuropsychopharmacology,* 15(03), 337−348. https://doi.org/10.1017/s1461145711000411

Chapter 11

Current treatment options in early-onset psychosis

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Introduction

There is a rising awareness that childhood, and particularly the adolescence period, is an important window of opportunity for early mental health intervention (Birchwood et al., 2014). For adolescents with early-onset psychosis (EOP; psychotic disorders with onset before age 18 years), delayed detection is typical, with a mean duration of untreated psychosis of about 19 months compared to 5 months in adults (Correll et al., 2018; Kane et al., 2016; Stentebjerg-Olesen et al., 2016). The treatment targets for EOP are generally the same as for psychosis with adult onset, due to comparable patterns of clinical symptoms and functional deficits. Yet, there are specific issues to consider for the treatment of psychotic disorders in adolescents. They, with schizophrenia in particular, more often have an insidious onset with higher frequency of negative symptoms, thought disorders, disorganized behavior, and comorbid psychiatric disorders (Eggers, 1978; Remschmidt & Theisen, 2005; Stentebjerg-Olesen et al., 2016). Furthermore, in adolescents, antipsychotic treatment is often less efficient than in adults and associated with more adverse effects which increases the risk of persistence into adulthood with less favorable prognosis (Schimmelmann et al., 2013). The poor prognosis is characterized by significant personal and societal costs (Kahn et al., 2015), low quality of life (Salomon et al., 2012), low rate of recovery (Jääskeläinen et al., 2013), substance misuse (Wisdom et al., 2011), high rates of violence and legal problems (Fazel et al., 2009; Maniglio, 2009; Munkner et al., 2005), low educational and vocational attainment (Dalsgaard et al., 2020), and reduced life-expectancy (Colton & Manderscheid, 2006; Hjorthøj et al., 2017; Nielsen et al., 2013; Nordentoft et al., 2013). Moreover, psychosis at any age gives rise to a large physical, social, and financial burden on the individual and their families and may

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00002-0

pose a negative impact on the mental health of the caregivers and family members (Broussard et al., 2013; Chan, 2011; Cuijpers & Stam, 2000; Jin & Mosweu, 2017; Martens & Addington, 2001; McDaid et al., 2016). Thus, it is crucial to emphasize early detection and intervention with focus on the involvement of patients and families in decision-making to ensure treatment adherence and long-term treatment plans.

General treatment principles

Early intervention for patients with schizophrenia, including antipsychotic treatment, improves prognosis (Nordentoft et al., 2013). However, due to the limited number of treatment trials, state-of-the-art therapeutic interventions in youth with psychosis suffer from lack of evidence. There is some evidence concerning antipsychotic medications, but extremely scarce evidence for psychosocial interventions. Current guidelines for interventions in youth with psychosis generally build on extrapolations from research in adults. Principles for the treatment of children and adolescents with EOP are described in the 2013 American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters (McClellan & Stock, 2013), the 2013 National Institute for Health and Clinical Excellence (NICE) guidance (Kendall et al., 2013), and the 2017 Canadian Treatment Guidelines on Psychosocial Treatment of Schizophrenia in Children and Youth (Lecomte et al., 2017). These guidelines state that clinicians should work in partnership with the young patient and their caregivers, while taking into consideration the developmental level, emotional maturity, and cognitive capacity of the patient.

Active psychotic symptoms are generally prioritized as the main treatment target and comorbid conditions may respond better to treatment once the acute symptoms of psychosis are stabilized. However, any life-threatening symptoms, such as suicidal behavior or severe aggressive behaviors, must be prioritized in the management and care. Moreover, substance abuse may act as a barrier for establishing effective treatment adherence, which may require an initial motivational phase. Although the use of coercion is a well-known ethical issue in child and adolescent psychiatry (Pelto-Piri et al., 2016), current guidelines do not provide recommendations concerning the use of coercive measures in admission and treatment of children and adolescents with psychosis. One exception is that the NICE guidelines recommend that healthcare professionals who undertake rapid tranquillization and/or restraint in children and adolescents with EOP are trained and competent in these procedures with this age group (Kendall et al., 2013).

Antipsychotic treatment

According to the clinical guidelines (Kendall et al., 2013; Lecomte et al., 2017; McClellan & Stock, 2013), antipsychotic treatment (primarily second-generation antipsychotics) is first-line intervention for schizophrenia-

spectrum disorders in youth. The overall principles for antipsychotic treatment in youth are similar to those used for adult patients (Kendall et al., 2013; National Institute for Health and Care Excellence, 2014). Nevertheless, in youth with schizophrenia below age 18 years, antipsychotic medications appear less efficient and are associated with more side effects compared to adult patients (Schimmelmann et al., 2013). The primary beneficial effect of antipsychotic treatment is the amelioration of positive symptoms and the reduction in the risk of relapse, while negative and cognitive symptoms are typically only weakly or questionably improved (McCutcheon et al., 2020). The goal is to maintain the medication at the lowest effective dose to minimize potential short- and long-term side effects.

Early response to antipsychotic medication appears to be predictive of the ultimate clinical effect in the longer run (Pagsberg et al., 2022). If the patient does not respond to antipsychotic treatment within the first 2−4 weeks, the chance of ultimate response is low. Therefore, clinicians should consider switching to another antipsychotic drug if the patient has not responded to a sufficient dose within the first 4 weeks of treatment. If possible, polypharmacy (i.e., the use of more than one antipsychotic drug in parallel) should be avoided due to the difficulty of predicting beneficial and harmful effects.

Choice of medication

The first choice of pharmacological treatment for individuals with schizophrenia at all ages are second-generation antipsychotics, which compared to first-generation antipsychotics are considered to have a reduced risk of side effects in the form of extrapyramidal symptoms (EPS) (Carbon et al., 2018; Correll et al., 2004). First-generation antipsychotics are dopamine receptor antagonists (DRO) while second-generation antipsychotics are serotonin-dopamine antagonists (Chokhawala & Stevens, 2022). Long acting injectable (LAI) formulations are available for several of the antipsychotics used in youth with EOP. Studies including adult patients with psychotic disorders suggest that the use of LAIs can increase treatment adherence and prevent hospital admissions (Kishimoto et al., 2018), and decrease mortality (Taipale et al., 2018). A recent study suggests that the majority of young adult patients (age 18−35 years) are willing to try treatment with a LAI when presented to this option in a supportive and team-based manner (Kane et al., 2019). However, LAIs have not been approved for the use in patients below age 18 years (neither in the US, nor in Europe). Despite the off-label status, LAI may be considered in young patients with low treatment adherence.

Meta-analyses have not shown significant differences in beneficial effects between different antipsychotics used in adolescents with schizophrenia, but side effect profiles differ (Krause et al., 2018; Pagsberg, Tarp, et al., 2017). One exception to this is the efficacy of clozapine regarding treatment-resistant schizophrenia. Clozapine (no LAI formulation) is the gold-standard for

treatment-resistant schizophrenia due to the firm evidence of its higher efficacy compared to other antipsychotics (Krause et al., 2018). However, due to the risk of severe and potentially life-threatening side effects, such as agranulocytosis and cardiac arrhythmia, clozapine is restricted to use in cases of nonresponse to at least two different antipsychotics (Adnan et al., 2022).

Aripiprazole (LAI formulation available) appears to have an advantageous side effect profile compared to other antipsychotics with respect to cardiometabolic and prolactin side effects. However, akathisia is common, but may be temporary (Pagsberg et al., 2017).

Paliperidone (LAI formulation available) has a tendency to produce EPS and prolactin increase (Smith et al., 2019).

Lurasidone (no LAI formulation) is a newer antipsychotic that appear to have an overall relatively lower efficacy compared to other antipsychotics, based on adult studies (Smith et al., 2019). Lurasidone has so far shown a quite an advantageous side effect profile, with a low risk of weight gain, only moderate hyperprolactinemia, and a safer metabolic profile (Solmi et al., 2020).

Quetiapine (no LAI formulation) appears relatively advantageous regarding EPS but is less advantageous with respect to metabolic side effects (Smith et al., 2019).

Olanzapine (LAI formulation available) is associated with a high risk of cardiometabolic side effects and is among the second-generation antipsychotics with the highest risk for weight gain. Olanzapine may be considered for patients with treatment-resistant psychosis, due to some evidence in adults of a relatively good antipsychotic effect compared to other antipsychotics (except for clozapine which is superior) (Smith et al., 2019).

Side effects

All patients prescribed antipsychotic agents should be advised of the importance of a healthy lifestyle, including cessation of smoking, healthy diet, and routine exercise (McClellan & Stock, 2013). In general, side effects should be managed by lowering the antipsychotic dose or changing the antipsychotic drug. Nevertheless, side effects are common in adolescents receiving antipsychotic treatment (Pagsberg et al., 2017). Comprehensive routine programs for monitoring side effects at fixed time-points can decrease the burden of these effects (Robinson et al., 2018). The most central side effects of antipsychotics are: (1) neuromotor; (2) metabolic; (3) cardiac; (4) endocrine; (5) autonomic; and (5) sedation (Chokhawala & Stevens, 2022). These are described in more detail below.

Neuromotor

Side effects in this category are disturbing for the patient and often result in low adherence or termination of the antipsychotic treatment. EPS are parkinsonian symptoms such as bradykinesia, rigidity and tremor usually

presenting during the first 2 weeks of antipsychotic treatment but can also occur later. They are often associated with a rapid dose increase. EPS are far more common with first-generation than second-generation antipsychotics. The risk for EPS is heightened for young males, for antipsychotic-naïve patients, and with parenteral administration (D'Souza & Hooten, 2022). This is also true for acute dystonia, which are sudden, sustained involuntary muscle spasms that can affect any muscle group, but mostly around the face, eye (oculogyration—a spasm of the eye muscles), jaw (trismus), neck (torticollis), or tongue. More seldom, spasms of the muscles along the spinal column can cause opisthotonus, in which the patient's head, neck, and spinal column enter an arching position. Acute dystonia can affect the throat and cause laryngospasm, which can endanger breathing. Acute EPS or dystonia are handled (intravenously or orally) with antiparkinsonian drugs (e.g., biperiden).

Tardive dyskinesias typically occur after long-term treatment, especially with first-generation antipsychotics (D'Souza & Hooten, 2022). Patients experience involuntary, repetitive, stiff, jerky movements primarily in the face (lips, jaw, tongue), called oro-bucco-lingual dyskinesia. Dyskinesia can also affect the limbs. The condition is often irreversible, even after dose reduction or drug termination. The symptoms cause discomfort and are socially stigmatizing.

Akathisia manifests itself by restlessness and a subjective urge to motion. If dose reduction or switching to another drug is not possible, short-term treatment with benzodiazepines or beta-blockers can ameliorate the symptoms.

Malignant neuroleptic syndrome is a very serious, but rare side effect usually occurring within the first 2 weeks of antipsychotic treatment or after rapid dose increase. Typically, the condition is characterized by parkinsonian and dystonia symptoms, fever, sweating, changes in mental state, tachycardia, tachypnea, drooling, unstable blood pressure and pulse, leukocytosis and increased plasma-creatinine kinase (due to muscle cell damage). The condition requires immediate termination of the antipsychotic and in-patient specialized treatment often at an intensive care unit including parenteral benzodiazepines and/or electroconvulsive therapy (ECT).

Metabolic

Side effects in this category can develop quickly in children and adolescents. After only a few weeks of treatment, substantial weight gain and increased blood-cholesterol and -lipid levels may occur. Antipsychotic treatment is a serious risk factor for the development of metabolic syndrome, a cluster of symptoms that increases the risk of heart disease, stroke, and type-2 diabetes. The symptoms of the metabolic syndrome (Jensen et al., 2019) include increased blood pressure, elevated blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels, and type-2-diabetes. Symptoms of the metabolic syndrome often result in nonadherence to

treatment. If nonpharmacological weight-lowering interventions or switching to another antipsychotic with a more favorable metabolic profile is insufficient (off-label) treatment with antidiabetics such as metformin (Zheng et al., 2015) or newer agents such as glucagon-like peptide-1 receptor agonists (Siskind et al., 2019) may be effective (Wang et al., 2021). Metformin is recommended by AACAPs practice parameters (McClellan & Stock, 2013) for patients with significant weight gain or evidence of metabolic syndrome if switching to a different antipsychotic agent with lower metabolic risk is not an option. Treatment with glucagon-like peptide-1 receptor agonists on this indication in youth is still experimental.

Cardiac

Antipsychotics can affect the electrical signal conduction in the heart with increased risk of cardiac arrhythmias (Li et al., 2021). The risk for cardiac arrhythmias is primarily observed as a prolonged QT−interval on the electrocardiogram (ECG). QT prolongation increases the risk of developing abnormal heart rhythms, including the life threatening arrhythmia Torsades de pointes. This type of arrhythmia can lead to cardiac arrest.

Endocrine

An increase in blood prolactin (Corell & Carlson, 2006) is more common in youth and is especially seen with the first-generation antipsychotics and with the second-generation antipsychotics risperidone and paliperidone. Hyperprolactinemia is often associated with clinical symptoms such as sexual dysfunction, galactorrhea, and amenorrhea. However, the possible short- and long-term implications in children and adolescents, including potential adverse effects on growth, pubertal development, and bone density, are scarcely studied. With partial dopamine agonists such as aripiprazole, *hypo*-prolactinemia may occur, and the consequences of this are even less known (Tasaki et al., 2021).

Autonomic

Examples of side effects in this category are accommodation disturbances of vision, increased/decreased salivation, nausea/vomiting, diarrhea/constipation, orthostatic hypotension, and sweating. These symptoms are not always directly observable and the patient/next-of-kin should be asked about this.

Sedative

Sedation is a common and disturbing side effect of antipsychotics causing problems is everyday functioning and reduced quality of life.

Side effect monitoring

Side effect monitoring should be particularly intense during the first months of treatment and in connection with medication changes (Stroup et al., 2019). Side

effects are monitored subjectively (self-reported by the patients) and objectively (rating scales and clinical/laboratory examinations). Unacceptable side effects (according to the patient and/or prescriber) should lead to dose-reduction, if possible; lifestyle changes when feasible; consideration of additional medications for side effect management or ultimately changing the medication.

Side effect monitoring should at a minimum include the assessment of body height and weight, and waist circumference (at baseline, 4, 8, and 12 weeks, and at least every 3 months thereafter); fasting glucose, fasting lipid profile, Hb1A1c (reflects mean blood glucose over a longer period); and blood pressure (at baseline and after 3 months, and then at least annually). Regarding ECG, there are no firm recommendations on follow-up intervals. At baseline, cardiovascular history and ECG should be assessed. If a cardiac risk profile is present (i.e., known cardiac disease, family history with cardiac arrhythmia, pacemaker treatment, etc.), a cardiac specialist should be consulted before initiating antipsychotic medication. During initiation of antipsychotic medication, a follow-up ECG should be taken after 1−2 weeks and then every 6 months or as needed.

Screening for clinical symptoms of side effects using structured rating scales (Lingjærde et al., 1987) should be done at baseline, at 4, 8, and 12 weeks, and at least every 3 months thereafter. There are no concrete recommendations on how often serum/plasma-prolactin (and associated clinical symptoms) should be assessed. Nevertheless, a practical approach is to follow the suggestions for the lipid lab work (at baseline and after 3 months of treatment, and then at least annually) or alternatively at baseline and then if clinical symptoms associated with hyperprolactinemia arise (Grigg et al., 2017).

Genetic variation

Individual variations in pharmacokinetics associated with genetic variation may affect the metabolization of the drug, such as allele variations in the Cytochrome P450 (CYP) enzyme system which catalyzes the biotransformation of certain psychotropic drugs (Wijesinghe, 2016). One example is aripiprazole which is metabolized in the liver by the CYP2D6 and CYP3A4 enzymes (Carrascal-Laso et al., 2021). While most of the population demonstrates extensive (normal) metabolism by these enzymes, a proportion shows poor metabolism (for CYP2D6, 5%−10% in Caucasians, but lower in Asians and Africans) which may lead to drug accumulation (Gaedigk et al., 2017). For some enzymes (e.g., CYP2D6), a proportion of the population demonstrates ultraextensive metabolism (e.g., low frequency in Caucasians of around 2% and up to 39% in certain African populations), which may lead to reduced drug concentrations at standard doses (Koopmans et al., 2021). Important drug-drug interactions or drug-food interactions can be predicted if two substrates or a substrate and an inhibitor of a particular Cytochrome P450 are coadministered. For example, azoles and antifungal agents inhibit CYP3A4 which may increase the concentration of those antipsychotics that

are metabolized by CYP3A4, for example, quetiapine (Fujita, 2004). Moreover, foods with complex chemical mixtures, such as fruits, alcoholic beverages, teas, and herbs, possess the ability to inhibit or induce the activity of drug-metabolizing enzymes (e.g., grapefruit juice inhibits CYP3A4) (Fujita, 2004). Moreover, since tobacco smoking induces CYP isoenzymes, reduction or cessation of smoking can lead to a reduced activity of CYP1A2 or other CYP isoenzymes potentially causing a clinically relevant increase in the drug level of CYP1A2 substrates (Wijesinghe, 2016). An example is that smoking behavior is associated with a substantial effect on clozapine blood levels. Therefore, a reduction in clozapine dose of 30% is recommended when a patient treated with clozapine stops smoking (Wagner et al., 2020).

Current guidelines do not support routine use of CYP genotyping in patients with schizophrenia, since this genetic variation is only one of many factors that determine the individual response to a drug. It can be used, if the patient despite adherence and sufficient dosage is not responding (suggests ultraextensive metabolizer) or if the patient experiences side effects at low doses (suggests poor metabolizer) (Spina & de Leon, 2016).

Therapeutic drug monitoring (TDM, measurements of drug concentrations in blood) (de Leon, Schoretsanitis, et al., 2020) may help minimize the effects of the genetic variability in drug metabolism and the effects of poor compliance. Moreover, TDM may help avoid toxicity caused by interactions with other medications or illicit drugs. The combination of information from both TDM and genotyping can facilitate identification and appropriate management of individuals prone to either excessively high or low serum concentrations of psychotropic agents (Mitchell, 2000). Nevertheless, clinical observation during slow up-titration is always mandatory in good clinical practice. Most guidelines recommend routine TDM of only clozapine to monitor plasma-concentrations during the initiation phase, and in cases without observable clinical effect (de Leon, Ruan, et al., 2020). Furthermore, TDM and/or genotyping of CYP450 can be carried out in case of individual needs (e.g., estimation of adherence or drug interactions, or atypical side effects), but TDM and/or genotyping is not recommended for guiding the treatment itself. Therapeutic intervals for antipsychotics are not well documented in that there are no strong correlations between plasma concentration and clinical effects (Hiemke et al., 2018).

Approved medications

In Europe, only a few second-generation antipsychotics have been approved for the treatment of schizophrenia in children and adolescents (aripiprazole and paliperidone from age 15 years and lurasidone from age 13 years) (European Medicines Agency, 2022). For children younger than 13 years, clinical practice is often to use antipsychotics off-label that are approved for children on other indications to ensure the largest possible evidence base concerning side effect

profiles to benefit the safety of patients. An example is using risperidone for treating psychosis in young children despite lack of approval for the psychosis indication. This is because risperidone is approved for children from age 5 years in Europe on the indication of severe conduct disorders combined with developmental disorders. Ziprasidone is approved for mania/bipolar mixed episodes from age 10 years in Europe. Although the first-generation antipsychotic haloperidol is formally approved for the treatment of youth with schizophrenia from age 13 years, it is seldom used due to increased risk of EPS and heart arrythmia.

In the US, aripiprazole, olanzapine, risperidone, quetiapine, and lurasidone are approved for schizophrenia from age 13 years, while paliperidone is approved from age 12 years (U. S. Food and Drug Administration, 2022).

Switching medication

When initiating a switch from one antipsychotic to another, the clinician must consider the different receptor affinities of the antipsychotics. The so-called dopamine rebound phenomena (manifesting itself as a sudden reemergence of psychosis) can occur when the level of dopamine blockade is not kept relatively constant during the switch process (Correll, 2010). This may occur due to several reasons: (1) if the new antipsychotic is underdosed; (2) if the switch is too abrupt from an antipsychotic with a short half-life (e.g., risperidone) to one with a long half-life (e.g., lurasidone); (3) if a dopamine antagonist (e.g., paliperidone) is switched too fast to an antipsychotic with markedly less dopamine affinity (e.g., quetiapine) or to a partial dopamine agonist (e.g., aripiprazole). Overlapping switches are generally needed when the preswitch antipsychotic has high affinity for D2, H1 or cholinergic receptors and the postswitch antipsychotic has lower affinity and/or is a partial agonist on that receptor. Hence, switches should always be individualized, and decisions should be made considering the patient's preferences. In acute circumstances, rapid discontinuation (e.g., due to severe side effects) or rapid initiation (e.g., due to acute psychotic exacerbation) may be needed. In most nonacute circumstances, controlled and slow crossover will often be the method of choice. When there is a need for cross-titration, one should be aware of the risk of added side effects with polypharmacy, as the patient will temporarily (often during a 1−2 week cross-titration period) be on two different antipsychotics during the switch. During the switch period, adjunctive pharmacological treatments can be considered for short-term use (National Institute for Health and Care Excellence, 2020), such as benzodiazepines in case of akathisia, agitation, anxiety, and insomnia, antihistamines for nausea and insomnia, or beta-blockers for akathisia (Correll, 2010).

Discontinuing medication

When dose reduction or complete discontinuation of an antipsychotic is planned, tapering should be undertaken slowly over several months when

feasible, especially when lower dosages have been reached, due to high D2 receptor occupancy at lower doses (Horowitz, Murray, et al., 2021). When discontinuing antipsychotics there is a risk of relapse, which in addition to the nature of the disease course itself, can be linked to neuroadaptations that persist after antipsychotic cessation. However, a gradual tapering may minimize this risk. Some studies suggest that adaptations to antipsychotic exposure can persist for months or years after stopping the medication (Horowitz, Jauhar, et al., 2021). It is therefore suggested that when antipsychotics are reduced, it should be done gradually (over months or years), by one-quarter or one-half of the most recent dose, sequentially (so that reductions become smaller and smaller in size as the total dose decreases), at intervals of 3–6 months, titrated to individual tolerance. The aim is to allow underlying adaptations time to resolve, possibly reducing the risk of relapse on antipsychotic discontinuation. Final dosages before complete cessation may need to be very small (as small as 1/40th of a therapeutic dose) to prevent a large decrease in D_2 blockade when stopped (Horowitz, Jauhar, et al., 2021).

Antipsychotic medication and pregnancy

Considerations and guidance concerning potential pregnancy is relevant for adolescent girls with EOP, since nonplanned pregnancies are increased in women with psychotic disorders and the risk of relapse of psychotic symptoms in pregnant women with schizophrenia is elevated (Larsen et al., 2015). Furthermore, some psychopharmacological medications are associated with very early teratogenicity (defects in a developing fetus), for example, valproate or carbamazepine (Mcallister-Williams et al., 2017). According to the NICE guideline CG192, medications containing valproate taken in pregnancy can cause malformations in 11% of infants and developmental disorders in 30%–40% of children (National Institute for Health and Care Excellence, 2020). Therefore, these medications must not be used in females, including young girls below the age of puberty, unless alternative treatments are unsuitable, or the terms of a pregnancy prevention program are met.

In a recent review, Andrade found no associations between fetal exposure to second-generation antipsychotics during pregnancy and a significantly increased risk of major congenital malformations (Andrade, 2021). The author concluded that the substantial benefits associated with use of antipsychotics in maternal mental health, when indicated, must be weighed against the unsubstantiated risks of fetal major congenital malformations in a shared decision-making process (Andrade, 2021). Some authors have recommended the use of olanzapine and quetiapine for pregnant women based on the largest amount on safety data on antipsychotics that do not indicate an increased risk of major congenital malformations. Guidelines concerning the treatment of pregnant and breast feeding women is beyond the scope of this chapter but can be found elsewhere (Larsen et al., 2015; Mcallister-Williams et al., 2017; National Institute for Health and Care Excellence, 2020).

Pharmacological treatment of other psychiatric symptoms

Adjunctive medications may be needed when young patients with psychosis present with comorbid psychiatric symptoms. For emergency treatment of acute agitation, benzodiazepines (e.g., lorazepam) can be used, but only for a limited period due to their addiction inducing potential. Alternatively, antipsychotics in the form of either additional (low) doses of the currently used antipsychotic or with addition of a low dose of a more sedating drug such as quetiapine, may be used. For sleep disturbances, melatonin, benzodiazepine-derivates (limited period) or low doses of quetiapine may be used. For depressive symptoms, selective serotonin reuptake inhibitors such as fluoxetine can be used, but caution is warranted when combining with antipsychotics due to the potential interaction via the CYP-system (Stroup et al., 2019)). For unstable mood, lithium or lamotrigine can be added.

Electroconvulsive therapy

While ECT is relatively well established in adult psychiatry, there is a lack of studies regarding the efficacy and safety of ECT in children and adolescents. The AACAP practice parameters recommend that ECT be used as an augmentation or alternative strategy in youth with schizophrenia as a last resort after pharmacotherapy (including a trial of clozapine) has failed (McClellan & Stock, 2013). The limited number of published studies suggests that ECT is a safe and effective treatment for children and adolescents with similar beneficial outcomes and side effects to those reported in adults, particularly for patients aged 15−18 years, for whom most of the data exist (Døssing & Pagsberg, 2021).

Psychosocial treatment

Psychosocial interventions such as psychoeducation and psychotherapy should be provided in combination with medication (Kendall et al., 2013; McClellan & Stock, 2013). The primary treatment-goal is symptomatic remission (no more than mild positive and negative symptoms) along with clinical and personal recovery. Clinical recovery emphasizes an individual's psychiatric symptoms and functioning, whereas personal recovery emphasizes adaptation to one's illness that includes maintaining an identity apart from the illness, and finding meaning, purpose, and hope in life. Improved clinical recovery leads to less symptoms and functional disability, which in turn leads to a higher quality of life, and thus, increased personal recovery (Austin et al., 2021; Yu et al., 2022).

According to current guidelines (Kendall et al., 2013; Lecomte et al., 2017), families are to be offered a family intervention (either single-family or multifamily group intervention) including the patient, particularly for preventing and reducing relapse. The family intervention encompasses

communication skills, problem solving, and psychoeducation. Second, cognitive behavioral therapy (CBT) following established, effective protocols (Morrison, 2017; Morrison et al., 2021), ought to be offered to assist in promoting recovery in youth with persisting symptoms and for those in remission. Third, for youth of compulsory school age, liaison with the school, or supported education programs provided, will ensure that ongoing education is maintained/provided. For patients above compulsory school age, supported employment programs are recommended. Fourth, clinicians need to give patients and their families psychoeducation including information regarding symptoms, course, treatment, and prognosis of their disorder. Fifth, cognitive remediation therapy (CRT), which is a behavioral training-based intervention aiming to improve cognitive processes, may be considered for young individuals who have persisting cognitive difficulties. Sixth, it is important to make social skills training available for youth who are experiencing difficulties with stress and anxiety related to social interactions.

Although guidelines recommend psychological interventions for youth with psychosis, the evidence for the age group is limited and studies indicate that these interventions alone are not sufficient to manage psychosis. A recent systematic review by Gergov and colleagues (Gergov et al., 2022) investigated the effectiveness of psychological interventions for young people aged 12−30 years with psychotic disorders across 25 studies. Ten of the included studies applied cognitive or behavioral therapy, while nine used CRT, and six used other types of therapies (integrative interventions combining psychoeducation and family/group interventions). The main finding suggested that while psychological interventions appear effective in reducing symptoms and improving functioning in individuals with psychosis, psychotherapy does not typically outperform control conditions when it comes to symptom reduction. Moreover, the results from different studies do not seem to favor strongly any specific type of treatment. The most consistent finding was with CRT, showing larger improvement in cognitive functioning compared to control conditions. Nevertheless, the authors emphasized that the main aspect in psychotherapy is not only to reduce symptoms, but also to provide an add-on to treat various psychological functions, from neurocognitive functioning to self-esteem and social functioning. The authors suggest using integrative interventions of combining psychoeducation and/or individual treatment with family or group interventions in the psychosocial treatment of young people suffering from psychotic disorders.

Early Intervention Services

An established model for psychosocial intervention in young adults with psychotic disorders is specialized Early Intervention Services (EIS). This model has shown superiority compared to treatment as usual for patients age 18 years and above (Bighelli et al., 2021; Correll et al., 2018; Nordentoft et al., 2014). However, a direct extrapolation from the results of these studies to

individuals with EOP is difficult, since only a few percent of the participants were below age 18 years.

An example of EIS is the Danish OPUS program for young adults aged 18−35 years with first-episode psychosis. This program consists of a 2-year intervention with assertive treatment including cognitive-behavioral case management, enhanced family involvement, and social skills training provided by a multidisciplinary team of health professionals (Albert et al., 2017; Petersen et al., 2005). Until now, no randomized controlled trials (RCT) have tested EIS in children and adolescents with psychosis. In the following, we describe the suggested components of specialized EIS for youth aged 12−18 years with psychosis, building on the original OPUS program (Jørgensen et al., 2000). This intervention is currently being tested in an ongoing RCT in Denmark (the OPUS YOUNG trial: Early intervention vs. treatment as usual for adolescents with first-episode psychosis, clinical trials registration: NCT04916626), comparing it to treatment as usual.

OPUS YOUNG

The specialized OPUS YOUNG team consists of a multidisciplinary staff that includes one child and adolescent psychiatrist and several clinical psychologists, nurses, social workers, physiotherapists, and vocational therapists. All team members, except the psychiatrist, functions as a case manager providing cognitive-behavioral case management (CBCM) (Hartmann et al., 2017). There is a minimum of five staff members per team, representing at least four different relevant professions. All staff members are initially and on-going trained and supervised in CBCM and shared decision making, securing that all team members get a basic understanding of the cognitive principles of the treatment.

Cognitive-behavioral case management

CBCM is comprised of several components such as psychoeducation, case formulation, stress management, crisis management, behavioral strategies, and family work (Hartmann et al., 2017). Other relevant themes presented in the collaboration with the patient and family are enforcing a healthy lifestyle, preventing and treating somatic illness, and addressing social needs. CBCM offers patients a cognitive therapeutic approach to support their autonomy, reduce stigma, and empower the individual in working toward personal recovery goals and illness self-management.

Psychoeducational family-based intervention

The psychoeducational family-based intervention covers programs that provide families with psychoeducation about psychotic disorders and related difficulties, and how to manage psychotic disorders, including strategies for problem-solving skills and communication strategies within the family

(McFarlane et al., 2003). Several studies in adults with schizophrenia have shown that family psychoeducation is associated with reduced rates of relapses (Pilling et al., 2002; Pitschel-Walz et al., 2001). The psychoeducational intervention often includes an option to join a multifamily group. The multifamily group includes six to seven patients with their parents and two trained group leaders. The group addresses many of the complex and difficult everyday problems that families with an adolescent may face, in addition to more illness-specific issues that most of the patients with psychosis are dealing with. The group encourages all participants to engage actively in the problem-solving processes.

Social cognition and interaction training

A core characteristic of individuals with schizophrenia is reduced social functioning (Boyer et al., 2013; Caqueo-Urízar et al., 2015). Impaired social functioning may stigmatize and marginalize youth with psychotic disorders, and in turn, increase the risk of social isolation and loneliness. Furthermore, impaired social functioning strongly predicts poor long-term recovery (Green, 1996; Green et al., 2000; Wykes & Spaulding, 2011). Hence, implementing best practices for improving social cognition and functioning is an important clinical goal in specialized EIS.

The impairments of social cognition in individuals with schizophrenia involve at least three broad domains: (1) emotion perception (the abilities of recognizing and identifying emotions in others); (2) attributional style (the ways in which people explain the cause of events in their lives); and (3) theory of mind (the ability to attribute mental states to ourselves and others, providing the ability to predict and interpret the behavior of others) (Penn et al., 2007). Social cognition and interaction training (SCIT) is the first coherent and comprehensive, stand-alone intervention targeting all three domains of social cognition (Penn et al., 2007). The SCIT program also targets underlying deficient processes, such as cognitive rigidity, jumping to conclusions, and intolerance of ambiguity. SCIT has proven effective in adults with schizophrenia by improving their performance in key social cognitive abilities and overall social functioning (Penn et al., 2007; Roberts et al., 2010). In a feasibility study, the Early Psychosis Prevention and Intervention Center (EPPIC) in Melbourne, Australia applied SCIT for patients aged 16–26 years. SCIT was acceptable for the young population (Bartholomeusz et al., 2013). The participants improved significantly on measures of emotion recognition and social and occupational functioning. As a result of the study's findings, the EPPIC group suggests that SCIT is especially efficacious if applied as early as possible in the course of illness due to greater brain plasticity in adolescent brain development.

Cognitive-behavioral therapy

Individual CBT is recommended for first-episode psychosis (Kuipers et al., 2014), even though the evidence is questionable. Two meta-analyses of CBT

for adults with psychotic disorders found effects in the small range on overall symptoms (Jauhar et al., 2014) and functioning (Laws et al., 2018). However, the benefits were not sustained after study completion, and no robust effects were found regarding psychotic symptoms, distress, or quality of life.

In children and adolescents with EOP, a systematic review of psychological interventions identified only one small study of CBT (n = 20) providing indications that psychological interventions might be effective (Anagnostopoulou et al., 2019). The aforementioned review by Gergov and colleagues included 10 studies of cognitive or behavioral therapy for young people with psychosis. The study found that only one of five studies assessing positive symptoms as an outcome reported that the cognitive or behavioral therapy significantly outperformed the control condition (Gergov et al., 2022). For reduction in negative symptoms and general psychopathology, the rates were even lower, with mostly no significant differences. With respect to global, social and occupational functioning, and quality of life, only two of seven studies including these outcomes found significant differences for cognitive or behavioral therapy versus control interventions. Regarding relapse, one of two studies on cognitive or behavioral therapy reported results favoring cognitive or behavioral therapy compared to control interventions.

The NICE guideline emphasizes the need for trials in children and adolescents, to build a youth-specific evidence base for the use of CBT in early intervention in EOP (Kendall et al., 2013). Despite the lack of strong evidence to support individual CBT for psychosis, it is still offered in seven out of 10 EIS programs recently reviewed (Correll et al., 2018). CBT is provided because it appears useful as one ingredient in the multifaceted interventions needed for the treatment of psychosis. The aim is typically to support autonomy, reduce stigma, and empower the individual to work toward personal recovery goals and illness self-management (Kane et al., 2016). In the ongoing OPUS YOUNG trial, these aims are targeted by the core components, particularly CBCM and SCIT in combination.

Prevention and treatment of substance abuse

Young people with psychosis are at high risk of getting involved in substance abuse (Köck et al., 2022). Thus, it is important to offer prevention and treatment of substance abuse integrated into EIS. This should preferably be carried out by the case manager. A Cochrane review of psychosocial interventions for cannabis use disorder (in adults) suggested that improvements in cannabis use frequency, and severity of dependence were highest when the treatment offered a combination of CBT and motivational enhancement therapy (Gates et al., 2016). The combination of CBT and motivational enhancement therapy has in Danish studies shown to be effective in reducing and cessation of cannabis use among young people (del Palacio-Gonzalez et al., 2022; Pedersen et al., 2021). A recent randomized control trial (the YouthDAT) examined the effects of four treatment

conditions for Danish youths aged 15–25 years. All four treatment conditions included CBT and motivational interviewing. Three conditions varied regarding additional strategies for increasing retention (giving vouchers and sending text reminders for appointments), offering optional low intensity aftercare, or a combination of these. The study found that the treatments combining vouchers and text reminders resulted in the best treatment retention rate (Pedersen et al., 2021). Additional treatment strategies, such as contingency management, text reminders, and low-intensity aftercare, predicted delayed readmission to treatment and fewer legal problems in patients with drug abuse. Mental health problems were common among the youth participating in the study. The treatments with additional strategies proved to be effective in youth with drug abuse and a psychiatric history (del Palacio-Gonzalez et al., 2022).

Support to siblings

Studies of the experiences and needs of siblings of young adults with first-episode psychosis treated in EIS teams found that siblings are greatly affected by the onset of psychosis in their brother or sister. Although siblings do not identify themselves as caregivers, most of them play a significant role in their brother's or sister's life (Friedrich et al., 2008; Sin et al., 2012). The siblings desire a dynamic, robust and accessible service, such as information and support from peer siblings, to meet their needs (Sin et al., 2012). It is important to offer psychoeducation and support for siblings. Moreover, due to the familiar high risk for psychosis and other mental illnesses, it is essential to reduce the level of stress in the sibling's everyday life (Friedrich et al., 2008). However, data to support psychoeducation for siblings of people with severe mental illness is still very limited according to a Cochrane review (Sin et al., 2015), especially studies on support for siblings of adolescents with psychosis is lacking.

Support from peers

An EIS in Melbourne, Australia used families as partners in mental health care in close collaboration with clinical teams to provide new family members with a range of interventions to assist recovery. It was noted that new families asked for contact with peer-families very early in the course of treatment (Leggatt & Woodhead, 2016). Peers can, by telling their personal history and experience about living with mental illness, help to increase hope for the future, broaden the knowledge about psychosis and schizophrenia, and help reduce stigmatization.

Transition to adult psychiatry or social services

It is important to actively bridge the gap between child and adolescent psychiatry and adult psychiatry, or social community care. This can be done by assisting in a safe transfer from one treatment facility to other services, for instance by following the principles of the "NICE guidelines for supporting young people in their transition to adult services" (Singh et al., 2016). These principles emphasize

allocating a named case manager to oversee, coordinate, and deliver transition support and advocate for the young person if needed, and to ensure that the plan for support is revised if the young person is not in contact with services after transfer.

A recent study, including 760 Spanish adolescents with a variety of psychiatric diagnoses, investigated when and how patients got lost to care during transition from child and adolescent to adult mental health services (Reneses et al., 2022). The authors found that a large number of youth dropped out of care as they approached the transition from child and adolescent to adult mental health services, and they experienced discontinuity of care during this critical period. Fifty-six percent of subjects experienced cessation of care before the transition age. Importantly, the risk of dropout was lower in subjects with more severe mental disorders, such as psychosis. This might indicate that professionals in the clinic are compliant with the NICE guidelines for young people with schizophrenia and other psychotic disorders.

Cognitive remediation therapy

CRT is a psychological treatment that supports the cognitive competencies of the affected individual. As a therapeutic intervention, CRT ranges from training basic cognitive functions to developing better problem-solving skills and metacognition. CRT is not based on a specific therapeutic direction, and it can be integrated with and function as a superstructure to other therapeutic traditions (Wykes et al., 2011). Only a few studies have investigated the effect of CRT in the early course of schizophrenia in adults, and results are still sparse (Keshavan et al., 2017; Ramsay et al., 2018). In children and adolescents with EOP, the recent review by Gergov and colleagues, however, showed more improvement in cognitive functioning with CRT compared to control interventions (Gergov et al., 2022).

Future directions

The gap in the literature on effective and safe treatments for adolescent psychosis needs to be addressed in future studies. Importantly, not only short-term outcomes, but also effects of interventions in the longer run warrant attention. There is a need to investigate new antipsychotic agents in comparison with traditionally used antipsychotics in placebo-controlled trials. Likewise, it is important to conduct RCTs of psychosocial treatments, such as Early Intervention Service models versus treatment as usual and to pursue further a focus on early detection of psychotic symptoms. Alternative new treatments should be investigated, both concerning new developments of psychopharmacological compounds and among psychosocial interventions. We emphasize an increased focus on individualizing treatments tailored to the individual patient's needs. Preventive strategies such as support and treatment of high-risk groups should likewise be prioritized.

Conclusions

The recommended treatment for adolescent psychosis is antipsychotic medication combined with psychosocial interventions. Specialized early intervention models focusing on recovery include both pharmacological and nonpharmacological elements. Second-generation antipsychotics with demonstrated clinical efficacy and safety in RCTs are generally the first pharmacological choice. A low-dose strategy should be adopted, and polypharmacy should be avoided. It is important to regularly monitor and respond to occurring adverse side effects.

The psychosocial treatment should preferably be managed by a multidisciplinary team with focus on individual and family resources and resilience, personalized interventions, management of comorbidities, coherence in treatment course, and collaborations with social and educational services. Central to the treatment is the allocation for the individual patient to a case manager who is responsible for the continuous contact and working alliance with the patient and family throughout the treatment.

Acknowledgments

Anne Katrine Pagsberg and Marianne Melau have no disclosures to report.

References

Adnan, M., Motiwala, F., Trivedi, C., Sultana, T., Mansuri, Z., & Jain, S. (2022). Clozapine for management of childhood and adolescent-onset schizophrenia: A systematic review and meta-analysis. *Journal of Child and Adolescent Psychopharmacology, 32*(1), 2–11. https://doi.org/10.1089/cap.2021.0092

Albert, N., Melau, M., Jensen, H., Emborg, C., Jepsen, J. R. M., Fagerlund, B., Gluud, C., Mors, O., Hjorthøj, C., & Nordentoft, M. (2017). Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: Randomised, superiority, parallel group trial in Denmark (OPUS II). *BMJ, 356*, i6681. https://doi.org/10.1136/bmj.i6681

Anagnostopoulou, N., Kyriakopoulos, M., & Alba, A. (2019). Psychological interventions in psychosis in children and adolescents: A systematic review. *European Child and Adolescent Psychiatry, 28*(6), 735–746. https://doi.org/10.1007/s00787-018-1159-3

Andrade, C. (2021). Major congenital malformations associated with exposure to second-generation antipsychotic drugs during pregnancy. *The Journal of Clinical Psychiatry, 82*(5). https://doi.org/10.4088/jcp.21f14252

Austin, S. F., Hjorthøj, C., Baagland, H., Simonsen, E., & Dam, J. (2021). Investigating personal and clinical recovery processes in people with first episode psychosis. *Early Intervention in Psychiatry*. https://doi.org/10.1111/eip.13258

Bartholomeusz, C. F., Allott, K., Killackey, E., Liu, P., Wood, S. J., & Thompson, A. (2013). Social cognition training as an intervention for improving functional outcome in first-episode psychosis: A feasibility study. *Early Intervention in Psychiatry, 7*(4), 421–426. https://doi.org/10.1111/eip.12036

Bighelli, I., Rodolico, A., García-Mieres, H., Pitschel-Walz, G., Hansen, W. P., Schneider-Thoma, J., Siafis, S., Wu, H., Wang, D., Salanti, G., Furukawa, T. A., Barbui, C., & Leucht, S. (2021). Psychosocial and psychological interventions for relapse prevention in schizophrenia: A systematic review and network meta-analysis. *The Lancet Psychiatry, 8*(11), 969−980. https://doi.org/10.1016/S2215-0366(21)00243-1

Birchwood, M., Lester, H., Mccarthy, L., Jones, P., Fowler, D., Amos, T., Freemantle, N., Sharma, V., Lavis, A., Singh, S., & Marshall, M. (2014). The UK national evaluation of the development and impact of Early Intervention Services (the National EDEN studies): Study rationale, design and baseline characteristics. *Early Intervention in Psychiatry, 8*(1), 59−67. https://doi.org/10.1111/eip.12007

Boyer, L., Millier, A., Perthame, E., Aballea, S., Auquier, P., & Toumi, M. (2013). Quality of life is predictive of relapse in schizophrenia. *BMC Psychiatry, 13*(1). https://doi.org/10.1186/1471-244x-13-15

Broussard, B., Kelley, M. E., Wan, C. R., Cristofaro, S. L., Crisafio, A., Haggard, P. J., Myers, N. L., Reed, T., & Compton, M. T. (2013). Demographic, socio-environmental, and substance-related predictors of duration of untreated psychosis (DUP). *Schizophrenia Research, 148*(1−3), 93−98. https://doi.org/10.1016/j.schres.2013.05.011

Caqueo-Urízar, A., Boyer, L., Baumstarck, K., & Gilman, S. E. (2015). Subjective perceptions of cognitive deficits and their influences on quality of life among patients with schizophrenia. *Quality of Life Research, 24*(11), 2753−2760. https://doi.org/10.1007/s11136-015-1019-2

Carbon, M., Kane, J. M., Leucht, S., & Correll, C. U. (2018). Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: A meta-analysis. *World Psychiatry, 17*(3), 330−340. https://doi.org/10.1002/wps.20579

Carrascal-Laso, L., Isidoro-García, M., Ramos-Gallego, I., & Franco-Martín, M. A. (2021). Review: Influence of the CYP450 genetic variation on the treatment of psychotic disorders. *Journal of Clinical Medicine, 10*(18), 4275. https://doi.org/10.3390/jcm10184275

Chan, S. W.c. (2011). Global perspective of burden of family caregivers for persons with schizophrenia. *Archives of Psychiatric Nursing, 25*(5), 339−349. https://doi.org/10.1016/j.apnu.2011.03.008

Chokhawala, K., & Stevens, L. (2022). Antipsychotic medications. In *StatPearls [internet]*. StatPearls Publishing.

Colton, C. W., & Manderscheid, R. W. (2006). Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Preventing Chronic Disease, 3*(2), 1−14. http://www.cdc.gov/pcd/.

Corell, C. U., & Carlson, H. E. (2006). Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(7), 771−791. https://doi.org/10.1097/01.chi.0000220851.94392.30

Correll, C. U. (2010). From receptor pharmacology to improved outcomes: Individualising the selection, dosing, and switching of antipsychotics. *European Psychiatry, 25*(2), s12−s21. https://doi.org/10.1016/S0924-9338(10)71701-6

Correll, C. U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., Craig, T. J., Nordentoft, M., Srihari, V. H., Guloksuz, S., Hui, C. L. M., Chen, E. Y. H., Valencia, M., Juarez, F., Robinson, D. G., Schooler, N. R., Brunette, M. F., Mueser, K. T., Rosenheck, R. A., … Kane, J. M. (2018). Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry, 75*(6), 555−565. https://doi.org/10.1001/jamapsychiatry.2018.0623

Correll, C. U., Leucht, S., & Kane, J. M. (2004). Lower risk for tardive dyskinesia associated with second-generation antipsychotics: A systematic review of 1-year studies. *American Journal of Psychiatry, 161*(3), 414−425. https://doi.org/10.1176/appi.ajp.161.3.414

Cuijpers, P., & Stam, H. (2000). Burnout among relatives of psychiatric patients attending psychoeducational support groups. *Psychiatric Services, 51*(3), 375−379. https://doi.org/10.1176/appi.ps.51.3.375

Dalsgaard, S., McGrath, J., Østergaard, S. D., Wray, N. R., Pedersen, C. B., Mortensen, P. B., & Petersen, L. (2020). Association of mental disorder in childhood and adolescence with subsequent educational achievement. *JAMA Psychiatry, 77*(8), 797−805. https://doi.org/10.1001/jamapsychiatry.2020.0217

Døssing, E., & Pagsberg, A. K. (2021). Electroconvulsive therapy in children and adolescents: A systematic review of current literature and guidelines. *Journal of ECT, 37*(3), 158−170. https://doi.org/10.1097/YCT.0000000000000761

D'Souza, R. S., & Hooten, W. M. (2022). Extrapyramidal symptoms. In *StatPearls [internet]*. StatPearls Publishing.

Eggers, C. (1978). Course and prognosis of childhood schizophrenia. *Journal of Autism and Childhood Schizophrenia, 8*(1), 21−36. https://doi.org/10.1007/BF01550275

European Medicines Agency. (2022). http://www.ema.europa.eu/en.

Fazel, S., Gulati, G., Linsell, L., Geddes, J. R., Grann, M., & McGrath, J. (2009). Schizophrenia and violence: Systematic review and meta-analysis. *PLoS Medicine, 6*(8), e1000120. https://doi.org/10.1371/journal.pmed.1000120

Friedrich, R. M., Lively, S., & Rubenstein, L. M. (2008). Siblings' coping strategies and mental health services: A national study of siblings of persons with schizophrenia. *Psychiatric Services, 59*(3), 261−267. https://doi.org/10.1176/ps.2008.59.3.261

Fujita, K. I. (2004). Food-drug interactions via human cytochrome P450 3A (CYP3A). *Drug Metabolism and Drug Interactions, 20*(4), 195−217. https://doi.org/10.1515/DMDI.2004.20.4.195

Gaedigk, A., Sangkuhl, K., Whirl-Carrillo, M., Klein, T., & Leeder, J. S. (2017). Prediction of CYP2D6 phenotype from genotype across world populations. *Genetics in Medicine, 19*(1), 69−76. https://doi.org/10.1038/gim.2016.80

Gates, P. J., Sabioni, P., Copeland, J., Le Foll, B., & Gowing, L. (2016). Psychosocial interventions for cannabis use disorder. *Cochrane Database of Systematic Reviews, 2016*(5). https://doi.org/10.1002/14651858.CD005336.pub4

Gergov, V., Milic, B., Löffler-Stastka, H., Ulberg, R., Vousoura, E., & Poulsen, S. (2022). Psychological interventions for young people with psychotic disorders: A systematic review. *Frontiers in Psychiatry, 13*. https://doi.org/10.3389/fpsyt.2022.859042

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry, 153*(3), 321−330. https://doi.org/10.1176/ajp.153.3.321

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff". *Schizophrenia Bulletin, 26*(1), 119−136. https://doi.org/10.1093/oxfordjournals.schbul.a033430

Grigg, J., Worsley, R., Thew, C., Gurvich, C., Thomas, N., & Kulkarni, J. (2017). Antipsychotic-induced hyperprolactinemia: Synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. *Psychopharmacology, 234*(22), 3279−3297. https://doi.org/10.1007/s00213-017-4730-6

Hartmann, J. A., McGorry, P. D., Schmidt, S. J., Amminger, G. P., Yuen, H. P., Markulev, C., Berger, G. E., Chen, E. Y. H., De Haan, L., Hickie, I. B., Lavoie, S., McHugh, M. J., Mossaheb, N., Nieman, D. H., Nordentoft, M., Riecher-Rössler, A., Schäfer, M. R., Schlögelhofer, M., Smesny, S., … Nelson, B. (2017). Opening the black box of cognitive-behavioural case management in clients with ultra-high risk for psychosis. *Psychotherapy and Psychosomatics, 86*(5), 292−299. https://doi.org/10.1159/000477551

Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., … Baumann, P. (2018). Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. *Pharmacopsychiatry, 51*(1−2), 9−62. https://doi.org/10.1055/s-0043-116492

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *The Lancet Psychiatry, 4*(4), 295−301. https://doi.org/10.1016/S2215-0366(17)30078-0

Horowitz, M. A., Jauhar, S., Natesan, S., Murray, R. M., & Taylor, D. (2021). A method for tapering antipsychotic treatment that may minimize the risk of relapse. *Schizophrenia Bulletin, 47*(4), 1116−1129. https://doi.org/10.1093/schbul/sbab017

Horowitz, M. A., Murray, R. M., & Taylor, D. (2021). Tapering antipsychotic treatment. *JAMA Psychiatry, 78*(2), 125−126. https://doi.org/10.1001/jamapsychiatry.2020.2166

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., Veijola, J., & Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin, 39*(6), 1296−1306. https://doi.org/10.1093/schbul/sbs130

Jauhar, S., McKenna, P. J., Radua, J., Fung, E., Salvador, R., & Laws, K. R. (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry, 204*(1), 20−29. https://doi.org/10.1192/bjp.bp.112.116285

Jensen, K. G., Correll, C. U., Rudå, D., Klauber, D. G., Decara, M. S., Fagerlund, B., Jepsen, J. R. M., Eriksson, F., Fink-Jensen, A., & Pagsberg, A. K. (2019). Cardiometabolic adverse effects and its predictors in children and adolescents with first-episode psychosis during treatment with quetiapine-extended release versus aripiprazole: 12-Week results from the tolerance and effect of antipsychotics in children and adolescents with psychosis (TEA) trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 58*(11), 1062−1078. https://doi.org/10.1016/j.jaac.2019.01.015

Jin, H., & Mosweu, I. (2017). The societal cost of schizophrenia: A systematic review. *PharmacoEconomics, 35*(1), 25−42. https://doi.org/10.1007/s40273-016-0444-6

Jørgensen, P., Nordentoft, M., Abel, M. B., Gouliaev, G., Jeppesen, P., & Kassow, P. (2000). Early detection and assertive community treatment of young psychotics: The Opus study. Rationale and design of the trial. *Social Psychiatry and Psychiatric Epidemiology, 35*(7), 283−287. https://doi.org/10.1007/s001270050240

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., O'Donovan, M., Correll, C. U., Kane, J. M., Van Os, J., & Insel, T. R. (2015). Schizophrenia. *Nature Reviews Disease Primers, 1*. https://doi.org/10.1038/nrdp.2015.67

Kane, J. M., Robinson, D. G., Schooler, N. R., Mueser, K. T., Penn, D. L., Rosenheck, R. A., Addington, J., Brunette, M. F., Correll, C. U., Estroff, S. E., Marcy, P., Robinson, J., Meyer-Kalos, P. S., Gottlieb, J. D., Glynn, S. M., Lynde, D. W., Pipes, R., Kurian, B. T., Miller, A. L., … Heinssen, R. K. (2016). Comprehensive versus usual community care for first-episode psychosis: 2-Year outcomes from the NIMH RAISE early treatment program. *American Journal of Psychiatry, 173*(4), 362−372. https://doi.org/10.1176/appi.ajp.2015.15050632

Kane, J. M., Schooler, N. R., Marcy, P., Achtyes, E. D., Correll, C. U., & Robinson, D. G. (2019). Patients with early-phase schizophrenia will accept treatment with sustained-release medication (long-acting injectable antipsychotics): Results from the recruitment phase of the PRELAPSE trial. *Journal of Clinical Psychiatry, 80*(3). https://doi.org/10.4088/JCP.18m12546

Kendall, T., Hollis, C., Stafford, M., & Taylor, C. (2013). Recognition and management of psychosis and schizophrenia in children and young people: Summary of NICE guidance. *BMJ (Online), 346*(7892). https://doi.org/10.1136/bmj.f150

Keshavan, M. S., Eack, S. M., Prasad, K. M., Haller, C. S., & Cho, R. Y. (2017). Longitudinal functional brain imaging study in early course schizophrenia before and after cognitive enhancement therapy. *NeuroImage, 151*, 55−64. https://doi.org/10.1016/j.neuroimage.2016.11.060

Kishimoto, T., Hagi, K., Nitta, M., Leucht, S., Olfson, M., Kane, J. M., & Correll, C. U. (2018). Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: A meta-analysis of prospective and retrospective cohort studies. *Schizophrenia Bulletin, 44*(3), 603−619. https://doi.org/10.1093/schbul/sbx090

Köck, P., Meyer, M., Elsner, J., Dürsteler, K. M., Vogel, M., & Walter, M. (2022). Co-Occurring mental disorders in transitional aged youth with substance use disorders—A narrative review. *Frontiers in Psychiatry*, 13. https://doi.org/10.3389/fpsyt.2022.827658

Koopmans, A. B., Braakman, M. H., Vinkers, D. J., Hoek, H. W., & van Harten, P. N. (2021). Meta-analysis of probability estimates of worldwide variation of CYP2D6 and CYP2C19. *Translational Psychiatry, 11*(1). https://doi.org/10.1038/s41398-020-01129-1

Krause, M., Zhu, Y., Huhn, M., Schneider-Thoma, J., Bighelli, I., Chaimani, A., & Leucht, S. (2018). Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *European Neuropsychopharmacology, 28*(6), 659−674. https://doi.org/10.1016/j.euroneuro.2018.03.008

Kuipers, E., Yesufu-Udechuku, A., Taylor, C., & Kendall, T. (2014). Management of psychosis and schizophrenia in adults: Summary of updated NICE guidance. *BMJ, 348*(feb12 1). https://doi.org/10.1136/bmj.g1173. g1173−g1173.

Larsen, E. R., Damkier, P., Pedersen, L. H., Fenger-Gron, J., Mikkelsen, R. L., Nielsen, R. E., Linde, V. J., Knudsen, H. E. D., Skaarup, L., & Videbech, P. (2015). Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatrica Scandinavica, 132*, 1−28. https://doi.org/10.1111/acps.12479

Laws, K. R., Darlington, N., Kondel, T. K., McKenna, P. J., & Jauhar, S. (2018). Cognitive behavioural therapy for schizophrenia - outcomes for functioning, distress and quality of life: A meta-analysis. *BMC Psychology, 6*(1). https://doi.org/10.1186/s40359-018-0243-2

Lecomte, T., Abidi, S., Garcia-Ortega, I., Mian, I., Jackson, K., Jackson, K., & Norman, R. (2017). Canadian treatment guidelines on psychosocial treatment of schizophrenia in children and youth. *Canadian Journal of Psychiatry, 62*(9), 648−655. https://doi.org/10.1177/0706743717720195

Leggatt, M., & Woodhead, G. (2016). Family peer support work in an early intervention youth mental health service. *Early Intervention in Psychiatry, 10*(5), 446−451. https://doi.org/10.1111/eip.12257

de Leon, J., Ruan, C. J., Schoretsanitis, G., & De Las Cuevas, C. (2020). A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. *Psychotherapy and Psychosomatics, 89*(4), 200−214. https://doi.org/10.1159/000507638

de Leon, J., Schoretsanitis, G., Kane, J. M., & Ruan, C. (2020). Using therapeutic drug monitoring to personalize clozapine dosing in Asians. *Asia-Pacific Psychiatry, 12*(2). https://doi.org/10.1111/appy.12384

Lingjærde, O., Ahlfors, U. G., Bech, P., Dencker, S. J., & Elgen, K. (1987). The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica, 76*, 1−100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x

Li, X.-Q., Tang, X.-R., & Li, L.-L. (2021). Antipsychotics cardiotoxicity: What's known and what's next. *World Journal of Psychiatry, 11*(10). https://doi.org/10.5498/WJP.V11.I10.736

Maniglio, R. (2009). Severe mental illness and criminal victimization: A systematic review. *Acta Psychiatrica Scandinavica, 119*(3), 180−191. https://doi.org/10.1111/j.1600-0447.2008.01300.x

Martens, L., & Addington, J. (2001). The psychological well-being of family members of individuals with schizophrenia. *Social Psychiatry and Psychiatric Epidemiology, 36*(3), 128−133. https://doi.org/10.1007/s001270050301

Mcallister-Williams, R. H., Baldwin, D. S., Cantwell, R., Easter, A., Gilvarry, E., Glover, V., Green, L., Gregoire, A., Howard, L. M., Jones, I., Khalifeh, H., Lingford-Hughes, A., McDonald, E., Micali, N., Pariante, C. M., Peters, L., Roberts, A., Smith, N. C., Taylor, D., … Young, A. H. (2017). British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. *Journal of Psychopharmacology, 31*(5), 519−552. https://doi.org/10.1177/0269881117699361

McClellan, J., & Stock, S. (2013). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(9), 976−990. https://doi.org/10.1016/j.jaac.2013.02.008

McCutcheon, R. A., Reis Marques, T., & Howes, O. D. (2020). Schizophrenia—An overview. *JAMA Psychiatry,* 77(2), 201−210. https://doi.org/10.1001/jamapsychiatry.2019.3360

McDaid, D., Park, A.-L., Iemmi, V., Adelaja, B., & Knapp, M. (2016). *Growth in the use of early intervention for psychosis services: An opportunity to promote recovery amid concerns on health care sustainability.* Personal Social Services Research Unit (PSSRU).

McFarlane, W. R., Dixon, L., Lukens, E., & Lucksted, A. (2003). Family psychoeducation and schizophrenia: A review of the literature. *Journal of Marital and Family Therapy, 29*(2), 223−245. https://doi.org/10.1111/j.1752-0606.2003.tb01202.x

Mitchell, P. B. (2000). Therapeutic drug monitoring of psychotropic medications. *British Journal of Clinical Pharmacology, 49*(4), 303−312. https://doi.org/10.1046/j.1365-2125.2000.00174.x

Morrison, A. P. (2017). A manualised treatment protocol to guide delivery of evidence-based cognitive therapy for people with distressing psychosis: Learning from clinical trials. *Psychosis, 9*(3), 271−281. https://doi.org/10.1080/17522439.2017.1295098

Morrison, A. P., Pyle, M., Byrne, R., Broome, M., Freeman, D., Johns, L., James, A., Husain, N., Whale, R., MacLennan, G., Norrie, J., Hudson, J., Peters, S., Davies, L., Bowe, S., Smith, J., Shiers, D., Joyce, E., Jones, W., … Maughan, D. (2021). Psychological intervention, antipsychotic medication or a combined treatment for adolescents with a first episode of psychosis: The MAPS feasibility three-arm RCT. *Health Technology Assessment, 25*(4), 1−124. https://doi.org/10.3310/HTA25040

Munkner, R., Haastrup, S., Joergensen, T., & Kramp, P. (2005). Incipient offending among schizophrenia patients after first contact to the psychiatric hospital system. *European Psychiatry, 20*(4), 321−326. https://doi.org/10.1016/j.eurpsy.2005.01.008

National Institute for Health and Care Excellence. (2014). *Psychosis and schizophrenia in adults: Prevention and management (clinical guideline [CG178]).* National Institute for Health and Care Excellence. http://www.nice.org.uk/guidance/cg178.

National Institute for Health and Care Excellence. (2020). *Antenatal and postnatal mental health: Clinical management and service guidance (clinical guideline [CG192]).* National Institute for Health and Care Excellence. http://www.nice.org.uk/guidance/cg192.

Nielsen, R. E., Uggerby, A. S., Jensen, S. O. W., & McGrath, J. J. (2013). Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades—A Danish nationwide study from 1980 to 2010. *Schizophrenia Research, 146*(1−3), 22−27. https://doi.org/10.1016/j.schres.2013.02.025

Nordentoft, M., Rasmussen, J.Ø., Melau, M., Hjorthøj, C. R., & Thorup, A. A. E. (2014). How successful are first episode programs? A review of the evidence for specialized assertive early intervention. *Current Opinion in Psychiatry, 27*(3), 167−172. https://doi.org/10.1097/YCO.0000000000000052

Nordentoft, M., Wahlbeck, K., Hällgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., Gissler, M., Laursen, T. M., & Burne, T. (2013). Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS ONE, 8*(1), e55176. https://doi.org/10.1371/journal.pone.0055176

Pagsberg, A. K., Jeppesen, P., Klauber, D. G., Jensen, K. G., Rudå, D., Stentebjerg-Olesen, M., Jantzen, P., Rasmussen, S., Saldeen, E. A. S., Lauritsen, M. B. G., Bilenberg, N., Stenstrøm, A. D., Nyvang, L., Madsen, S., Werge, T. M., Lange, T., Gluud, C., Skoog, M., Winkel, P., … Fink-Jensen, A. (2017). Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: The multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *The Lancet Psychiatry, 4*(8), 605−618. https://doi.org/10.1016/S2215-0366(17)30166-9

Pagsberg, A. K., Krogmann, A., Jeppesen, P., von Hardenberg, L., Klauber, D. G., Jensen, K. G., Rudå, D., Decara, M. S., Jepsen, J. R. M., Fagerlund, B., Fink-Jensen, A., Correll, C. U., & Galling, B. (2022). Early antipsychotic nonresponse as a predictor of nonresponse and nonremission in adolescents with psychosis treated with aripiprazole or quetiapine: Results from the TEA trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 61*(8), 997−1009. https://doi.org/10.1016/j.jaac.2021.11.032

Pagsberg, A. K., Tarp, S., Glintborg, D., Stenstrøm, A. D., Fink-Jensen, A., Correll, C. U., & Christensen, R. (2017). Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(3), 191−202. https://doi.org/10.1016/j.jaac.2016.12.013

del Palacio-Gonzalez, A., Hesse, M., Thylstrup, B., Pedersen, M. U., & Pedersen, M. M. (2022). Effects of contingency management and use of reminders for drug use treatment on readmission and criminality among young people: A linkage study of a randomized trial. *Journal of Substance Abuse Treatment*, 133. https://doi.org/10.1016/j.jsat.2021.108617

Pedersen, M. U., Hesse, M., Thylstrup, B., Jones, S., Pedersen, M. M., & Frederiksen, K. S. (2021). Vouchers versus reminders to prevent dropout: Findings from the randomized youth drug abuse treatment project (youthDAT project). *Drug and Alcohol Dependence, 218*. https://doi.org/10.1016/j.drugalcdep.2020.108363

Pelto-Piri, V., Kjellin, L., Lindvall, C., & Engström, I. (2016). Justifications for coercive care in child and adolescent psychiatry, a content analysis of medical documentation in Sweden. *BMC Health Services Research, 16*(1). https://doi.org/10.1186/s12913-016-1310-0

Penn, D. L., Roberts, D. L., Combs, D., & Sterne, A. (2007). Best practices: The development of the social cognition and interaction training program for schizophrenia spectrum disorders. *Psychiatric Services, 58*(4), 449−451. https://doi.org/10.1176/appi.ps.58.4.449

Petersen, L., Jeppesen, P., Thorup, A., Abel, M.-B., Øhlenschlæger, J., Christensen, T.Ø., Krarup, G., Jørgensen, P., & Nordentoft, M. (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ, 331*(7517), 602. https://doi.org/10.1136/bmj.38565.415000.e01

Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Martindale, B., Orbach, G., & Morgan, C. (2002). Psychological treatments in schizophrenia: II. Meta-Analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychological Medicine, 32*(5), 783−791. https://doi.org/10.1017/S0033291702005640

Pitschel-Walz, G., Leucht, S., Bäuml, J., Kissling, W., & Engel, R. R. (2001). The effect of family interventions on relapse and rehospitalization in schizophrenia—A meta-analysis. *Schizophrenia Bulletin, 27*(1), 73–92. https://doi.org/10.1093/oxfordjournals.schbul.a006861

Ramsay, I. S., Fryer, S., Boos, A., Roach, B. J., Fisher, M., Loewy, R., Vinogradov, S., & Mathalon, D. H. (2018). Response to targeted cognitive training correlates with change in thalamic volume in a randomized trial for early schizophrenia. *Neuropsychopharmacology, 43*(3), 590–597. https://doi.org/10.1038/npp.2017.213

Remschmidt, H., & Theisen, F. M. (2005). Schizophrenia and related disorders in children and adolescents. *Journal of Neural Transmission, 69*, 121–141. https://doi.org/10.1007/3-211-31222-6_7. Supplement.

Reneses, B., Escudero, A., Tur, N., Agüera-Ortiz, L., Moreno, D. M., Saiz-Ruiz, J., Rey-Bruguera, M., Pando, M. F., Bravo-Ortiz, M. F., Moreno, A., Rey-Mejías, Á., & Singh, S. P. (2022). The black hole of the transition process: Dropout of care before transition age in adolescents. *European Child and Adolescent Psychiatry.* https://doi.org/10.1007/s00787-021-01939-8

Roberts, D. L., Penn, D. L., Labate, D., Margolis, S. A., & Sterne, A. (2010). Transportability and feasibility of social cognition and interaction training (SCIT) in community settings. *Behavioural and Cognitive Psychotherapy, 38*(1), 35–47. https://doi.org/10.1017/S1352465809990464

Robinson, D. G., Schooler, N. R., Correll, C. U., John, M., Kurian, B. T., Marcy, P., Miller, A. L., Pipes, R., Trivedi, M. H., & Kane, J. M. (2018). Psychopharmacological treatment in the RAISE-ETP study: Outcomes of a manual and computer decision support system based intervention. *American Journal of Psychiatry, 175*(2), 169–179. https://doi.org/10.1176/appi.ajp.2017.16080919. American Psychiatric Association.

Salomon, J. A., Vos, T., Hogan, D. R., Gagnon, M., Naghavi, M., Mokdad, A., Begum, N., Shah, R., Karyana, M., Kosen, S., Farje, M. R., Moncada, G., Dutta, A., Sazawal, S., Dyer, A., Seiler, J., Aboyans, V., Baker, L., Baxter, A., … Murray, C. J. (2012). Common values in assessing health outcomes from disease and injury: Disability weights measurement study for the global burden of disease study 2010. *The Lancet, 380*(9859), 2129–2143. https://doi.org/10.1016/s0140-6736(12)61680-8

Schimmelmann, B. G., Schmidt, S. J., Carbon, M., & Correll, C. U. (2013). Treatment of adolescents with early-onset schizophrenia spectrum disorders: In search of a rational, evidence-informed approach. *Current Opinion in Psychiatry, 26*(2), 219–230. https://doi.org/10.1097/YCO.0b013e32835dcc2a

Singh, S. P., Anderson, B., Liabo, K., & Ganeshamoorthy, T. (2016). Supporting young people in their transition to adults' services: Summary of NICE guidance. *BMJ, 353*, i2225. https://doi.org/10.1136/bmj.i2225

Sin, J., Jordan, C. D., Barley, E. A., Henderson, C., & Norman, I. (2015). Psychoeducation for siblings of people with severe mental illness. *Cochrane Database of Systematic Reviews, 2015*(5). https://doi.org/10.1002/14651858.CD010540.pub2

Sin, J., Moone, N., Harris, P., Scully, E., & Wellman, N. (2012). Understanding the experiences and service needs of siblings of individuals with first-episode psychosis: A phenomenological study. *Early Intervention in Psychiatry, 6*(1), 53–59. https://doi.org/10.1111/j.1751-7893.2011.00300.x

Siskind, D., Hahn, M., Correll, C. U., Fink-Jensen, A., Russell, A. W., Bak, N., Broberg, B. V., Larsen, J., Ishøy, P. L., Vilsbøll, T., Knop, F. K., Kisely, S., & Ebdrup, B. H. (2019). Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: A systematic review and individual participant data meta-analysis. *Diabetes, Obesity and Metabolism, 21*(2), 293–302. https://doi.org/10.1111/dom.13522

Smith, R. C., Leucht, S., & Davis, J. M. (2019). Maximizing response to first-line antipsychotics in schizophrenia: A review focused on finding from meta-analysis. *Psychopharmacology, 236*(2), 545–559. https://doi.org/10.1007/s00213-018-5133-z

Solmi, M., Fornaro, M., Ostinelli, E. G., Zangani, C., Croatto, G., Monaco, F., Krinitski, D., Fusar-Poli, P., & Correll, C. U. (2020). Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: A large scale systematic meta-review of 78 adverse effects. *World Psychiatry, 19*(2), 214−232. https://doi.org/10.1002/wps.20765

Spina, E., & de Leon, J. (2016). What is the role of CYP genotyping in psychiatry? *Evidence-Based Psychiatric Care, 2*, 108−122.

Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, P. (2016). Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: A systematic review. *Journal of Child and Adolescent Psychopharmacology, 26*(5), 410−427. https://doi.org/10.1089/cap.2015.0097

Stroup, T. S., Gerhard, T., Crystal, S., Huang, C., Tan, Z., Wall, M. M., Mathai, C., & Olfson, M. (2019). Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. *JAMA Psychiatry,* 76(5), 508−515. https://doi.org/10.1001/jamapsychiatry.2018.4489

Taipale, H., Mittendorfer-Rutz, E., Alexanderson, K., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., Enkusson, D., Leval, A., Sermon, J., Tanskanen, A., & Tiihonen, J. (2018). Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophrenia Research,* 197, 274−280. https://doi.org/10.1016/j.schres.2017.12.010

Tasaki, M., Yasui-Furukori, N., Yokoyama, S., Shinozaki, M., Sugawara, N., & Shimoda, K. (2021). Hypoprolactinemia and hyperprolactinemia in male schizophrenia patients treated with aripiprazole and risperidone and their relationships with testosterone levels. *Neuropsychopharmacology Reports, 41*(3), 379−384. https://doi.org/10.1002/npr2.12190

U. S. Food and Drug Administration. (2022). http://www.fda.gov/drugs.

Wagner, E., McMahon, L., Falkai, P., Hasan, A., & Siskind, D. (2020). Impact of smoking behavior on clozapine blood levels—A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica, 142*(6), 456−466. https://doi.org/10.1111/acps.13228

Wang, Y., Wang, D., Cheng, J., Fang, X., Chen, Y., Yu, L., Ren, J., Tian, Y., & Zhang, C. (2021). Efficacy and tolerability of pharmacological interventions on metabolic disturbance induced by atypical antipsychotics in adults: A systematic review and network meta-analysis. *Journal of Psychopharmacology, 35*(9), 1111−1119. https://doi.org/10.1177/02698811211035391

Wijesinghe, R. (2016). A review of pharmacokinetic and pharmacodynamic interactions with antipsychotics. *Mental Health Clinician, 6*(1), 21−27. https://doi.org/10.9740/mhc.2016.01.021

Wisdom, J. P., Manuel, J. I., & Drake, R. E. (2011). Substance use disorder among people with first-episode psychosis: A systematic review of course and treatment. *Psychiatric Services, 62*(9), 1007−1012. https://doi.org/10.1176/ps.62.9.pss6209_1007

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *American Journal of Psychiatry, 168*(5), 472−485. https://doi.org/10.1176/appi.ajp.2010.10060855

Wykes, T., & Spaulding, W. D. (2011). Thinking about the future cognitive remediation therapy–what works and could we do better? *Schizophrenia Bulletin, 37*(Suppl. 2), S80−S90. https://doi.org/10.1093/schbul/sbr064

Yu, Y., Shen, M., Niu, L., Liu, Y.e., Xiao, S., & Tebes, J. K. (2022). The relationship between clinical recovery and personal recovery among people living with schizophrenia: A serial mediation model and the role of disability and quality of life. *Schizophrenia Research, 239*, 168−175. https://doi.org/10.1016/j.schres.2021.11.043

Zheng, W., Li, X. B., Tang, Y. L., Xiang, Y. Q., Wang, C. Y., & De Leon, J. (2015). Metformin for weight gain and metabolic abnormalities associated with antipsychotic treatment: Meta-analysis of randomized placebo-controlled trials. *Journal of Clinical Psychopharmacology, 35*(5), 499−509. https://doi.org/10.1097/JCP.0000000000000392

Chapter 12

Long-term development and outcome of early-onset psychosis

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Introduction

When a young person is affected by a psychotic disorder, such as a schizophrenia spectrum disorder or an affective disorder with psychotic features, it has major implications for the individual, as well as for the family and friends. It is therefore crucial to focus on providing the best and most effective treatment that takes into account both the needs of the patient and his or her family. Questions that often arise both for the patient and the family are: How bad is this going to be? How long will it last? Will I be able to study and work again? Will my life be as I expected, or will I have to deal with a completely different perspective? For the mental health service providers, the answers to these questions are important when planning for how long a young person should be treated in the primary health care sector (e.g., private psychiatric practices and general practitioners) or the secondary health care sector (e.g., outpatient and inpatient psychiatric hospitals), and when planning what kind of social support that is needed.

Today, schizophrenia and related psychotic disorders are mainly considered to be neurodevelopmental disorders, with developmental abnormalities observable from early childhood before the onset of psychotic illness (Bora & Murray, 2014; Mollon & Reichenberg, 2018). However, previously the majority of scholars considered schizophrenia to be a neurodegenerative disorder (Kraepelin, 1919) with a very poor anticipated prognosis for the affected individuals who were in need of long-term hospitalization. These pessimistic

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00009-3

expectations were to some degree founded on "the clinicians' illusion", meaning that clinicians can get a negatively biased impression of the prognosis as they mainly see the proportion of patients with the worst prognosis and the highest need of treatment (Cohen & Cohen, 1984). When population-based follow-up studies became available, the picture became more nuanced. In this chapter, we will review current knowledge about the prognosis in different areas of outcomes for adolescents with psychotic disorders.

Sociodemographics

Labor market affiliation, education, and income

As psychotic illnesses often occur early in life, they have serious consequences for educational achievement and labor market affiliation. A review of employment status among patients with schizophrenia found that the exclusion from the labor market was one of the major obstacles for social inclusion and a significant cause of stigma (Marwaha & Johnson, 2004). In the review, reported employment rates for persons diagnosed with schizophrenia varied widely between studies, from 8% to 35% in European studies (most studies reported between 10% and 20%), with developing countries in general reporting higher employment rates (Marwaha & Johnson, 2004). Furthermore, the review found that over the last 50 years, the difference in employment rates between persons with a psychotic disorder and the general population has increased. However, the findings were hampered by the large discrepancy in the reported data (e.g., description of employment and diagnosis) (Marwaha & Johnson, 2004). Therefore, register-based studies might present a more reliable way to assess employment rates for patients diagnosed with a psychotic disorder.

In recent years, the proportion of individuals with schizophrenia spectrum disorders in Denmark in education or unsupported regular employment has increased (KL, 2017). Still, the employment rate is relatively low. A Danish nationwide register-based study showed that 25% of individuals with early-onset schizophrenia (diagnosed before age 18 years) were in education or employed in unsupported work (6% education; 19% unsupported work) in the last year of follow-up (mean follow-up was 9.5 ± 5.0 years) (Vernal et al., 2020). This was slightly more than for individuals diagnosed with schizophrenia in adulthood, where 17% were in education or employed in unsupported work (2% education; 15% unsupported work) (Vernal et al., 2020). The increased employment rate among patients with psychosis in Denmark might be due to possibilities of reduced-hours jobs and employment support. For individuals in Denmark with onset of schizophrenia between 15 and 25 years of age, the cumulative earning between ages 25 and 61 years is 14% of the amount earned by individuals not diagnosed with schizophrenia (Hakulinen et al., 2019). Some individuals with a less chronic course of schizophrenia (i.e., not receiving treatment in a psychiatric inpatient or outpatient clinic after

the age of 25 years) have a higher working capacity. Of those, the cumulative income is 39% of the amount earned by same-age individuals not diagnosed with schizophrenia (Hakulinen et al., 2019).

Suffering from a psychotic illness severely affects the possibility of later employment, and there is a large potential socioeconomic gain as well as potential gain in personal well-being by increasing the access to the labor market. The likelihood of being employed is affected by several factors with regard to the individual course of the illness but also to society and the organization of the labor market and social benefits. The large discrepancies in reported employment rates indicate that for many it is not only an intrinsic illness factor that makes them unable to work, and that social factors may be at least as important. Among others, stigmatization, low self-confidence, and lack of vocational support are mentioned by individuals with schizophrenia as barriers to obtaining or maintaining employment (Marwaha & Johnson, 2004). Clinicians should therefore not adopt a fatalistic approach to new patients, but remember that most patients with a first-episode psychosis want to work, and that interventions that are effective in helping people with severe mental illnesses have been developed (Christensen et al., 2019; Rinaldi et al., 2010).

Children and cohabitation

Reduced fertility rates among individuals with psychotic disorders have been confirmed in several studies. Recently, a Danish nationwide cohort study found reduced fertility rates among individuals from 15 years of age diagnosed with schizophrenia, followed by bipolar disorder, major depressive disorder, and the remaining psychiatric disorders consisting of all other admissions to psychiatric hospitals, including personality disorders (Laursen & Munk-Olsen, 2010). Men with schizophrenia spectrum disorders had the lowest observed fertility rate compared to the general population. Furthermore, the reproductive rate increased with time since first psychiatric admission. This could suggest a selection mechanism where individuals with less symptoms tend to have more children. At the 10-year follow-up of the UK-based AESOP study (Etiology and Ethnicity in Schizophrenia and Other Psychosis; a naturalistic population-based cohort of 295 individuals with a first episode psychosis), 44.5% had become parents, and the majority of these lived with their underaged children (Dazzan et al., 2020). Still, another Danish nationwide study found that mothers and fathers diagnosed with schizophrenia had a 40% and 20%, respectively, higher risk of having their children placed in out-of-home care (Ranning et al., 2015). In addition, the risk of having a child placed in out-of-home care increased among single parents compared to cohabiting parents (Ranning et al., 2015). Since more women than men have single parent status, this might contribute to the gender difference where more women than men have their children placed in out-of-home care. Furthermore, fathers seem to compensate less for the mother's lack of caregiving, whereas

mothers tend to compensate if the father is ill (Ranning et al., 2015). A third Danish cohort study including parents diagnosed with schizophrenia and bipolar disorder, found that around 50% of spouses to individuals with schizophrenia presented with a mental disorder (Greve et al., 2021). In summary, individuals with psychotic disorders have significantly lower fertility compared to the general population. Even so, a considerable proportion of individuals with psychotic disorders become parents (Campbell et al., 2012; Howard et al., 2004; Maybery & Reupert, 2018; Schrank et al., 2016). Although parents with a psychotic disorder have increased risk of having their child placed in out-of-home care, the majority (based on studies from the UK and Denmark) live and provide for their underaged children (Dazzan et al., 2020; Ranning et al., 2015).

Service use

For patients diagnosed with schizophrenia, the use of in-patient services is highest in the first years after treatment contact. In the following years, the mean use of bed days decreases and more than half of first-episode patients have no hospitalizations after the first 2 years, and 6%−10% will live in supported housing facilities (Secher et al., 2015). However, there is a large heterogeneity in service use, and the average number covers a huge difference in need of services. Compared to patients with adult-onset schizophrenia, adolescents with early-onset schizophrenia spend more days hospitalized during the first years after being diagnosed, but the number of annual days hospitalized do not differ thereafter compared to adults (Vernal et al., 2020). This might be due to different procedures in child and adolescent versus adult psychiatric services and may not necessarily be due to a more severe manifestation of schizophrenia in children and adolescents. The use of bed days in psychiatric hospitals and supported housing facilities is highly depended on available services and whether a health insurance is needed to get access to these services. The aforementioned numbers are from register-based studies from Denmark, where services are universally available, free of charge for the individual and financed by taxes.

Substance abuse

Individuals diagnosed with a psychotic disorder more frequently have substance use disorders compared to individuals without psychosis. In fact, approximately one-third of children and adolescents with schizophrenia spectrum disorders meet the criteria of a substance use disorder including alcohol, illicit drugs, and other substances, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) criteria of substance use disorder (Stentebjerg-Olesen et al., 2016). Studies of adult patients have found robust associations

between substance abuse and the risk of developing schizophrenia later in life (Moore et al., 2007; Nielsen et al., 2017). This association is found for almost any kind of substance abuse, including alcohol, but it is strongest for cannabis (Nielsen et al., 2017). In adults, a diagnosis of schizophrenia is also associated with later development of subsequent substance use disorder (Petersen et al., 2019).

Only a few studies have examined longitudinal associations between early-onset psychosis and substance abuse. A Danish nationwide register-based study found that 22% of patients with early-onset schizophrenia had a comorbid substance use disorder at follow-up (mean follow-up was 9.5 ± 5.0 years) compared to 6% premorbid the psychosis diagnosis (Vernal et al., 2020). These results indicate that the frequency of substance use disorders increases in the years following a diagnosis of schizophrenia. However, this study was restricted to hospital-based diagnoses which hold low sensitivity, as many individuals meet criteria of a substance used disorder without being diagnosed (Hansen et al., 2000), resulting in a low incidence of substance use disorders. Moreover, the results should be seen in relation to the young age of the individuals with early-onset schizophrenia as substance use disorders are typically diagnosed later in life.

Comorbid substance use is linked to poorer outcomes in patients with psychotic disorders. Cannabis use is associated, in a dose−response relationship, to symptom severity and functional impairments in adolescents with early-onset psychosis (Bagot et al., 2015). Thus, individuals who initiate cannabis use early and are frequent users are at increased risk of severe outcomes. Furthermore, individuals who discontinue substance use after being diagnosed with a psychotic disorder have outcomes similar to individuals with a psychotic disorder who have never used substances (Clausen et al., 2014; Weibell et al., 2017). Therefore, an integrated treatment and prevention plan for substance use in adolescents with early-onset psychosis is important and an effective way to improve outcomes among these patients.

Mortality and suicidality

Schizophrenia is associated with increased mortality from all causes of death. The overall mortality rate in patients with schizophrenia is approximately three times higher and their life expectancy is 10−15 years shorter, than in the general population (Laursen et al., 2019; Nordentoft et al., 2013; Plana-Ripoll et al., 2019). This excess risk is partly explained by death from suicide and accidents, but also by death due to medical conditions such as cardiovascular disorders and cancer. In Danish register-based cohort studies, patients with schizophrenia have approximately three times higher risk of dying from a medical condition compared to the general population, while the risk of dying from accidents is approximately six times higher, and the risk of suicide is between 15 and 30 times higher (Laursen et al., 2019; Nordentoft et al., 2013;

Plana-Ripoll et al., 2019). The overall mortality rate was generally higher for men than for women with schizophrenia. Furthermore, when looking at survival curves among Danish individuals at 60 years of age, approximately 10% of individuals from the general population had died compared to 30% of individuals with schizophrenia (Laursen et al., 2019).

Another Danish register-based cohort study found that death secondary to a medical condition typically occurs when patients with schizophrenia are in their 50s or 60s, while the same occurs one to two decades later in life for individuals from the general population (Erlangsen et al., 2017).

Based on proportions of mortality, the risk of dying from suicide was previously estimated to be as high as 10% for patients diagnosed with schizophrenia (Miles, 1977). However, more appropriate measures, such as case fatality rates, have shown that the long-term risk of suicide is rather 5%–6%, but increases if the patients have a history of suicide attempt (Nordentoft et al., 2011; Palmer et al., 2005). Already before first contact with psychiatric services, almost one-third of adult patients with schizophrenia have attempted suicide, most of them within the last year before first contact (Bertelsen et al., 2007), and the first years after first contact are associated with higher risk than later years (Nordentoft et al., 2011). Therefore, it is of outmost importance that suicide prevention is integrated as a mandatory element in the treatment of first-episode psychosis.

Medication

A Cochrane review from 2013 consisting of 13 trials of adolescent patients with psychotic disorders between 13 and 18 years of age found no convincing difference of efficacy between first- and second-generation antipsychotics in the treatment of adolescent psychosis (Kumar et al., 2013). The review could only conclude regarding short-term effects as there were no long-term studies included, and the overall findings were hampered by the low number of studies. However, a network meta-analysis from 2016 including 11 randomized controlled trials of adolescent patients with early-onset schizophrenia aged between 10 and 17 years (five of the studies were also included in the prior mentioned Cochrane review) published between 2003 and 2013, indicated that haloperidol, a first-generation antipsychotic, was the most effective treatment of psychosis, but also the drug that the participants were most likely to discontinue (Harvey et al., 2016). As the effect of haloperidol was driven by one study which included a total of 39 patients, the results should be interpreted with caution. There are only a few studies comparing the efficacy of long-term antipsychotic drug treatment in adolescent patients with psychotic disorders. In the Danish Tolerability and Efficacy of Antipsychotics randomized controlled trial (TEA-trial), the treatment effects of the second-generation antipsychotics quetiapine and aripiprazole were compared in children and adolescents (Pagsberg et al., 2017). The study found no significant difference between the

two agents in rate of positive psychotic symptoms after 12 weeks of treatment (Pagsberg et al., 2017). A naturalistic study including 47 adolescent patients with schizophrenia and schizoaffective disorder (mean age of 15.5 years) performed follow-up assessments after 6 months, 3, 5, 8, and 11 years, with assessments of treatment effectiveness of various antipsychotics and clinical improvements on psychotic symptoms and long-term functioning (Cianchetti & Ledda, 2011). Two participants discontinued their medication and remained in remission until the end of the follow-up period after 11 years. Of the remaining participants, all but one had trials of at least two antipsychotics. Clozapine was found to be superior to all other included drugs, both in treatment efficacy and in time to discontinuation. Only 20% of participants who initiated clozapine treatment discontinued, compared to 100% of olanzapine, 86% of haloperidol, and 72% of risperidone treated patients (Cianchetti & Ledda, 2011). Due to potential severe adverse side effects (Iqbal et al., 2003), clozapine is considered a third choice in most treatment algorithms, but there are studies indicating that clozapine has a unique effect in patients with refractory early-onset psychosis (Sporn et al., 2007). These findings are supported in meta-analyses of clozapine treatment demonstrating that younger age is a positive predictor of response to clozapine (Okhuijsen-Pfeifer et al., 2020). Long-term follow-up studies of patients with first-episode psychosis show that 40% of patients do not continue their antipsychotic treatment (Gotfredsen et al., 2017). This finding is in stark contrast to discontinuation studies reporting that 70–90% of patients with schizophrenia who discontinue their antipsychotic medication suffer a psychotic relapse (Thompson et al., 2018; Zipursky et al., 2014). This gap in knowledge has not been fully explained, but there are now several ongoing trials testing gradual dose reduction compared to maintenance treatment in remitted first-episode patients (Wunderink et al., 2013).

All patients with a psychotic disorder are likely to, at some time point, discontinue their antipsychotic treatment. There is no clear evidence as to how long antipsychotic treatment should be continued after a psychotic episode, but current guidelines suggest 1–2 years of treatment after remission. This is often unacceptable to patients and might be especially true for adolescent patients who might be more sensitive to adverse side effects from antipsychotics such as weight gain, extrapyramidal symptoms, sedation, increased prolactin, and metabolic disturbances (Correll, 2011; Fraguas et al., 2011; Kumar et al., 2013). Therefore, management of antipsychotic treatment requires strict attention to possible side effects, choice of drug, and titration of doses.

Cognition

Cognitive deficits are recognized as a core symptom of schizophrenia, and to a lesser degree of other psychotic disorders (Heinrichs & Zakzanis, 1998). The controversy regarding cognitive deficits has been conceptualized as a debate between the neurodevelopmental and the neurodegenerative hypotheses

(Kurtz, 2005). While most investigators agree that cognitive deficits are found in children prior to the development of adult schizophrenia (Reichenberg et al., 2010), others have found that there is a continued deterioration just prior and after the onset of psychosis among adult individuals diagnosed with chronic and first episode schizophrenia (Pantelis et al., 2009). Meta-analytic data have also shown cognitive deficits in patients with clinical high-risk for psychosis and that the conversion to psychosis was predicted by deficits in the domains of verbal fluency, verbal and visual memory, and working memory (Poli, 2014). However, this does not necessarily imply that there is a decline from at-risk state to full-blown psychosis. In another meta-analysis, Bora and Murray found that the level of cognitive functioning increased over time both in individuals at clinical high-risk and with first-episode psychosis (Bora & Murray, 2014). Similar findings have been found in the Danish OPUS study, a randomized controlled trial examining early intervention services among 578 individuals with psychotic disorders (mean age was 27 years) (Bergh et al., 2016). A 10-year follow-up from this study demonstrated that treatment in early intervention services improved cognitive functioning compared to treatment as usual (Bergh et al., 2016).

Moreover, several studies have found stable cognitive deficits over time in patients with schizophrenia (Kurtz, 2005), at least in young and middle-aged patients. The Chicago follow-up study which included patients between 17 and 32 years of age (mean age was 22.9 years) with schizophrenia, other psychotic disorders, and major depressive disorder without psychotic features, found stable cognitive deficits or a slight improvement in cognitive outcomes over a 20-year follow-up period (Bonner-Jackson et al., 2010). Contrary to these findings, in one of the most recent long-term follow-up studies of first-episode patients (the Suffolk Mental Health Study), a declining level of cognitive functioning was found among patients with first admissions for psychosis from 15 to 60 years of age over a 20-year period (Fett et al., 2020). In this study, the patients with schizophrenia demonstrated a greater decline in cognitive functioning compared to patients with affective psychosis and other psychotic disorders at both the 2-year and the 20-year follow-up. Notably, over the 18 years period, there was no change in verbal fluency in any of the patient groups. However, there was a significant increase in verbal knowledge, and significant decline in the other cognitive domains (i.e., verbal/visual memory, attention, processing speed, and executive functions) for all patient groups. The magnitude of cognitive change was generally not associated with age at baseline, but the impairment became more prominent with age compared with healthy controls (Fett et al., 2020).

When assessing cognitive functioning over time in patients with psychotic disorders, the results are most likely influenced, either positively or negatively, by the use of antipsychotic medication. A network meta-analysis including nine randomized controlled trials examined the long-term (median trial duration of 1 year) cognitive effects of antipsychotic treatment in

patients with schizophrenia. The second-generation antipsychotics quetiapine, olanzapine, and risperidone demonstrated significantly better effects on global cognitive functioning compared to amisulpride (second-generation) and haloperidol (first-generation) (Désaméricq et al., 2014). Contrary to the aforementioned meta-analysis, a naturalistic follow-up study of 186 adult participants diagnosed with schizophrenia reported improved cognitive functioning with discontinuation of antipsychotics at baseline and after 3.5 years (Albert et al., 2019). During the follow-up, the patients who discontinued their antipsychotic medication improved significantly more in all cognitive domains, including motor task, processing speed, and verbal fluency, compared to those with sustained use of antipsychotics (Albert et al., 2019). This finding is hampered by the fact that those patients who discontinue their medication without experiencing a psychotic relapse probably belong to a selected subsample. There is one meta-analysis of 4135 patients with schizophrenia particularly examining processing speed, which found that higher doses of antipsychotics were associated with greater impairment in processing speed (Knowles et al., 2010). Unfortunately, detailed information on type of antipsychotics was not reported. However, there were no moderating effects of age or chronicity of psychosis. Also, a randomized controlled trial including 42 participants randomized to maintenance treatment or guided discontinuation, found improved cognitive performance for both groups after 4 to 6 months of follow-up in the attention, working memory, verbal memory, processing, and motor speed domains. In addition, the group randomized to guided discontinuation improved significantly more than the maintenance group in the processing speed domain (Faber et al., 2012). This finding indicates that at least the processing speed domain is affected by the use and dosage of antipsychotic medication.

In summary, there is consistent evidence for cognitive impairments in patients diagnosed with a psychotic disorder, and that symptoms are present prior to onset of psychosis. Currently, the consensus is that these deficits are rather stable over time, but there seems to be evidence of an accelerated decline with age compared to healthy controls (Fett et al., 2020). The effect of antipsychotic medication on cognitive performance is understudied, and there is indication that some of the deficits can be affected by the use of antipsychotic medication.

Long-term prognosis

Clinical predictors of outcomes

Of all individuals diagnosed with schizophrenia, only about 5% are diagnosed before they turn 18 years (Stenstrøm et al., 2010; Thomsen, 1996; Thorup et al.,

2007). Still, there is scientific evidence that individuals with adolescent- and adult-onset psychosis largely share the same clinical predictors of outcome.

A systematic review from 2016 compared patients with early- and adult-onset psychosis and found a greater proportion of schizophrenia spectrum diagnoses in the early-onset group (Stentebjerg-Olesen et al., 2016). This review was based on five clinical studies from Australia, Canada, and Norway, consisting of 353 patients with early-onset psychosis (mean age at onset was 16.2 years), and 1220 patients with adult-onset psychosis (mean age at onset was 23.5 years) (Stentebjerg-Olesen et al., 2016). At baseline, the early-onset group had a 3.5 times longer duration of untreated psychosis compared to the adult-onset group (18.7 ± 6.2 months vs. 5.4 ± 3.1 months) (Stentebjerg-Olesen et al., 2016). From the same systematic review, another analysis based on 28 studies including 1505 patients found that longer duration of untreated psychosis significantly predicted less improvement in global functioning. Still, the mean global functioning scores improved over time. Moreover, good premorbid adjustment, such as high-quality peer relationships and good school performance at baseline, predicted better outcomes after 1–4 years of follow-up on various parameters including remission rates, quality of life, and global and social functioning. In addition, poor premorbid adjustment or developmental delays predicted higher negative symptoms and worse illness severity at follow-up. Furthermore, higher scores of negative and positive symptoms at baseline predicted worse symptom severity at follow-up. On the other hand, lower scores of negative symptoms at baseline predicted higher remission rates and better social functioning after 1–4 years, while lower scores of positive symptoms at baseline predicted better quality of life after 1–4 years (Stentebjerg-Olesen et al., 2016). Gender or age at onset was not found to have any significant effects on the course of illness among adolescents (Stentebjerg-Olesen et al., 2016). The effects of gender differences were also investigated in another systematic review from 2012 including 21 studies of individuals with early-onset schizophrenia (Clemmensen et al., 2012). Here, the authors found that males generally had less favorable outcomes, but this result should be interpreted with caution since only five of the 21 studies reported outcomes stratified for gender.

In summary, systematic review data of patients with early-onset psychosis found a greater incidence of schizophrenia spectrum disorders and longer duration of untreated psychosis among adolescent patients compared to patients with adult-onset psychosis. In accordance with the adult literature, a longer duration of untreated illness, a diagnosis of schizophrenia, poorer premorbid adjustment, and greater symptom severity (most pronounced for negative symptoms) at baseline were all found to be predictors of worse clinical outcomes. In addition, there was no evidence for age-related differences in the course of illness among adolescents with psychosis. Furthermore,

gender among adolescents with early-onset psychosis has not been found to be a consistent predictor on the course of illness.

Positive and negative symptoms

In the adult literature, baseline psychotic symptoms or early psychopathology is often a prognostic factor of long-term outcomes. At the 10-year follow-up of the OPUS trial, a longer duration of untreated psychosis predicted higher level of positive symptoms at follow-up (Austin et al., 2015). Still, more than 70% of patients achieved a significant reduction of positive symptoms at the 10-year follow-up. The majority of these patients achieved this reduction of positive symptoms within the first year of treatment and had mild or no positive symptoms at the 10-year follow-up (Austin et al., 2015). For negative symptoms, the prognosis was less optimistic. Fifty percent of individuals had no reduction of negative symptoms during the 10-year period, and for the 28% who experienced a reduction in negative symptoms, only minor changes were detected (Austin et al., 2015). As previously mentioned, a higher level of negative symptoms at baseline often predicts worse long-term outcomes. Systematic reviews of adolescents with psychotic disorders found that a higher level of psychotic symptom severity at baseline, especially pronounced for negative symptoms, predicted worse illness severity and poor outcomes at follow-up (Díaz-Caneja et al., 2015; Stentebjerg-Olesen et al., 2016). Furthermore, a diagnosis of schizophrenia was associated with less improvement of negative symptoms (Stentebjerg-Olesen et al., 2016) and greater disability or dependency at follow-up (Albert et al., 2019). One systematic review reported symptom dimensions at baseline and found that the most frequent symptoms recorded among adolescents were auditory hallucinations (Stentebjerg-Olesen et al., 2016). Also, delusions followed by thought disorders and bizarre behavior were common (Stentebjerg-Olesen et al., 2016). Furthermore, around 50% had negative symptoms at baseline and 52% experienced flat/blunted affect (Stentebjerg-Olesen et al., 2016). In summary, psychotic symptom severity and predominantly negative symptoms are closely related to clinical outcomes including remission and recovery. Since adolescents tend to have a higher prevalence of negative symptoms at diagnosis onset, they are a particularly vulnerable group.

Recovery

A systematic review from 2012 including 21 studies of individuals with early-onset schizophrenia (n = 422, mean age at onset was 16.4 years) found that 15.4% of patients had a good outcome, 24.5% had a moderate outcome, and 60% had a poor outcome based on general-, global-, and study specific functioning scales (Clemmensen et al., 2012). However, there was a small but

significant decrease in good and moderate outcomes and an increase in poor outcome the longer the follow-up time.

For "mixed samples" (i.e., studies of individuals with combined data on early-onset schizophrenia and other early-onset psychotic disorders), 19.6% were in the good outcome category, 33.6% had a moderate outcome, and 46.8% had a poor outcome. When comparing the two groups, there were significant differences with a larger part of mixed samples experiencing a good or moderate outcome in comparison with those with strictly early-onset schizophrenia (Clemmensen et al., 2012). This finding has been verified by other studies where a diagnosis of schizophrenia takes a more chronic and disabling course compared to affective psychosis (Henry et al., 2010).

A meta-analysis focusing on individuals with schizophrenia spectrum disorders with onset after 16 years of age found a 13.5% recovery rate (Jääskeläinen et al., 2013). The recovery definition was strictly defined as both clinical and social functioning with a 2-year duration criterion of good outcome for either clinical or social outcome. Here, there was no difference in the recovery rate according to gender, follow-up time, first-episode psychosis, or multi-episode samples. In another meta-analysis from 2017, Lally and colleagues investigated recovery in patients over 16 years of age with first-episode psychosis (Lally et al., 2017). Based on 35 included studies, the authors identified an overall recovery rate of 38% among the patients across diagnostic group. When stratifying the sample, the authors found that 85% of individuals with affective psychosis (four studies) achieved recovery, compared to 34% of patients with nonaffective psychosis (19 studies), and 30% of patients with schizophrenia (12 studies). In a third meta-analysis including adult patients with schizophrenia, no associations were found between age at onset and clinical outcomes, such as remission rates, positive symptoms, and total symptom severity (Immonen et al., 2017). Small but significant correlations were found between lower age at onset and more hospitalizations and relapses, and between poorer social/occupational functioning and reduced global outcomes. These studies are far from conclusive, and in a Danish long-term nationwide register-based study of 16,337 people, there was no evidence that individuals with early-onset psychosis had a generally poorer outcome than individuals with adult-onset psychosis (Vernal et al., 2020). The aforementioned studies demonstrate that psychosis is not a progressive deteriorating illness but rather a cardinal feature in a spectrum of illnesses where the percentage of patients who recover varies widely. This variation is both due to the severity of the diagnosis as well as the definition and duration criteria of "good" outcome. Earlier, the prevailing view was that early-onset psychosis was associated with chronic impairment and disabling outcomes. However, a great part of the literature lacked long-term follow-up investigations and most studies used small sample sizes with the risk of selection bias as well as poor representativeness. In addition, a substantial part of the studies contains

individuals diagnosed many decades ago which influences the poor long-term prognosis.

Overall, the findings confirm the importance of early intervention services, which has proven to be highly effective on several clinical outcomes compared to treatment as usual. A meta-analysis based on 10 randomized controlled trials (six of the trials included patients under the age of 18 years and total mean age was 27.5 years) found convincing effects of early intervention services in psychosis on all of the following: psychiatric hospitalization; global functioning, including school attendance and work employment; symptom severity; remission; and clinical recovery (Correll et al., 2018). Furthermore, it appears that early intervention services might even be more beneficial to young individuals with the possibility of greater improvement of long-term functional outcomes compared to patients with adult-onset schizophrenia (Amminger et al., 2011). In sum, since adolescents with early-onset psychosis have a higher prevalence of unfavorable predictors of outcomes at baseline, such as longer duration of untreated illness, a diagnosis of schizophrenia, poorer premorbid adjustment and negative symptoms, they also have a potential for worse outcomes compared to patients with adult-onset psychosis. Still, findings are not consistent, and there is no consensus in the newer literature that those who develop psychosis at a younger age suffer a worse outcome than those who develop psychosis at an older age.

Conclusion

At the age of 16, K was referred by his general practitioner to an early psychosis detection unit in Denmark. He reported depressed mood, auditory hallucinations, and suicidal thoughts, and he was referred to the child and adolescence department for further examination and treatment. K showed problems with social interactions and lack of adequate affective responses to serious suicidal act. He was diagnosed with Asperger syndrome and treated with sertraline for depressive symptoms. After nearly 1½ years of treatment, his mood improved, and he started a special educational school for people with autism spectrum disorder (i.e., *a school that focuses on individual special needs to improve the chances on the ordinary labor market among young individuals who have not yet obtained a youth education). When K was 19 years of age, he saw a private consultant psychiatrist who diagnosed K with attention deficit disorder and prescribed atomoxetine. A month later, K was submitted to the psychiatric ward with suicidal thoughts. K described an acute sense of anxiety when being around many people, but he was unable to describe why he was anxious. On further investigation, he reported that he had audible thoughts which sometimes were so loud that other people could hear them. On a weekly basis he also experienced external thoughts being placed in his head, and he suspected that his parents were putting them there. K had experienced these symptoms for more than a year and had not experienced a*

worsening of symptoms after being prescribed atomoxetine. K was diagnosed with paranoid schizophrenia and the diagnoses of attention deficit disorder and Asperger syndrome were removed. Furthermore, K was prescribed aripiprazole and referred to an early intervention and treatment unit where he received long acting injectables and subsequently reported reduction of auditory hallucinations and cessation of though insertions.

In the safe space of hindsight, it is easy to point out that the psychotic symptoms K reported at age 16 years should have been more thoroughly investigated. But the meaning of this story is not to point fingers, but rather illustrate the complexity of the clinical world and how the clinicians' approaches are shaped by the institutions where they work and the patients they usually treat.

In conclusion, we will emphasize that a diagnosis of psychosis is a wide spectrum of different diagnoses and therefore the course and outcome of these illnesses are rather heterogeneous. Overall, it is important to provide early intervention in all ages no matter the age of psychosis onset in order to improve long-term outcomes. Since so many studies report longer duration of untreated illness among adolescents, it might indicate a treatment gap with room for improvement for both early detection of psychosis as well as starting early treatment for individuals with early-onset psychosis.

Acknowledgments

The authors declare no conflicts of interest.

References

Albert, N., Randers, L., Allott, K., Jensen, H. D., Melau, M., Hjorthoj, C., & Nordentoft, M. (2019). Cognitive functioning following discontinuation of antipsychotic medication. A naturalistic sub-group analysis from the OPUS II trial. *Psychological Medicine, 49*(7), 1138−1147. https://doi.org/10.1017/S0033291718001836

American Psychiatric Association. (2000). *Diagnostic and statistical Manual of mental disorders (DSM-IV)*. American Psychiatric Association.

Amminger, G. P., Henry, L. P., Harrigan, S. M., Harris, M. G., Alvarez-Jimenez, M., Herrman, H., Jackson, H. J., & Mcgorry, P. D. (2011). Outcome in early-onset schizophrenia revisited: Findings from the early psychosis prevention and intervention centre long-term follow-up study. *Schizophrenia Research, 131*(1−3), 112−119. https://doi.org/10.1016/j.schres.2011.06.009

Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., & Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10year follow-up study in the OPUS cohort. *Schizophrenia Research, 168*(1−2), 84−91. https://doi.org/10.1016/j.schres.2015.07.021

Bagot, K. S., Milin, R., & Kaminer, Y. (2015). Adolescent initiation of cannabis use and early-onset psychosis. *Substance Abuse, 36*(4), 524−533. https://doi.org/10.1080/08897077.2014.995332

Bergh, S., Hjorthøj, C., Sørensen, H. J., Fagerlund, B., Austin, S., Secher, R. G., Jepsen, J. R., & Nordentoft, M. (2016). Predictors and longitudinal course of cognitive functioning in

schizophrenia spectrum disorders, 10 years after baseline: The OPUS study. *Schizophrenia Research, 175*(1−3), 57−63. https://doi.org/10.1016/j.schres.2016.03.025

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlæger, J., Le Quach, P., Christensen, T.Ø., Krarup, G., Jørgensen, P., & Nordentoft, M. (2007). Suicidal behaviour and mortality in first-episode psychosis: The OPUS trial. *British Journal of Psychiatry, 191*(51), s140−s146. https://doi.org/10.1192/bjp.191.51.s140

Bonner-Jackson, A., Grossman, L. S., Harrow, M., & Rosen, C. (2010). Neurocognition in schizophrenia: A 20-year multi-follow-up of the course of processing speed and stored knowledge. *Comprehensive Psychiatry, 51*(5), 471−479. https://doi.org/10.1016/j.comppsych.2010.02.005

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin, 40*(4), 744−755. https://doi.org/10.1093/schbul/sbt085

Campbell, L., Hanlon, M. C., Poon, A. W. C., Paolini, S., Stone, M., Galletly, C., Stain, H. J., & Cohen, M. (2012). The experiences of Australian parents with psychosis: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry, 46*(9), 890−900. https://doi.org/10.1177/0004867412455108

Christensen, T. N., Wallstrøm, I. G., Stenager, E., Bojesen, A. B., Gluud, C., Nordentoft, M., & Eplov, L. F. (2019). Effects of individual placement and support supplemented with cognitive remediation and work-focused social skills training for people with severe mental illness: A randomized clinical trial. *JAMA Psychiatry, 76*(12), 1232−1240. https://doi.org/10.1001/jamapsychiatry.2019.2291

Cianchetti, C., & Ledda, M. G. (2011). Effectiveness and safety of antipsychotics in early onset psychoses: A long-term comparison. *Psychiatry Research, 189*(3), 349−356. https://doi.org/10.1016/j.psychres.2011.03.020

Clausen, L., Hjorthoj, C. R., Thorup, A., Jeppesen, P., Petersen, L., Bertelsen, M., & Nordentoft, M. (2014). Change in cannabis use, clinical symptoms and social functioning among patients with first-episode psychosis: A 5-year follow-up study of patients in the OPUS trial. *Psychological Medicine, 44*(1), 117−126. https://doi.org/10.1017/S0033291713000433

Clemmensen, L., Vernal, D. L., & Steinhausen, H. C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry*, 12. https://doi.org/10.1186/1471-244X-12-150

Cohen, P., & Cohen, J. (1984). The clinician's illusion. *Archives of General Psychiatry, 41*(12), 1178−1182. https://doi.org/10.1001/archpsyc.1984.01790230064010

Correll, C. U. (2011). Addressing adverse effects of antipsychotic treatment in young patients with schizophrenia. *The Journal of Clinical Psychiatry, 72*(1), e01. https://doi.org/10.4088/JCP.9101tx6c

Correll, C. U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., Craig, T. J., Nordentoft, M., Srihari, V. H., Guloksuz, S., Hui, C. L. M., Chen, E. Y. H., Valencia, M., Juarez, F., Robinson, D. G., Schooler, N. R., Brunette, M. F., Mueser, K. T., Rosenheck, R. A., … Kane, J. M. (2018). Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry, 75*(6), 555−565. https://doi.org/10.1001/jamapsychiatry.2018.0623

Dazzan, P., Lappin, J. M., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., Onyejiaka, A., Croudace, T., Jones, P. B., Murray, R. M., Fearon, P., Doody, G. A., & Morgan, C. (2020). Symptom remission at 12-weeks strongly predicts long-term recovery from the first episode of psychosis. *Psychological Medicine, 50*(9), 1452−1462. https://doi.org/10.1017/S0033291719001399

Désaméricq, G., Schurhoff, F., Meary, A., Szöke, A., Macquin-Mavier, I., Bachoud-Lévi, A. C., & Maison, P. (2014). Long-term neurocognitive effects of antipsychotics in schizophrenia: A network meta-analysis. *European Journal of Clinical Pharmacology, 70*(2), 127−134. https://doi.org/10.1007/s00228-013-1600-y

Díaz-Caneja, C. M., Pina-Camacho, L., Rodríguez-Quiroga, A., Fraguas, D., Parellada, M., & Arango, C. (2015). Predictors of outcome in early-onset psychosis: A systematic review. *NPJ Schizophrenia, 1*(1). https://doi.org/10.1038/npjschz.2014.5

Erlangsen, A., Andersen, P. K., Toender, A., Laursen, T. M., Nordentoft, M., & Canudas-Romo, V. (2017). Cause-specific life-years lost in people with mental disorders: A nationwide, register-based cohort study. *The Lancet Psychiatry, 4*(12), 937−945. https://doi.org/10.1016/S2215-0366(17)30429-7

Faber, G., Smid, H. G. O. M., Van Gool, A. R., Wiersma, D., & Van Den Bosch, R. J. (2012). The effects of guided discontinuation of antipsychotics on neurocognition in first onset psychosis. *European Psychiatry, 27*(4), 275−280. https://doi.org/10.1016/j.eurpsy.2011.02.003

Fett, A. K. J., Velthorst, E., Reichenberg, A., Ruggero, C. J., Callahan, J. L., Fochtmann, L. J., Carlson, G. A., Perlman, G., Bromet, E. J., & Kotov, R. (2020). Long-term changes in cognitive functioning in individuals with psychotic disorders: Findings from the Suffolk county mental health project. *JAMA Psychiatry, 77*(4), 387−396. https://doi.org/10.1001/jamapsychiatry.2019.3993

Fraguas, D., Correll, C. U., Merchán-Naranjo, J., Rapado-Castro, M., Parellada, M., Moreno, C., & Arango, C. (2011). Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: Comprehensive review of prospective head-to-head and placebo-controlled comparisons. *European Neuropsychopharmacology, 21*(8), 621−645. https://doi.org/10.1016/j.euroneuro.2010.07.002

Gotfredsen, D. R., Wils, R. S., Hjorthoj, C., Austin, S. F., Albert, N., Secher, R. G., Thorup, A. A. E., Mors, O., & Nordentoft, M. (2017). Stability and development of psychotic symptoms and the use of antipsychotic medication—Long-term follow-up. *Psychological Medicine, 47*(12), 2118−2129. https://doi.org/10.1017/S0033291717000563

Greve, A. N., Uher, R., Als, T. D., Jepsen, J. R. M., Mortensen, E. L., Gantriis, D. L., Ohland, J., Burton, B. K., Ellersgaard, D., Christiani, C. J., Spang, K. S., Hemager, N., Plessen, K. J., Thorup, A. A. E., Bliksted, V., Nordentoft, M., & Mors, O. (2021). A nationwide cohort study of nonrandom mating in schizophrenia and bipolar disorder. *Schizophrenia Bulletin, 47*(5), 1342−1350. https://doi.org/10.1093/schbul/sbab021

Hakulinen, C., McGrath, J. J., Timmerman, A., Skipper, N., Mortensen, P. B., Pedersen, C. B., & Agerbo, E. (2019). The association between early-onset schizophrenia with employment, income, education, and cohabitation status: Nationwide study with 35 years of follow-up. *Social Psychiatry and Psychiatric Epidemiology, 54*(11), 1343−1351. https://doi.org/10.1007/s00127-019-01756-0

Hansen, S. S., Munk-Jørgensen, P., Guldbæk, B., Solgård, T., Lauszus, K. S., Albrechtsen, N., Borg, L., Egander, A., Faurholdt, K., Gilberg, A., Gosden, N. P., Lorenzen, J., Richelsen, B., Weischer, K., & Bertelsen, A. (2000). Psychoactive substance use diagnoses among psychiatric in-patients. *Acta Psychiatrica Scandinavica, 102*(6), 432−438. https://doi.org/10.1034/j.1600-0447.2000.102006432.x

Harvey, R. C., James, A. C., & Shields, G. E. (2016). A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. *CNS Drugs, 30*(1), 27−39. https://doi.org/10.1007/s40263-015-0308-1

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology, 12*(3), 426–445. https://doi.org/10.1037/0894-4105.12.3.426

Henry, L. P., Amminger, G. P., Harris, M. G., Yuen, H. P., Harrigan, S. M., Prosser, A. L., Schwartz, O. S., Farrelly, S. E., Herrman, H., Jackson, H. J., & McGorry, P. D. (2010). The EPPIC follow-up study of first-episode psychosis: Longer-term clinical and functional outcome 7 years after index admission. *Journal of Clinical Psychiatry, 71*(6), 716–728. https://doi.org/10.4088/JCP.08m04846yel

Howard, L. M., Thornicroft, G., Salmon, M., & Appleby, L. (2004). Predictors of parenting outcome in women with psychotic disorders discharged from mother and baby units. *Acta Psychiatrica Scandinavica, 110*(5), 347–355. https://doi.org/10.1111/j.1600-0447.2004.00375.x

Immonen, J., Jääskeläinen, E., Korpela, H., & Miettunen, J. (2017). Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Intervention in Psychiatry, 11*(6), 453–460. https://doi.org/10.1111/eip.12412

Iqbal, M. M., Rahman, A., Husain, Z., Mahmud, S. Z., Ryan, W. G., & Feldman, J. M. (2003). Clozapine: A clinical review of adverse effects and management. *Annals of Clinical Psychiatry, 15*(1), 33–48. https://doi.org/10.1023/A:1023228626309

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., Veijola, J., & Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin, 39*(6), 1296–1306. https://doi.org/10.1093/schbul/sbs130

KL. (2017). *Udvikling i beskæftigelse blandt psykiatriske patienter.* KL Analysenotat. www.kl.dk/media/13814/xgdnjv5nueiot2wnnwet.pdf.

Knowles, E. E. M., David, A. S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: Reexamining the evidence. *American Journal of Psychiatry, 167*(7), 828–835. https://doi.org/10.1176/appi.ajp.2010.09070937

Kraepelin, E. (1919). *Dementia praecox and paraphrenia*. Chicago Medical Book Co.

Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A., & Russell, P. S. (2013). Atypical antipsychotics for psychosis in adolescents. *Cochrane Database of Systematic Reviews*, (10) https://doi.org/10.1002/14651858.CD009582.pub2, 2013.

Kurtz, M. M. (2005). Neurocognitive impairment across the lifespan in schizophrenia: An update. *Schizophrenia Research, 74*(1), 15–26. https://doi.org/10.1016/j.schres.2004.07.005

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K. C., Gaughran, F., & Murray, R. M. (2017). Remission and recovery from first-episode psychosis in adults: Systematic review and meta-analysis of long-term outcome studies. *British Journal of Psychiatry, 211*(6), 350–358. https://doi.org/10.1192/bjp.bp.117.201475

Laursen, T. M., & Munk-Olsen, T. (2010). Reproductive patterns in psychotic patients. *Schizophrenia Research, 121*(1–3), 234–240. https://doi.org/10.1016/j.schres.2010.05.018

Laursen, T. M., Plana-Ripoll, O., Andersen, P. K., McGrath, J. J., Toender, A., Nordentoft, M., Canudas-Romo, V., & Erlangsen, A. (2019). Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? *Schizophrenia Research, 206*, 284–290. https://doi.org/10.1016/j.schres.2018.11.003

Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment: A review. *Social Psychiatry and Psychiatric Epidemiology, 39*(5), 337–349. https://doi.org/10.1007/s00127-004-0762-4

Maybery, D., & Reupert, A. E. (2018). The number of parents who are patients attending adult psychiatric services. *Current Opinion in Psychiatry, 31*(4), 358–362. https://doi.org/10.1097/YCO.0000000000000427

Miles, C. P. (1977). Conditions predisposing to suicide: A review. *Journal of Nervous and Mental Disease, 164*(4), 231–246. https://doi.org/10.1097/00005053-197704000-00002

Mollon, J., & Reichenberg, A. (2018). Cognitive development prior to onset of psychosis. *Psychological Medicine, 48*(3), 392−403. https://doi.org/10.1017/S0033291717001970

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet, 370*(9584), 319−328. https://doi.org/10.1016/S0140-6736(07)61162-3

Nielsen, S. M., Toftdahl, N. G., Nordentoft, M., & Hjorthoj, C. (2017). Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: A nationwide population based register study. *Psychological Medicine, 47*(9), 1668−1677. https://doi.org/10.1017/S0033291717000162

Nordentoft, M., Mortensen, P. B., & Pedersen, C. B. (2011). Absolute risk of suicide after first hospital contact in mental disorder. *Archives of General Psychiatry, 68*(10), 1058−1064. https://doi.org/10.1001/archgenpsychiatry.2011.113

Nordentoft, M., Wahlbeck, K., Hällgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., Gissler, M., Laursen, T. M., & Burne, T. (2013). Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS ONE, 8*(1), e55176. https://doi.org/10.1371/journal.pone.0055176

Okhuijsen-Pfeifer, C., Sterk, A. Y., Horn, I. M., Terstappen, J., Kahn, R. S., & Luykx, J. J. (2020). Demographic and clinical features as predictors of clozapine response in patients with schizophrenia spectrum disorders: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 111*, 246−252. https://doi.org/10.1016/j.neubiorev.2020.01.017

Pagsberg, A. K., Jeppesen, P., Klauber, D. G., Jensen, K. G., Rudå, D., Stentebjerg-Olesen, M., Jantzen, P., Rasmussen, S., Saldeen, E. A. S., Lauritsen, M. B. G., Bilenberg, N., Stenstrøm, A. D., Nyvang, L., Madsen, S., Werge, T. M., Lange, T., Gluud, C., Skoog, M., Winkel, P., … Fink-Jensen, A. (2017). Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: The multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *The Lancet Psychiatry, 4*(8), 605−618. https://doi.org/10.1016/S2215-0366(17)30166-9

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A reexamination. *Archives of General Psychiatry, 62*(3), 247−253. https://doi.org/10.1001/archpsyc.62.3.247

Pantelis, C., Wood, S. J., Proffitt, T. M., Testa, R., Mahony, K., Brewer, W. J., Buchanan, J. A., Velakoulis, D., & McGorry, P. D. (2009). Attentional set-shifting ability in first-episode and established schizophrenia: Relationship to working memory. *Schizophrenia Research, 112*(1−3), 104−113. https://doi.org/10.1016/j.schres.2009.03.039

Petersen, S. M., Toftdahl, N. G., Nordentoft, M., & Hjorthøj, C. (2019). Schizophrenia is associated with increased risk of subsequent substance abuse diagnosis: A nation-wide population-based register study. *Addiction, 114*(12), 2217−2226. https://doi.org/10.1111/add.14746

Plana-Ripoll, O., Pedersen, C. B., Agerbo, E., Holtz, Y., Erlangsen, A., Canudas-Romo, V., Andersen, P. K., Charlson, F. J., Christensen, M. K., Erskine, H. E., Ferrari, A. J., Iburg, K. M., Momen, N., Mortensen, P. B., Nordentoft, M., Santomauro, D. F., Scott, J. G., Whiteford, H. A., Weye, N., … Laursen, T. M. (2019). A comprehensive analysis of mortality-related health metrics associated with mental disorders: A nationwide, register-based cohort study. *The Lancet, 394*(10211), 1827−1835. https://doi.org/10.1016/S0140-6736(19)32316-5

Poli, F. (2014). Cognitive functioning in prodromal psychosis. *JAMA Psychiatry, 69*(6), 562−571.

Ranning, A., Laursen, T. M., Thorup, A., Hjorthøj, C., & Nordentoft, M. (2015). Serious mental illness and disrupted caregiving for children: A nationwide, register-based cohort study. *Journal of Clinical Psychiatry, 76*(8), e1006−e1014. https://doi.org/10.4088/JCP.13m08931

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., Poulton, R., & Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal of Psychiatry, 167*(2), 160–169. https://doi.org/10.1176/appi.ajp.2009.09040574

Rinaldi, M., Killackey, E., Smith, J., Shepherd, G., Singh, S. P., & Craig, T. (2010). First episode psychosis and employment: A review. *International Review of Psychiatry, 22*(2), 148–162. https://doi.org/10.3109/09540261003661825

Schrank, B., Rumpold, T., Gmeiner, A., Priebe, S., & Aigner, M. (2016). Parenthood among people with psychotic disorders: Gender differences in a non-selective clinical sample. *Psychiatry Research, 246*, 474–479. https://doi.org/10.1016/j.psychres.2016.10.020

Secher, R. G., Hjorthøj, C. R., Austin, S. F., Thorup, A., Jeppesen, P., Mors, O., & Nordentoft, M. (2015). Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. *Schizophrenia Bulletin, 41*(3), 617–626. https://doi.org/10.1093/schbul/sbu155

Sporn, A. L., Vermani, A., Greenstein, D. K., Bobb, A. J., Spencer, E. P., Clasen, L. S., Tossell, J. W., Stayer, C. C., Gochman, P. A., Lenane, M. C., Rapoport, J. L., & Gogtay, N. (2007). Clozapine treatment of childhood-onset schizophrenia: Evaluation of effectiveness, adverse effects, and long-term outcome. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(10), 1349–1356. https://doi.org/10.1097/chi.0b013e31812eed10

Stenstrøm, A. D., Christiansen, E., Dehlholm-Lambertsen, B., Nøhr-Jensen, P., & Bilenberg, N. (2010). Stigende incidensrate af skizofreni hos børn og unge. *Ugeskrift for Laeger, 172*(31). http://www.ugeskriftet.dk/portal/page/portal/LAEGERDK/UGESKRIFT_FOR_LAEGER/TIDLIGERE_NUMRE/2010/UFL_2010_31/UFL_2010_172_31_2131.

Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, P. (2016). Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: A systematic review. *Journal of Child and Adolescent Psychopharmacology, 26*(5), 410–427. https://doi.org/10.1089/cap.2015.0097

Thompson, A., Winsper, C., Marwaha, S., Haynes, J., Alvarez-Jimenez, M., Hetrick, S., Realpe, A., Vail, L., Dawson, S., & Sullivan, S. A. (2018). Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: Systematic review. *BJPsych Open, 4*(4), 215–225. https://doi.org/10.1192/bjo.2018.17

Thomsen, P. H. (1996). Schizophrenia with childhood and adolescent onset—A nationwide register-based study. *Acta Psychiatrica Scandinavica, 94*(3), 187–193. https://doi.org/10.1111/j.1600-0447.1996.tb09847.x

Thorup, A., Waltoft, B. L., Pedersen, C. B., Mortensen, P. B., & Nordentoft, M. (2007). Young males have a higher risk of developing schizophrenia: A Danish register study. *Psychological Medicine, 37*(4), 479–484. https://doi.org/10.1017/S0033291707009944

Vernal, D. L., Boldsen, S. K., Lauritsen, M. B., Correll, C. U., & Nielsen, R. E. (2020). Long-term outcome of early-onset compared to adult-onset schizophrenia: A nationwide Danish register study. *Schizophrenia Research, 220*, 123–129. https://doi.org/10.1016/j.schres.2020.03.045

Weibell, M. A., Hegelstad, W. T. V., Auestad, B., Bramness, J., Evensen, J., Haahr, U., Joa, I., Johannessen, J. O., Larsen, T. K., Melle, I., Opjordsmoen, S., Rund, B. R., Simonsen, E., Vaglum, P., McGlashan, T., McGorry, P., & Friis, S. (2017). The effect of substance use on 10-year outcome in first-episode psychosis. *Schizophrenia Bulletin, 43*(4), 843–851. https://doi.org/10.1093/schbul/sbw179

Wunderink, L., Nieboer, R. M., Wiersma, D., Sytema, S., & Nienhuis, F. J. (2013). Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry, 70*(9), 913−920. https://doi.org/10.1001/jamapsychiatry.2013.19

Zipursky, R. B., Menezes, N. M., & Streiner, D. L. (2014). Risk of symptom recurrence with medication discontinuation in first-episode psychosis: A systematic review. *Schizophrenia Research, 152*(2−3), 408−414. https://doi.org/10.1016/j.schres.2013.08.001

Chapter 13

Ethical considerations and current research practices in adolescent psychosis

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Introduction

Adolescence is a crucial phase of life, characterized by intense bio-psycho-social changes (Yurgelun-Todd, 2007) and the completion of several developmental milestones, both interpersonal (e.g., empowerment, development of intimate relationships) and intrapsychic (e.g., identity construction, appropriation of bodily changes). While its onset is generally linked to puberty, the end of this period of development is more controversial (Sacks, 2003). According to the World Health Organization, adolescence corresponds to ages 10–19 years, whereas the years 15–24 are considered "youth" (World Health Organization, 2014). This ambiguity is well reflected in the literature with the appearance of novel terms for this age period, such as "emerging adulthood" or "young adulthood" (Shadili, 2014). It also reveals the presence of inconsistencies in the boundaries of definitions. According to several experts, such chronological boundaries may be questionable and have been the subject of discussion for many years (Sacks, 2003). Moreover the occurrence of an accelerated brain maturation in girls suggests that their intellectual-emotional development may be earlier than in boys at least on a group-basis (Lenroot & Giedd, 2010). Taken together, these reflections indicate that, rather than a common transition for all at the same point in time, entry into adulthood represents an individual stage that is rarely synchronous with the civil majority established at 18 years (Kilicel et al., 2021).

Adolescent Psychosis. https://doi.org/10.1016/B978-0-323-89832-4.00010-X

In addition to being a period of intense change, adolescence can represent a pivotal moment in the trajectories of developmental psychopathology. Indeed, the transition from childhood to adolescence is also undoubtedly a period of vulnerability (Jones, 2013; Kilicel et al., 2021; Lenroot & Giedd, 2010; Lerner et al., 2011; Lewin-Bizan et al., 2010; Shadili, 2014), both from a developmental and an ethical point of view. Concerning the vulnerability for developing psychiatric problems, it is estimated that 75% of psychiatric disorders are manifested by the age of 25 years (Gore et al., 2011), and that they interfere with the performance of developmental tasks, hindering psychosocial functioning in a lasting way (McGorry et al., 2018). Adolescence therefore represents a key period for prevention and early therapeutic intervention in psychiatry, which has been widely addressed in the literature (Sossauer et al., 2019). In ethical terms, adolescents are vulnerable because their interests are not as fully represented in society as those of adults, their needs tend to be neglected, and their rights are prone to being violated (Schachter et al., 2005; Tavaglione et al., 2015).

The progressive and highly variable interindividual development during adolescence leads to a number of ethical issues in medical research (Hoop et al., 2008). These issues become even more striking in adolescent psychiatry and especially in adolescents with psychotic disorders for several reasons. Firstly, adolescence represents a gray area in terms of informed consent. This is specifically accentuated in patients with psychosis because of the complex impact of the illness on the patient's decision-making capacity (see Section Gray area in terms of informed consent for more details). Secondly, the problem of stigma and self-stigma related to a psychotic disorder diagnosis may have an even stronger impact than in adults, as the adolescent's personality is still developing, and adolescents may identify profoundly with their disorder.

In this chapter, we will focus on several specific ethical issues relating to research with adolescents suffering from psychosis. We will, however, not provide a systematic review for ethical concerns regarding clinical research with minors, such as informed consent and stigma related to mental disorders in general. Previous literature reviews have already systematically addressed central issues relevant to adolescence, based on the general ethical principles of medical research involving humans (Emanuel et al., 2000; Lysaght et al., 2012).

Ethical considerations in adolescent psychosis research

Any ethical reflection on this topic must start with the fundamental norm that all age groups in the population should have equal access to evidence-based health care. Since the evidence for health care interventions in a specific age group requires research into the same age group, research targeting adolescents is crucial to offer evidence-based health care to this vulnerable population. It is thus ethically problematic to avoid conducting clinical research with adolescents. This avoidance has been the case for many decades in the field of psychosis, based on the unproven presumption that participants may be

stigmatized by the approaches to study of precursors or manifest psychotic disorders. In the long run, clinical research of adolescents with psychosis and other mental disorders may rather reduce stigmatization as it leads to more knowledge about cause, course, prognosis, and treatment of these debilitating disorders (Alaghband-Rad et al., 1995).

Judith Rapoport at the National Institute of Mental Health (NIMH) in the United States conducted a pioneering work aiming to clinically characterize children and young adolescents with psychotic symptoms. She established the first modern cohort of children with psychotic symptoms emerging before the age of 18 and even diagnosed before the age of 13 years (childhood-onset) (Green et al., 1992). This pioneer work opened up a transition from mainly focusing on adult psychosis to acknowledging the importance of child and adolescent psychosis. However, this development has been rather slow and has suffered from numerous obstacles in the conceptualization of these disorders. For example, professionals taking care of these young people often lacked the specific knowledge concerning the nature of their symptoms and failed to ask specifically about the symptoms in depth, as if ignoring the symptoms would make the problems disappear (Fusar-Poli et al., 2021). An advanced body of research suggests that early detection and intervention may not only reduce transition to psychosis but also improve the clinical and functional outcome of the patients independently from the transition (Catalan et al., 2021). A preventive approach to psychotic disorders will be crucial for the next decades. Research focusing on early antecedents, as well as risk and protective factors, may thus significantly modify the course of the disorder in a given individual, as well as in a population.

Early diagnosis and treatment

With respect to early diagnosis, it seems crucial to know whether effective ways to mitigate the course of the disease exist that may in turn prevent symptom development and slow the progression in a chronic illness. It is also ethically important to determine the percentage of adolescents with subtle signs of psychosis, precursors of psychosis who develop full-fledged psychosis, and who experience a natural remission without treatment. This context would then allow differentiating as accurately as possible between those who need treatment and those who do not. However, due to the relatively humble amount of evidence derived in this area this is not yet the case (Catalan et al., 2021).

Research practices have increasingly moved toward early diagnosis and intervention. As described in detail in the previous chapters, current research practices in adolescent psychosis are based on scientific evidence accumulated over the last 30 years. This evidence distinguishes the different phases of psychosis: the clinical high-risk for psychosis (CHR), the first episode of psychosis (with the duration of untreated psychosis), and the evolution after the first episode (critical period, illness requiring long-term treatment, etc.).

This shift has also led to ethical questions associated with the research practice, typically concerning the area of selective and indicated prevention (Mrazek & Haggerty, 1994). The sooner we start with psychiatric interventions in the oligosymptomatic phase (i.e., having few or minor symptoms), or even the presymptomatic phase where prognosis is still uncertain, the higher are the chances of effective disease-modifying interventions (Arango et al., 2018). However, the higher are also the risks of false-positive identification and stigmatization, or even unnecessary treatment with potential adverse effects (Lane et al., 2020; Wright et al., 2011).

Genetic information

Ethical issues may arise particularly from genetic testing or presymptomatic biomarker testing, enabling prediction of psychosis well before the onset of symptoms, but potentially also entailing genetic information that impacts on close relatives, such as siblings of the tested person. In particular, the advent of the polygenic risk scores raises these concerns. The polygenic risk score is an indication of risk, based on a wealth of genetic markers associated with a disorder or a trait derived in large populations to allow for the determination of a risk probability for a specific disorder in an individual (Agerbo et al., 2015). However, since the technical and scientific questions regarding the polygenic risk scores are still not satisfactorily resolved, the ethical concerns, such as the dangers of stigmatization, overdiagnosis and overtreatment, and the introduction into clinical practice are highly debated (Lewis & Green, 2021).

Brain maturation and its impact on cognitive and social skills development

An important aspect when discussing the ethical aspects of research in adolescent psychiatry concerns brain maturation and its consequences for several cognitive and behavioral skills during development. Without presenting this topic exhaustively in this chapter, we wish to highlight the huge heterogeneity of brain maturation during adolescence and young adulthood. In a machine learning study that aimed to determine the age of people from brain images, artificial intelligence was the least accurate in 7−20-year-olds (Arain et al., 2013). Indeed, brain maturation depends on several factors, such as sex, socio-economic level, nutrition, and life experiences, but also on other, more clearly biological factors in relation to brain development. On average, the brain reaches full maturation by the age of 25 years (Casey et al., 2008; Fuster, 2002). In particular, the lateral prefrontal lobe matures last. This brain region is responsible for the so-called higher-order executive functions (Tekin & Cummings, 2002), such as task initiation, organization, planning, mental flexibility, and self-regulation to achieve a goal (Steinberg et al., 2018). This translates into increased sensitivity to sensation seeking and problems with

cognitive control and self-regulation among adolescents and young adults. Sensation seeking peaks at age 19 years and declines afterward, whereas self-regulation increased steadily and reaches its plateau between the ages of 23 and 26 years (Steinberg et al., 2018). This maturation has several determinants where sex differences in the development of the brain and more specifically the ability to regulate impulses play an important role.

Moreover, the degree of maturity of the emotional network, including salience/motivation of the human brain develops in asynchrony with the networks mediating cognitive control. Indeed, the ventral striatum, which mediates reward stimuli, consolidation, and salience network in motivation, matures earlier (Casey et al., 2008), whereas the cognitive control network of the prefrontal cortex matures later (Fuster, 2002). This asynchrony may explain why adolescents show difficulties in adjusting the decision-making process using cognitive control when emotional salience is intense (Tekin & Cummings, 2002). Along the same lines, the temporal gap between puberty, which impels adolescents toward thrill seeking, and the slow maturation of the cognitive-control system, which regulates these impulses, makes adolescence a time of heightened inclination toward risky behavior (Decety & Michalska, 2010; Frith, 2007; Gardner & Steinberg, 2005; Ochsner, 2004). For instance, immature social cognition and the search for positive emotions by peers may be related to the tendency of young people to take more risks in the presence of a peer, and this effect does not disappear until after the age of 24 years (Choudhury et al., 2006; Eisenberg et al., 2005). This progressive inter-, and intraindividually variable maturation concerns also other domains closely related to social cognition, such as empathy and moral judgment that are subject to profound maturation processes until adulthood (Faden et al., 1986; Munir & Earls, 1992). It is thus important to consider the developmental age of young individuals rather than their chronological age when considering their actual maturity and especially their capacity of taking autonomous and well-reflected decisions. This could be accomplished by exploring their understanding of the research topic and role as participants. Moreover, one can explore their general level of reflection regarding decision-making and consequences of nonparticipation.

In conclusion, the variability of brain maturation and the cognitive and behavioral skills have several repercussions on the ethical aspects of research among adolescents, both in terms of their discernment and the ability to take the full responsibility of their actions. This is even more evident for individuals suffering from mental disorders, who present with more marked variability and heterogeneity in this maturation process compared to normative development (Galván, 2017).

Informed consent

Several important documents have firmly established the principle that individuals must give their voluntary informed consent before participating in

research, such as the Nuremberg Code ("The Nuremberg Code (1947)," 1996), the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), and the Declaration of Helsinki (World Medical Association, 2013). These three documents have constituted guidelines of human research in the era post World War II (Ungar et al., 2006). The practices, however, concerning the informed consent of minors are not entirely clear and vary between countries, sometimes even within countries. While majority is reached at the age of 18 years in most countries, certain decisions concerning their own health may be taken well before that age, based on the type of question and the intellectual maturity of the minor. A wide consensus exists that adolescents, starting from the age of 14 years, are capable of making at least some health care decisions for themselves. A healthcare provider must therefore obtain the consent of the adolescent before releasing sensitive health information to anyone else, including their parents or legal guardians. This emphasizes the autonomy of young people in adolescence. However, even in a state of decisional incapacity for a given decision, many ethicists and researchers emphasize that an informed *assent* should be obtained from the minor (Soll et al., 2020). The term "assent" includes adequate and age-adapted information to the child. In the age group of 10−12 years, the minor is often invited to sign the informed consent form along with the caregivers. The graded transition into adulthood during adolescence mirrors the increasing capacity of young people to make autonomous choices concerning their own health. In some countries, no clear age boundaries for increasing autonomy are defined so it is considered on a case-by-case basis. It is an open ethical and political question in what way chronological age should be prioritized over an individual evaluation of the young person's decision-making capacity. Moreover, we need to better determine how shared decision-making and responsibility can be fostered along this transition phase of emerging decision-making capacity (Sawyer & Rosenberg, 2020).

Gray area in terms of informed consent

Globally speaking, informed consent has been conceptualized as having three main elements: information sharing, decision-making capacity, and voluntariness (Appelbaum et al., 1982). Information sharing occurs when researchers provide potential participants with all relevant information about the research protocol. Such information must include the purpose, the procedures involved, any foreseeable risks, and potential benefits. Researchers should educate the participants and/or their legal guardians about the usual standard of evidence−based care and the experimental character of certain study procedures, as well as alternatives to research participation (Roberts, 2002). Decision-making capacity generally defined consists of four abilities: (1) comprehend the information necessary for the decision; (2) appreciate the

significance of the choice in the context of one's life; (3) reason (i.e., weigh information, compare options, consider consequences); and (4) make a choice and communicate it (Spencer et al., 2017). Voluntariness is the ability to make a free, uncoerced decision. This component is influenced by several factors, including: developmental factors; illness-related factors; psychological, cultural, religious, and family-related factors; expectations; and external features and pressures, such as social, political, or monetary ones (World Medical Association, 2013).

The presentation of these three main elements of informed consent may differ at the intra- and interindividual level depending on the clinical stage of the disease (e.g., CHR → first episode of psychosis → psychosis in need for long-term treatment) and the developmental phase. Indeed, we here consider a population that often experiences an atypical cognitive developmental trajectory compared to a healthy reference group, with a varying degree of severity and difficulty in the long run (Mollon et al., 2018; Reichenberg et al., 2010; Øie et al., 2021). Therefore, as we have seen in the previous paragraph, the participants may have a variable capacity to understand the consequences of their choices. In addition, symptom severity, especially in the case of psychosis, may affect their capacity to provide informed consent. However, the pathology or diagnosis in itself is not sufficient to question someone's decisional capacity. Hence, one should always perform an individual evaluation of the patient's decisional capacity. Furthermore, the issue of informed consents for adolescents is also affected by the legislation in each country (and culture) in terms of recognition of maturity.

These central components thus warrant evaluation at an individual level before the informed consent may be accepted. The range of legitimate research studies remains limited if a potential study participant does not have the prerequisite decisional capacity to provide informed consent. This concerns especially studies that do not offer the chance of a direct, therapeutic benefit, but "only" entail the possibility of collective benefit in the future (e.g., biomarker studies, observational studies). However, many studies offer other possibilities valuable to the participant, including quick access to advanced investigations (e.g., neuroimaging) which might not even be considered otherwise; being met with appreciation, experiencing a sense of meaning and making a contribution; and having the opportunity for an educative or even therapeutic discussion with healthcare professionals. Ethical guidelines usually stipulate that research without a directly intended health benefit is only justified if the risks and burden for the research subject are minimal (CIOMS, 2016).

Stigma and self-stigma related to the diagnosis

Another important concern is stigmatization by early psychiatric labeling. This is an important point as previous research suggests that using accurate

psychiatric terminology in a cautious way and educating the community in psychiatric health literacy may reduce the risk of stigmatization ((Wood et al., 2015); Corcoran, 2016). Several regional examples of efforts in improving health literacy exist in different countries. In Australia, the Headspace initiative was created as a response to an increasing need of more accessible and effective health care services for youth with mental and substance use disorders (McGorry et al., 2007, 2019). This initiative has inspired other countries, such as Denmark, to establish their own Headspace clinical centers with low threshold access that provide a dialogue and information material to young people.

Schizophrenia, and more generally psychotic disorders, are highly stigmatizing disorders (Gronholm et al., 2017b). Indeed, subjects affected by a psychotic disorder belong to the most stigmatized minority groups within our society (The Schizophrenia Commission, 2012). Several research studies have shown that the majority of society holds negative beliefs about individuals with psychosis and considers them as dangerous, unpredictable and in some way responsible for their disorder (Link et al., 2004). This situation is reflected in the subjective experience of people suffering from psychosis who, in several patient-centered qualitative studies, describe that they experience stigma and discrimination on a regular basis (Wood et al., 2015; Mukolo et al., 2010). Even if most of the research conducted on stigma in psychosis concerns the adult population (Corcoran, 2016), many researchers and clinicians agree that the question of stigma may be even more important during adolescence (Angermeyer & Matschinger, 2003; Yung et al., 2010). Indeed, adolescents represent a population with an emerging personality that can be strongly influenced by the negative judgment of people (mostly peers) toward them, and who may therefore experience the negative effects of stigmatization even more intensely.

The increasing interest in the CHR condition has led to the introduction of the attenuated psychosis syndrome in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). Hence, many health professionals as well as user associations have raised legitimate concerns that the stigma associated with psychotic disorders, with its associations of otherness, dangerousness, and incurability (Yang et al., 2010), may also be transferred to the psychosis risk condition (Woods & McGlashan, 2011; Yang et al., 2013; Yung et al., 2010). As shown to be the case for individuals with a full-blown psychotic disorder, potential stigma-related consequences for adolescents at CHR may include: (1) internalized stigma (adolescents see themselves as defective or unworthy); (2) identity engulfment (adolescents see the illness as defining who they are, rather than as something they have); (3) shame (the label is kept secret and concealed); and (4) discrimination from others (expressed as devaluation or unfair treatment) (Yung et al., 2010). Clinicians and researchers are concerned that the label of psychosis risk could threaten a young person's sense of self (by incurring subsequent identity labeling, such as fragile, damaged, sick, or crazy) and curtail their aspirations in terms of education, employment, romantic

attachments, or parenthood (Yung et al., 2010). Sadly, even several years after the introduction of this diagnosis, there are still relatively few studies that have assessed how the effect of self-stigma or the perception of others with a similar diagnosis affect adolescent development. One study did not report higher degrees of stigma among individuals at CHR compared to individuals with nonpsychotic diagnoses (Parrish et al., 2019). In a second study of adolescents at CHR, stress related to stigma was associated with increased suicidal ideation and mediated by social isolation (Xu et al., 2016). Differently, a recent systematic review on this topic showed more mixed results. On the one side, the general public endorses stigmatizing attitudes toward individuals at CHR, and this attitude is more frequent in people with a low educational level or with no direct experience of this syndrome (Colizzi et al., 2020). In line with this evidence, individuals at CHR experience more internalized stigma and perceive more discrimination than healthy individuals or patients with nonpsychotic disorders (Colizzi et al., 2020). Moreover, stigma increases the likelihood of poor outcome, transition to full-blown psychosis, disengagement from social services, and family stigma among individuals at CHR (Colizzi et al., 2020). On the other side, a CHR diagnosis appears to be equally associated with both positive (e.g., validation and relief) and negative effects (e.g., status loss and discrimination) (Colizzi et al., 2020). The different perspectives may reflect the fact that more knowledge about and familiarity with psychosis were associated with lower stigma (McGorry et al., 2018). These findings reinforce the potential gain for mental health awareness campaigns in reducing stigma but also raise questions about factors contributing to lower rates of stigma in this population.

Practical considerations in adolescent psychosis research

As we have seen, adolescents with psychosis represent a population in particular need of research. However, due to their phase of development between childhood and adult life, as well as their specific symptoms, some ethical questions may arise in a quite distinct way. We hence address those points of attention more in detail in the following paragraphs. These points have mainly emerged from our work as clinical scientists when conducting studies in this population, in collaboration with a clinical ethicist. We wish to emphasize that these ethical aspects may change with time and that their subjective relevance has emerged by the research practice in the context of our own research culture and in accordance with specifics of legislature of several countries and research environments.

Communication

A central part of successful research recruitment of adolescents and their caregivers is clear communication of the research purpose. The planned

research procedures should be explained in an appropriate and easily understandable way to the young person and the parents. It seems crucial to anticipate and explore the concerns and phantasies that may arise in the adolescents, especially in those with psychotic distortions of reality. For example, asking an adolescent with psychotic thoughts to participate in a study that includes a brain scan could induce the idea that something with their brain is not "normal" or that the researchers may be able to "see their thoughts," which may be difficult to share and control for the adolescent (Gronholm et al., 2017a). It is thus of highest priority that the explanations given in written and oral forms are as thorough as possible. Moreover, if feasible, the researchers should present their plans and get feedback from representatives for adolescent patient/user organizations or young people (and their caregivers) with personal experiences with the illness in question (focus groups). This may improve the information given and clarify the research questions asked. The early inclusion of reflections from individuals in analogous situations via user organizations or focus groups may allow the research team to address those aspects even without the research participants mentioning them explicitly.

Focus groups

A focus group is the gathering of several individuals to conduct a group interview to have their feedback on a study subject or study method. This contributes greatly to improving representativeness of participants, as well as the dissemination of project results. User representatives improve research strategies by contributing with an understanding of the culture and context of specific groups in the population, and their mode of communication. In addition, as already implemented in many research groups, the user representatives give feedback and advise on study applications to the grant sources and may be heavily involved in the planning and implementation of a study. In a second step, this knowledge will help shape the way of communication with the individuals targeted in the study. Moreover, the reflections and experiences from the focus groups will play an important role in approaching the key people in the environment that may support and contribute to "destigmatizing" participation in research projects and provide a framework and a logistical support. This network lobbying must be an integral part of the planning of a research study.

Representativity

Another communication issue is how to reach out to populations and groups that are traditionally underrepresented in many studies. Examples of this may be adolescents: (1) from single parent households; (2) with addiction problems; (3) facing academic failures; (4) with migration background; (5) with other comorbid mental health problems; or (6) with parents who themselves have mental or addiction problems. It may be particularly difficult to recruit

adolescent participants from minorities because they may be less accessible through schools (more heterogeneous patterns of educations after the basic education). It is thus of high interest that the researcher aims to include representative samples of affected individuals to overcome the obstacles that often are not expressed explicitly and may remain unknown (Feldstein, 2018). This is easier to achieve in Scandinavian countries with the existent population registries (Thorup et al., 2015) and more difficult to realize in other countries. However, the principle may be kept in mind even in other contexts. Examples of obstacles could be mistrust of researchers or to participate as a "subject" in a research study. Other barriers could be the practical difficulty to gain and retain contact or other logistical obstacles that typically increase with a lower socio-economic status. Here again, feasibility studies and collaborations with focus groups during the phase of study preparation, where representatives of traditionally underrepresented groups are invited, may create empirically supported and individualized successful strategies (Peterson-Sweeney, 2005).

Furthermore, network lobbying also includes community and user representatives, development of targeted messages and materials for specific audiences (educators, families, youth, scientists), and continued and consistent outreach. This was brilliantly shown in the ABCD study, where this kind of outreach constitutes an integral part of the consortium activities (Hoffman et al., 2018). The ABCD study is the largest existing study to date focusing on brain development, with 21 participating centers across the US with high emphasis on the representativity of the participants (The Adolescent Brain Cognitive Development (ABCD) Study, 2022). Lastly, it is also essential to avoid "super-healthy" control or reference groups, as well as nonrepresentative cohorts (e.g., self-referral based on advertisements on the social media or a limitation to students from one school) for studies in young people that examine biological, cognitive, and emotional development.

Length of the research protocol, and adherence to longitudinal studies

There are no standard rules for the suitable duration of a session with a study participant or the set-up of a research protocol. This is because the tolerability of a long examination will depend on the participant's psychological disposition and the accessibility and flexibility of the research staff. However, in our experience, the planning of a positive research experience for the participant and the family includes careful information and a flexible strategy in trying to adapt to the needs of the young person. This has been the case for several studies working with children, adolescents, and families in long-term follow-up studies, where adherence to the study is one of the key elements to the success of the project. It is also clear that some protocols may be difficult to handle for certain participants, such as asking an adolescent with an acute psychotic episode to lie still in the MRI scanner. MRI scanning may require

the presence of a professional during the whole examination, especially for children and young adolescents, close to the participant in the scanner room, if so wished. The participant can always terminate the examination or require pauses.

It is important to prepare the participant and the family well by giving them detailed information about the procedures and length of the examinations. By doing this, the families feel more at ease in an unknown situation and in control of the research sessions. As such, they are better able to support the research participant (child or adolescent). This kind of preparation is crucial in studies that include potentially anxiety-provoking examinations, such as electroencephalography (EEG), MRI scanning, blood sampling, or other interventions. In a longitudinal perspective, these examinations should be postponed until the child and the family have created a relationship of trust to the research team (Thorup et al., 2018). This will, however, not always be possible and may thus hinder knowledge concerning important developmental aspects in these populations. Some of the key features to help families feel comfortable with longer research sessions are the priorities of the research team, such as: (1) be greeted by friendly and empathic staff members in a positive atmosphere; (2) provide leisure-time activities for the persons who are not examined; (3) show gratitude toward the family for their investment of time; and (4) stress the confidentiality of the information given. Other important practical aspects regarding acceptance of longer protocols and adherence to longitudinal studies may be: (1) having the same staff overseeing the study; (2) provide frequent breaks with snacks and drinks; (3) compensate each visit; and (4) be accessible to the families before or after the examinations by providing business cards and sharing the details of the website (Poulton et al., 2015; Thorup et al., 2015). An important element, especially in longitudinal studies is to ask the participants for feedback/evaluation after the examinations, as well as to provide feedback to the participants in terms of summary meetings, or written reports. This helps adjust the study protocol if needed and create an alliance with the participants.

In conclusion, although the length of research sessions may be limited to 1−2 h depending on the age, disorder, and situation of the adolescent (direct diagnostic interview, MRI scanning), the integration of a protocol of longer duration with several sessions is still possible. This might require a diversified process that, at the same time, provides a stable and flexible framework for the examination.

Interview format

Most of the research projects focusing on adolescents with psychosis to date have only to a limited extent integrated digital resources in their protocols. This is surprising as questions of accessibility to the examination site and time constraints may pose important obstacles for participation in a study for many

adolescents. Consequently, this may affect the representativity of research samples and the generalizability of studies. Especially in the field of mental health where the confidentiality and the relationship of trust play important roles, the idea of digital consultations has long been perceived as alienating and inappropriate. However, in some countries, disadvantaged by long distances, researchers have practiced this type of approach for decades with excellent adherence (Bolle et al., 2018). Finally, recent technological advances during the Covid-19 pandemic have accelerated the development and use of digital tools in medicine in general, including in psychiatry and psychotherapy (Di Carlo et al., 2021).

In some mental health clinics, the majority of sessions during the pandemic have been carried out using digital tools with a high acceptance and good results (Sasangohar et al., 2020). It may be difficult to meet a new person for the first time via the screen, especially for adolescents, because the meeting is limited to the visual and auditory perceptions, whereas sensory and olfactory perceptions are not transmitted through the screen. Also, the dialogue has another quality in that the speakers need to reach an agreement on taking their turns, which for adolescents may be a less pleasant situation. In addition, adolescents report a feeling of awkwardness in the situation of seeing a video of themselves, as well as knowing that the other can view them and their environment. Certain groups of adolescents, such as those with depressive symptoms, higher stress levels, and/or suicidal ideation, may be more prone to use digital resources (Toscos et al., 2019). This is in line with today's adolescents being digital natives and generally having a lower threshold to use digital technology than adults from older generations.

The COVID-19 pandemic has shown that it may be wise to prepare for digital consultations independently of the place of residence. The use of digital resources offers an accessible solution during major obstacles, such as an unplanned lockdown or difficulties with transportation, and allows the client and therapist to maintain their relationship. Many clinics are developing the approaches needed to improve the therapeutic tools specific to this technology. For future research, this may present as an important avenue to increase the number of participants in research studies, as well as the representativeness (Polillo et al., 2021). For example, young people in the prodromal phase may reject participation in research conducted in a large medical center, whereas they could be interested in contributing to a project that allows participation directly from their homes (McDonald et al., 2019). At the same time, phantasms and fears related to the use of technology need to be explored in a sensitive manner. For adolescents with paranoid ideas, the use of digital approaches may minimize their participation due to the perception to be monitored with continuous or iterative surveillance.

Data collection and sharing

Researchers need to stay attentive in the planning phase and abstain from parts of the data collection if their usefulness cannot be guaranteed or if a reduced number of variables would equally allow for the planned analyses. Any collected data should be scientifically justified. In this respect, it is warranted to publish research protocols, including statistical plans of analysis, in databases and journals devoted to these questions (e.g., clinicaltrials.gov), before embarking on data collection. This may avoid "fishing expeditions" and a too heavy burden on the research participants (Catalan et al., 2021).

In the era of "personalized medicine" and "artificial intelligence," one of the goals is to collect big datasets and to use as much information as possible for the individualized tailoring of preventive, prognostic, and therapeutic approaches. However, these innovative and important multicenter databases often include a wealth of data and are sometimes without the explicit consent of the participants. The previous practice of not collecting a specific consent raises significant ethical doubts. This is also the case with regard to the financial interests of enterprises in the private sector, such as insurance companies, which developed these databases in collaboration with clinical researchers. A broad and general consent, as it is being implemented in many hospitals, is certainly an improvement, but it still raises ethical questions. For example, do we have to recontact the adolescent participants once they reach decision-making capacity when we want to use data for which we only have a prior proxy consent from their legal guardians? This is now the case in most approaches to a general consent.

The future may call for data-sharing principles between patients, health systems, and enterprises that may profit directly from the inclusion of these patient data. Examples may be the empowerment of patient associations that help decide how to assure the patient's benefit, although the benefit may not concern the same patient but future patients with similar symptoms. New principles with the involvement of patient groups will help ensuring that disadvantages and advantages are equally distributed (McCoy et al., 2020). A recent publication more specifically addresses the question of the use of patient data to build up artificial intelligence algorithms in companies to improve diagnostic approaches (Larson et al., 2020). The authors argue that it is unethical for providers to exchange clinical data with other parties for payments that exceed costs (thus with a profit). The role of the providers is rather to safeguard patient privacy and act as ethical "data stewards" to ensure proper ethical use of patient data (Larson et al., 2020).

Deidentification

Questions of safeguarding privacy and anonymity are especially challenging in radiology, neuroimaging practice and, to an even larger extent, genetic research where limitations to deidentification of patient identity exist.

Although powerful deidentification strategies of medical imaging information (header information) are practiced in many studies, several medical imaging formats (computed tomography [CT] and MRI) may be subject to reformatting. By using techniques such as cinematic rendering, it is possible to create images of the human skin surface and link them to specific individuals, especially based on MRI/CT of the head and neck region, which allow generating images of the face (Parker et al., 2021). The same applies to genetic research, a field characterized by rapid changes and advances, which poses specific challenges regarding informed decisions about participation in genetic research studies. It is important that the legal systems regulating this kind of research are in coherence with the advances in technology and the social changes in the society. Participants should be well informed of how their privacy, anonymity, and confidentiality are guaranteed in each specific study. A contributing factor to this is to identify social practices and structures for collection and use of genetic information to increase the participants' confidence about their genetic privacy (Clayton et al., 2018). Furthermore, it is important to identify the factors that influenced the participants in their decision to provide their genetic material to specific studies (Clayton et al., 2018). In order for adolescents to make informed choices about their genetic material, they should thus possess knowledge concerning these risks and challenges before deciding about the participation in a specific study.

Incidental findings

In mental health research and particularly in research using brain imaging and other standardized instruments, there is a risk of incidental findings, and its handling should be planned well ahead of the start of the study. For example, the discovery of psychiatric symptomatology of a healthy participant during a diagnostic interview may have potentially serious implications for the individual. Subjects might have been aware of the problems at the outset, but not of the size of the problems and the need to see a specialist for follow-up and possible treatment. The subjects may thus feel that they have entered the study as a healthy person and leave it with a diagnosis or an "at risk state" that they did not ask or prepare for. However, a dialogue at the outset of the study and ideally in conjunction with the written information may help to clarify the subjects' needs, wishes and priorities. If the person opts for a treatment when this is required, their participation in a longitudinal study of an observational character may be jeopardized, because the natural outcome will be modified in consequence of the implemented treatment.

A similar situation may apply, yet even more problematic, if incidental findings (i.e., pathological or "borderline" pathological findings) are discovered during structural MRI examinations, which may have important lifelong consequences, for example due to health insurance questions (Marshall & Hadskis, 2009). In respecting the participants' preferences, it is often the rule

to inform them that their scans will not be analyzed in a qualitative, individual, and diagnostic manner as part of a radiological evaluation, but in a quantitative way as part of a research sample. This approach may pose ethical questions regarding the mission of the physicians involved in the work. In rare cases a life-threatening condition with a possible treatment may not come to the attention of the participant, and hence the chances of a positive outcome may be lost. However, reflecting on the potentially distressing or harmful consequences of examinations on many other study participants, it seems appropriate not to impose findings of uncertain relevance on the participants that they have not asked for. The rule is thus to inform participants that these medical examinations will not substitute the examinations that they should undergo in case of symptoms. Nevertheless, if incidental findings are found that require action as determined by a neuroradiologist, the participant will be referred for further medical investigation, as this is the case for other incidental clinical findings that are evaluated to be pathological. A recent study reported that research MRI scans should be reviewed for incidental findings, based on a survey, indicating that the larger part of participants wanted all results reported back to them, whereas stakeholders (such as members of the ethical committee and investigators) preferred providing only those reports with clear clinical significance for the well-being of the individual (Phillips et al., 2015). No single manner of handling incidental findings in neuroimaging thus exists so far and the matter needs more discussion. The agreements should always state how incidental findings will be handled.

Future directions and conclusion

In recent years, the interest for clinical research in individuals with psychosis has progressively shifted toward detection and treatment approaches in the earliest nonspecific stages of the disease trajectory. Indeed, the high prevalence and impact of mental disorders in young people, the limitations of current diagnostic systems and risk identification approaches, the diffuse symptom patterns in early stages, and their polymorphic, pluripotent and transdiagnostic trajectories, all indicate the need to develop a new diagnostic and predictive strategy to encompass a broader range of input and output target syndromes. This has led to the definition of a broader "at risk" state named Clinical High At Risk Mental State (CHARMS) (McGorry et al., 2018). This term refers to a broad composite definition of a syndrome warranting treatment in its own right due to help seeking and distress associated with presenting symptoms (McGorry et al., 2018). This approach facilitates the hope that an earlier identification of pathological processes that might lead to mental illness may enable therapeutic and preventive approaches, thus lowering the future disease burden. This shift has also been made possible by the development of digital tools, advanced statistical modeling (e.g., machine learning), and new genetic

and epigenetic knowledge (Fusar-Poli et al., 2021) that will allow for an increasingly preventive and personalized medical approach.

Consequently, the increased interest in a broader, transdiagnostic paradigm has boosted research in universal and selective prevention strategies (mental/physical health promotion in the general population or in at-risk populations) in adolescents. Currently, this seems to represent one of the most promising research domains in mental health research (Fusar-Poli et al., 2021). Nevertheless, this approach raises several ethical and social issues, which will need to be explored further and discussed with the stakeholders in a participatory approach. We have mentioned some of these areas of ethical consideration and reflection that call for further debate, such as: (1) the assurance of informed consent and assent, depending on the decisional capacity of the person; (2) the risk of stigmatization and self-stigmatization; (3) the minimization of study-related burden; (4) data sharing across large biobanks and the issue of data protection (e.g., in genetic studies); and (5) the handling of incidental findings, particularly in brain imaging studies. Finally, several recent developments and points merit further exploration and refinement. These include the implication of consultation by digital solutions, the adequate representation of minority groups in studies of adolescents, as well as the importance of giving thorough feedback to the research participants, which may enhance participation. If we take seriously the specific rights and needs of adolescents, as individuals, as research subjects, and as patients, we should strive toward the best possible health care for this population, which must include ethically responsible research.

Acknowledgments

The authors declare no conflict of interest and thank the editors for the invitation to contribute to this reflection, as well as to their contribution in identifying relevant topics and structuring the chapter.

References

Agerbo, E., Sullivan, P. F., Vilhjálmsson, B. J., Pedersen, C. B., Mors, O., Børglum, A. D., Hougaard, D. M., Hollegaard, M. V., Meier, S., Mattheisen, M., Ripke, S., Wray, N. R., & Mortensen, P. B. (2015). Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: A Danish population-based study and meta-analysis. *JAMA Psychiatry, 72*(7), 635–641. https://doi.org/10.1001/jamapsychiatry.2015.0346

Alaghband-Rad, J., McKenna, K., Gordon, C. T., Albus, K. E., Hamburger, S. D., Rumsey, J. M., Frazier, J. A., Lenane, M. C., & Rapoport, J. L. (1995). Childhood-onset schizophrenia: The severity of premorbid course. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(10), 1273–1283. https://doi.org/10.1097/00004583-199510000-00012

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (Vol. 5). American Psychiatric Association.

Angermeyer, M. C., & Matschinger, H. (2003). The stigma of mental illness: Effects of labelling on public attitudes towards people with mental disorder. *Acta Psychiatrica Scandinavica, 108*(4), 304−309. https://doi.org/10.1034/j.1600-0447.2003.00150.x

Appelbaum, P. S., Roth, L. H., & Lidz, C. (1982). The therapeutic misconception: Informed consent in psychiatric research. *International Journal of Law and Psychiatry, 5*(3−4), 319−329. https://doi.org/10.1016/0160-2527(82)90026-7

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment, 9*, 449−461. https://doi.org/10.2147/NDT.S39776

Arango, C., Díaz-Caneja, C. M., McGorry, P. D., Rapoport, J., Sommer, I. E., Vorstman, J. A., McDaid, D., Marín, O., Serrano-Drozdowskyj, E., Freedman, R., & Carpenter, W. (2018). Preventive strategies for mental health. *The Lancet Psychiatry, 5*(7), 591−604. https://doi.org/10.1016/S2215-0366(18)30057-9

Bolle, S. R., Trondsen, M. V., Stensland, G.Ø., & Tjora, A. (2018). Usefulness of videoconferencing in psychiatric emergencies – a qualitative study. *Health and Technology, 8*(1−2), 111−117. https://doi.org/10.1007/s12553-017-0189-z

Casey, B. J., Jones, R. M., & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences, 1124*, 111−126. https://doi.org/10.1196/annals.1440.010

Catalan, A., Salazar de Pablo, G., Vaquerizo Serrano, J., Mosillo, P., Baldwin, H., Fernández-Rivas, A., Moreno, C., Arango, C., Correll, C. U., Bonoldi, I., & Fusar-Poli, P. (2021). Annual research review: Prevention of psychosis in adolescents − systematic review and meta-analysis of advances in detection, prognosis and intervention. *Journal of Child Psychology and Psychiatry, 62*(5), 657−673. https://doi.org/10.1111/jcpp.13322

Choudhury, S., Blakemore, S. J., & Charman, T. (2006). Social cognitive development during adolescence. *Social Cognitive and Affective Neuroscience, 1*(3), 165−174. https://doi.org/10.1093/scan/nsl024

CIOMS. (2016). *International Ethical Guidelines for Health-related Research Involving Humans* (Fourth Edition). Geneva: Council for International Organizations of Medical Sciences (CIOMS).

Clayton, E. W., Halverson, C. M., Sathe, N. A., & Malin, B. A. (2018). A systematic literature review of individuals' perspectives on privacy and genetic information in the United States. *PLoS One, 13*(10). https://doi.org/10.1371/journal.pone.0204417

Colizzi, M., Ruggeri, M., & Lasalvia, A. (2020). Should we be concerned about stigma and discrimination in people at risk for psychosis? A systematic review. *Psychological Medicine, 50*(5), 705−726. https://doi.org/10.1017/S0033291720000148

Corcoran, C. M. (2016). Ethical and epidemiological dimensions of labeling psychosis risk. *AMA Journal of Ethics, 18*(6), 633−642. https://doi.org/10.1001/journalofethics.2016.18.6.msoc2-1606

Decety, J., & Michalska, K. J. (2010). Neurodevelopmental changes in the circuits underlying empathy and sympathy from childhood to adulthood. *Developmental Science, 13*(6), 886−899. https://doi.org/10.1111/j.1467-7687.2009.00940.x

Di Carlo, F., Sociali, A., Picutti, E., Pettorruso, M., Vellante, F., Verrastro, V., Martinotti, G., & di Giannantonio, M. (2021). Telepsychiatry and other cutting-edge technologies in COVID-19 pandemic: Bridging the distance in mental health assistance. *International Journal of Clinical Practice, 75*(1). https://doi.org/10.1111/ijcp.13716

Eisenberg, N., Cumberland, A., Guthrie, I. K., Murphy, B. C., & Shepard, S. A. (2005). Age changes in prosocial responding and moral reasoning in adolescence and early adulthood. *Journal of Research on Adolescence, 15*(3), 235–260. https://doi.org/10.1111/j.1532-7795.2005.00095.x

Emanuel, E. J., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *Journal of the American Medical Association, 283*(20), 2701–2711. https://doi.org/10.1001/jama.283.20.2701

Faden, R., Beauchamp, T., & King, N. (1986). *A history and theory of informed consent*. Oxford University Press.

Feldstein, E. (2018). Conditional disclosure on pathways to care: Coping preferences of young people at risk of psychosis. *Developmental Cognitive Neuroscience, 32*, 130–137.

Frith, C. D. (2007). The social brain?. In *Philosophical transactions of the royal society B: biological sciences* (Vol. 362, pp. 671–678) Royal Society. https://doi.org/10.1098/rstb.2006.2003. Issue 1480.

Fusar-Poli, P., Correll, C. U., Arango, C., Berk, M., Patel, V., & Ioannidis, J. P. A. (2021). Preventive psychiatry: A blueprint for improving the mental health of young people. *World Psychiatry, 20*(2), 200–221. https://doi.org/10.1002/wps.20869

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology, 31*(3–5), 373–385. https://doi.org/10.1023/A:1024190429920

Galván, A. (2017). Adolescence, brain maturation and mental health. *Nature Neuroscience, 20*(4), 503–504. https://doi.org/10.1038/nn.4530

Gardner, M., & Steinberg, L. (2005). Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: An experimental study. *Developmental Psychology, 41*(4), 625–635. https://doi.org/10.1037/0012-1649.41.4.625

Gore, F. M., Bloem, P. J. N., Patton, G. C., Ferguson, J., Joseph, V., Coffey, C., Sawyer, S. M., & Mathers, C. D. (2011). Global burden of disease in young people aged 10-24 years: A systematic analysis. *The Lancet, 377*(9783), 2093–2102. https://doi.org/10.1016/S0140-6736(11)60512-6

Green, W. H., Padron-Gayol, M., Hardesty, A. S., & Bassiri, M. (1992). Schizophrenia with childhood onset: A phenomenological study of 38 cases. *Journal of the American Academy of Child & Adolescent Psychiatry, 31*(5), 968–976. https://doi.org/10.1097/00004583-199209000-00027

Gronholm, P. C., Thornicroft, G., Laurens, K. R., & Evans-Lacko, S. (2017a). Conditional disclosure on pathways to care: Coping preferences of young people at risk of psychosis. *Qualitative Health Research, 27*(12), 1842–1855. https://doi.org/10.1177/1049732316680337

Gronholm, P. C., Thornicroft, G., Laurens, K. R., & Evans-Lacko, S. (2017b). Mental health-related stigma and pathways to care for people at risk of psychotic disorders or experiencing first-episode psychosis: A systematic review. *Psychological Medicine, 47*(11), 1867–1879. https://doi.org/10.1017/S0033291717000344

Hoffman, E. A., Howlett, K. D., Breslin, F., & Dowling, G. J. (2018). Outreach and innovation: Communication strategies for the ABCD study. *Developmental Cognitive Neuroscience, 32*, 138–142. https://doi.org/10.1016/j.dcn.2018.04.001

Hoop, J. G., Smyth, A. C., & Roberts, L. W. (2008). Ethical issues in psychiatric research on children and adolescents. *Child and Adolescent Psychiatric Clinics of North America, 17*(1), 127–148. https://doi.org/10.1016/j.chc.2007.07.003

Jones, P. B. (2013). Adult mental health disorders and their age at onset. *British Journal of Psychiatry, 202*(54), s5−s10. https://doi.org/10.1192/bjp.bp.112.119164

Kilicel, D., Badoud, D., von Plessen, K. J., & Armando, M. (2021). La maturation cérébrale chez les jeunes et la transition des patients consultants en pédopsychiatrie : y a-t-il une incohérence. *Cahiers de Psychologie Clinique, 57*(2), 15−40. https://doi.org/10.3917/cpc.057.0015

Lane, N. M., Hunter, S. A., & Lawrie, S. M. (2020). The benefit of foresight? An ethical evaluation of predictive testing for psychosis in clinical practice. *NeuroImage: Clinical, 26*, 102228. https://doi.org/10.1016/j.nicl.2020.102228

Larson, D. B., Magnus, D. C., Lungren, M. P., Shah, N. H., & Langlotz, C. P. (2020). Ethics of using and sharing clinical imaging data for artificial intelligence: A proposed framework. *Radiology, 295*(3), 675−682. https://doi.org/10.1148/radiol.2020192536

Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain and Cognition, 72*(1), 46−55. https://doi.org/10.1016/j.bandc.2009.10.008

Lerner, R. M., Lerner, J. V., Lewin-Bizan, S., Bowers, E. P., Boyd, M. J., Mueller, M. K., Schmid, K. L., & Napolitano, C. M. (2011). Positive youth development: Processes, programs, and problematics. *Journal of Youth Development, 6*(3), 38−62. https://doi.org/10.5195/jyd.2011.174

Lewin-Bizan, S., Bowers, E. P., & Lerner, R. M. (2010). One good thing leads to another: Cascades of positive youth development among American adolescents. *Development and Psychopathology, 22*(4), 759−770. https://doi.org/10.1017/S0954579410000441

Lewis, A. C. F., & Green, R. C. (2021). Polygenic risk scores in the clinic: New perspectives needed on familiar ethical issues. *Genome Medicine, 13*(1). https://doi.org/10.1186/s13073-021-00829-7

Link, B. G., Yang, L. H., Phelan, J. C., & Collins, P. Y. (2004). Measuring mental illness stigma. *Schizophrenia Bulletin, 30*(3), 511−541. https://doi.org/10.1093/oxfordjournals.schbul.a007098

Lysaght, T., Capps, B., Subramaniam, M., & Chong, S. A. (2012). Translational and clinical research in Singapore: Ethical issues in a longitudinal study of the prodromal phase of schizophrenia. *Early Intervention in Psychiatry, 6*(1), 3−10. https://doi.org/10.1111/j.1751-7893.2011.00318.x

Marshall, J., & Hadskis, M. R. (2009). Canadian research ethics boards, MRI research risks, and MRI risk classification. *IRB Ethics and Human Research, 31*(4), 9−15.

McCoy, M. S., Joffe, S., & Emanuel, E. J. (2020). Sharing patient data without exploiting patients. *JAMA - Journal of the American Medical Association, 323*(6), 505−506. https://doi.org/10.1001/jama.2019.22354

McDonald, M., Christoforidou, E., Van Rijsbergen, N., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., & Uhlhaas, P. J. (2019). Using online screening in the general population to detect participants at clinical high-risk for psychosis. *Schizophrenia Bulletin, 45*(3), 600−609. https://doi.org/10.1093/schbul/sby069

McGorry, P. D., Hartmann, J. A., Spooner, R., & Nelson, B. (2018). Beyond the "at risk mental state" concept: Transitioning to transdiagnostic psychiatry. *World Psychiatry, 17*(2), 133−142. https://doi.org/10.1002/wps.20514

McGorry, P. D., Tanti, C., Stokes, R., Hickie, I. B., Carnell, K., Littlefield, L. K., & Moran, J. (2007). headspace: Australia's National Youth Mental Health Foundation–where young minds come first. *The Medical Journal of Australia, 187*(7), S68−S70.

McGorry, P. D., Trethowan, J., & Rickwood, D. (2019). Creating headspace for integrated youth mental health care. *World Psychiatry, 18*(2), 140−141. https://doi.org/10.1002/wps.20619

Mollon, J., David, A. S., Zammit, S., Lewis, G., & Reichenberg, A. (2018). Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry, 75*(3), 270–279. https://doi.org/10.1001/jamapsychiatry.2017.4327

Mrazek, P. J., & Haggerty, R. J. (Eds.). (1994). *Reducing risks for mental disorders: Frontiers for preventive intervention research*. National Academies Press (US. https://doi.org/10.17226/2139

Mukolo, A., Heflinger, C. A., & Wallston, K. A. (2010). The stigma of childhood mental disorders: A conceptual framework. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(2), 92–103. https://doi.org/10.1097/00004583-201002000-00003

Munir, K., & Earls, F. (1992). Ethical principles governing research in child and adolescent psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(3), 408–414. https://doi.org/10.1097/00004583-199205000-00005

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont report: ethical principles and guidelines for the protection of human subjects of research*. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Ochsner, K. N. (2004). Current directions in social cognitive neuroscience. *Current Opinion in Neurobiology, 14*(2), 254–258. https://doi.org/10.1016/j.conb.2004.03.011

Øie, M. G., Sundet, K., Haug, E., Zeiner, P., Klungsøyr, O., & Rund, B. R. (2021). Cognitive performance in early-onset schizophrenia and attention-deficit/hyperactivity disorder: A 25-year follow-up study. *Frontiers in Psychology*, 11. https://doi.org/10.3389/fpsyg.2020.606365

Parker, W., Jaremko, J. L., Cicero, M., Azar, M., El-Emam, K., Gray, B. G., Hurrell, C., Lavoie-Cardinal, F., Desjardins, B., Lum, A., Sheremeta, L., Lee, E., Reinhold, C., Tang, A., & Bromwich, R. (2021). Canadian association of radiologists white paper on de-identification of medical imaging: Part 2, practical considerations. *Canadian Association of Radiologists Journal, 72*(1), 25–34. https://doi.org/10.1177/0846537120967345

Parrish, E. M., Kim, N. S., Woodberry, K. A., & Friedman-Yakoobian, M. (2019). Clinical high risk for psychosis: The effects of labelling on public stigma in a undergraduate population. *Early Intervention in Psychiatry, 13*(4), 874–881. https://doi.org/10.1111/eip.12691

Peterson-Sweeney, K. (2005). The use of focus groups in pediatric and adolescent research. *Journal of Pediatric Health Care, 19*(2), 104–110. https://doi.org/10.1016/j.pedhc.2004.08.006

Phillips, J. P., Cole, C., Gluck, J. P., Shoemaker, J. M., Petree, L. E., Helitzer, D. L., Schrader, R. M., & Holdsworth, M. T. (2015). Stakeholder opinions and ethical perspectives support complete disclosure of incidental findings in mri research. *Ethics and Behavior, 25*(4), 332–350. https://doi.org/10.1080/10508422.2014.938338

Polillo, A., Voineskos, A. N., Foussias, G., Kidd, S. A., Sav, A., Hawley, S., Soklaridis, S., Stergiopoulos, V., & Kozloff, N. (2021). Using digital tools to engage patients with psychosis and their families in research: Survey recruitment and completion in an early psychosis intervention program. *JMIR Mental Health, 8*(5), e24567. https://doi.org/10.2196/24567

Poulton, R., Moffitt, T. E., & Silva, P. A. (2015). The dunedin multidisciplinary health and development study: Overview of the first 40 years, with an eye to the future. *Social Psychiatry and Psychiatric Epidemiology, 50*(5), 679–693. https://doi.org/10.1007/s00127-015-1048-8

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., Poulton, R., & Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal of Psychiatry, 167*(2), 160–169. https://doi.org/10.1176/appi.ajp.2009.09040574

Roberts, L. W. (2002). Informed consent and the capacity for voluntarism. *American Journal of Psychiatry, 159*(5), 705−712. https://doi.org/10.1176/appi.ajp.159.5.705

Sacks, D. (2003). Age limits and adolescents. *Paediatrics & Child Health, 8*(9). https://doi.org/10.1093/pch/8.9.577, 577−577.

Sasangohar, F., Bradshaw, M. R., Carlson, M. M., Flack, J. N., Fowler, J. C., Freeland, D., Head, J., Marder, K., Orme, W., Weinstein, B., Kolman, J. M., Kash, B., & Madan, A. (2020). Adapting an outpatient psychiatric clinic to telehealth during the COVID-19 pandemic: A practice perspective. *Journal of Medical Internet Research, 22*(10), e22523. https://doi.org/10.2196/22523

Sawyer, K., & Rosenberg, A. R. (2020). How should adolescent heath decision-making authority be shared? *AMA Journal of Ethics, 22*(5), 372−379.

Schachter, D., Kleinman, I., & Harvey, W. (2005). Informed consent and adolescents. *Canadian Journal of Psychiatry, 50*(9), 534−540. https://doi.org/10.1177/070674370505000906

Shadili, G. (2014). Adolescents et jeunes adultes. *Information Psychiatrique, 90*(1), 11−19. https://doi.org/10.1684/ipe.2013.1141

Soll, D., Guraiib, M. M., Rollins, N. C., & Reis, A. A. (2020). Improving assent in health research: A rapid systematic review. *BMC Medical Research Methodology, 20*(1). https://doi.org/10.1186/s12874-020-01000-3

Sossauer, L., Schindler, M., & Hurst, S. (2019). Vulnerability identified in clinical practice: A qualitative analysis. *BMC Medical Ethics, 20*(1). https://doi.org/10.1186/s12910-019-0416-4

Spencer, B. W. J., Shields, G., Gergel, T., Hotopf, M., & Owen, G. S. (2017). Diversity or disarray? A systematic review of decision-making capacity for treatment and research in schizophrenia and other non-affective psychoses. *Psychological Medicine, 47*(11), 1906−1922. https://doi.org/10.1017/S0033291717000502

Steinberg, L., Icenogle, G., Shulman, E. P., Breiner, K., Chein, J., Bacchini, D., Chang, L., Chaudhary, N., Giunta, L. D., Dodge, K. A., Fanti, K. A., Lansford, J. E., Malone, P. S., Oburu, P., Pastorelli, C., Skinner, A. T., Sorbring, E., Tapanya, S., Tirado, L. M. U., … Takash, H. M. S. (2018). Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. *Developmental Science, 21*(2), e12532. https://doi.org/10.1111/desc.12532

Tavaglione, N., Martin, A. K., Mezger, N., Durieux-Paillard, S., François, A., Jackson, Y., & Hurst, S. A. (2015). Fleshing out vulnerability. *Bioethics, 29*(2), 98−107. https://doi.org/10.1111/bioe.12065

Tekin, S., & Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. *Journal of Psychosomatic Research, 53*(2), 647−654. https://doi.org/10.1016/S0022-3999(02)00428-2

The Adolescent brain cognitive development (ABCD) study.(2022). https://abcdstudy.org/.

The nuremberg code (1947). *BMJ, 313*(7070), (1996), 1448. https://doi.org/10.1136/bmj.313.7070.1448

The Schizophrenia Commission. (2012). The abandoned illness: A report from the schizophrenia commission. *Rethink Mental Illness*. http://www.schizophreniacommission.org.uk/the-report/.

Thorup, A. A. E., Hemager, N., Søndergaard, A., Gregersen, M., Prøsch, Å. K., Krantz, M. F., Brandt, J. M., Carmichael, L., Melau, M., Ellersgaard, D. V., Burton, B. K., Greve, A. N., Uddin, M. J., Ohland, J., Nejad, A. B., Johnsen, L. K., Ver Loren van Themaat, A. H., Andreassen, A. K., Vedum, L., … Nordentoft, M. (2018). The Danish high risk and resilience study—via 11: Study protocol for the first follow-up of the VIA 7 cohort −522 children born to parents with schizophrenia spectrum disorders or bipolar disorder and controls being Re-examined for the first time at age 11. *Frontiers in Psychiatry*, 9. https://doi.org/10.3389/fpsyt.2018.00661

Thorup, A. A. E., Jepsen, J. R., Ellersgaard, D. V., Burton, B. K., Christiani, C. J., Hemager, N., Skjærbæk, M., Ranning, A., Spang, K. S., Gantriis, D. L., Greve, A. N., Zahle, K. K., Mors, O., Plessen, K. J., & Nordentoft, M. (2015). The Danish high risk and resilience study - VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry, 15*(1). https://doi.org/10.1186/s12888-015-0616-5

Toscos, T., Coupe, A., Flanagan, M., Drouin, M., Carpenter, M., Reining, L., Roebuck, A., & Mirro, M. J. (2019). Teens using screens for help: Impact of suicidal ideation, anxiety, and depression levels on youth preferences for telemental health resources. *JMIR Mental Health, 6*(6), e13230. https://doi.org/10.2196/13230

Ungar, D., Joffe, S., & Kodish, E. (2006). Children are not small adults: Documentation of assent for research involving children. *Journal of Pediatrics, 149*(1), S31−S33. https://doi.org/10.1016/j.jpeds.2006.04.048

Wood, L., Burke, E., Byrne, R., Pyle, M., Chapman, N., & Morrison, A. (2015). Stigma in psychosis: A thematic synthesis of current qualitative evidence. *Psychosis, 7*(2), 152−165. https://doi.org/10.1080/17522439.2014.926561

Woods, S. W., & McGlashan, T. H. (2011). The risk-benefit ratio of the proposed DSM-5 attenuated psychosis syndrome. *American Journal of Psychiatry, 168*(12), 1338. https://doi.org/10.1176/appi.ajp.2011.11081276

World Health Organization. (2014). *Health for the world's adolescents: A second chance in the second decade: Summary.* World Health Organization. https://apps.who.int/iris/handle/10665/112750.

World Medical Association. (2013). Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA, 310*(20), 2191−2194. https://doi.org/10.1001/jama.2013.281053

Wright, A., Jorm, A. F., & Mackinnon, A. J. (2011). Labeling of mental disorders and stigma in young people. *Social Science and Medicine, 73*(4), 498−506. https://doi.org/10.1016/j.socscimed.2011.06.015

Xu, Z., Müller, M., Heekeren, K., Theodoridou, A., Metzler, S., Dvorsky, D., Oexle, N., Walitza, S., Rössler, W., & Rüsch, N. (2016). Pathways between stigma and suicidal ideation among people at risk of psychosis. *Schizophrenia Research, 172*(1−3), 184−188. https://doi.org/10.1016/j.schres.2016.01.048

Yang, L. H., Anglin, D. M., Wonpat-Borja, A. J., Opler, M. G., Greenspoon, M., & Corcoran, C. M. (2013). Public stigma associated with psychosis risk syndrome in a college population: Implications for peer intervention. *Psychiatric Services, 64*(3), 284−288. https://doi.org/10.1176/appi.ps.003782011

Yang, L. H., Wonpat-Borja, A. J., Opler, M. G., & Corcoran, C. M. (2010). Potential stigma associated with inclusion of the psychosis risk syndrome in the DSM-V: An empirical question. *Schizophrenia Research, 120*(1−3), 42−48. https://doi.org/10.1016/j.schres.2010.03.012

Yung, A. R., Nelson, B., Thompson, A. D., & Wood, S. J. (2010). Should a "risk syndrome for psychosis" be included in the DSMV? *Schizophrenia Research, 120*(1−3), 7−15. https://doi.org/10.1016/j.schres.2010.03.017

Yurgelun-Todd, D. (2007). Emotional and cognitive changes during adolescence. *Current Opinion in Neurobiology, 17*(2), 251−257. https://doi.org/10.1016/j.conb.2007.03.009

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