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The Aging Brain

Course Guidebook

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Dr. Polk's research combines functional imaging of the human brain with computational modeling and behavioral methods to investigate the neural architecture underlying cognition. Some of his major projects have investigated changes in neural representations as we age, contributions of nature versus nurture to neural organization, and differences in the brains of smokers who quit compared with those who do not. Dr. Polk regularly collaborates with scientists at the University of Texas at Dallas and at the Max Planck Institute for Human Development in Berlin, where he is a frequent visiting scientist. At the University of Michigan, he is an associate chair of the Department of Psychology and the chair of the Health Sciences and Behavioral Sciences Institutional Review Boards.

Dr. Polk regularly teaches large lecture courses as well as small seminars on topics ranging from the human mind and brain, to cognitive psychology, to computational modeling of cognition. His teaching at the University

of Michigan has been recognized by numerous awards, including the Excellence in Education Award from the College of Literature, Science, and the Arts and the Arthur F. Thurnau Professorship, the university's highest undergraduate teaching award. He also was featured in the University of Michigan's Professors Reaching Out for Students (PROFS) lecture series and was named to The Princeton Review's list of the Best 300 Professors in the United States.

Dr. Polk's previous Great Course is *The Addictive Brain*. ■

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SUPPLEMENTAL MATERIAL

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The Aging Brain

Scope

Aging is associated with subtle declines in some cognitive abilities, but not others. As we age, we become a little more forgetful, get distracted more easily, and can't process information quite as quickly as we once did. We also become more susceptible to certain brain diseases, such as Alzheimer's disease, dementia, and stroke. At the same time, however, our knowledge, memory of cognitive skills, emotional processing, and many other aspects of mental life tend to remain stable or even improve with age. Why is that? And is there anything we can do to help our brains age more gracefully? This course answers these questions, and many others, by explaining what happens to our brains as we age and by discussing approaches to keeping our minds and brains healthy as we get older.

The first major section of the course explores the biological mechanisms that cause the physical deterioration associated with aging. One lecture discusses evidence demonstrating that many aspects of aging are actually genetic and explains how the structure of our DNA imposes a limit on the number of times our cells can divide. Another lecture explains how accumulating damage at a cellular and molecular level contributes to the physical changes associated with aging. These findings raise some interesting questions that the course will also address. Given that aging is associated with physical deterioration and death, should we think of it as a disease? And why hasn't natural selection already gotten rid of it?

After establishing these building blocks, the course turns to the brain itself. One lecture focuses on how aging affects the brain on a structural level, particularly in the prefrontal cortex, hippocampus, and white matter. The relationship between these structural changes and age-related changes in memory, attention, and processing speed is explained in depth. The next lecture explores changes in brain function and how the brain actually reorganizes itself to compensate for age-related deterioration. The course

also devotes lectures to two aspects of mental life that many people worry about as they age: mood and memory. It also covers the major diseases of the aging, including Alzheimer's disease, stroke, and Parkinson's disease. How these diseases progress and how they're treated, as well as risk factors to avoid and research aimed at finding a cure, are all discussed in depth.

The third major section of the course focuses on strategies that have been scientifically demonstrated to help the brain age more gracefully. The course explores how physical, social, and mental activity can improve brain function and delay, or even prevent, some of the cognitive declines associated with aging. What we eat and the amount of stress we experience can also have a profound effect, and the course explores why this is true and recommends steps we can take to eat healthier and reduce stress in our lives. Finally, the last lecture looks at the future of research on the aging brain, including promising approaches that offer the hope of slowing, stopping, or potentially even reversing the effects of aging on our bodies and our brains.

After taking this course, you will have a new understanding of what happens to the brain as we age, and why. And that understanding will give you new insight into the behavioral and cognitive changes that often accompany aging. You will know how aging affects us at the cellular, neural, and behavioral levels, and also how it doesn't. Perhaps most importantly, you will know what you can do, including specific strategies you can adopt, to help keep your mind and brain sharp and healthy as you get older.

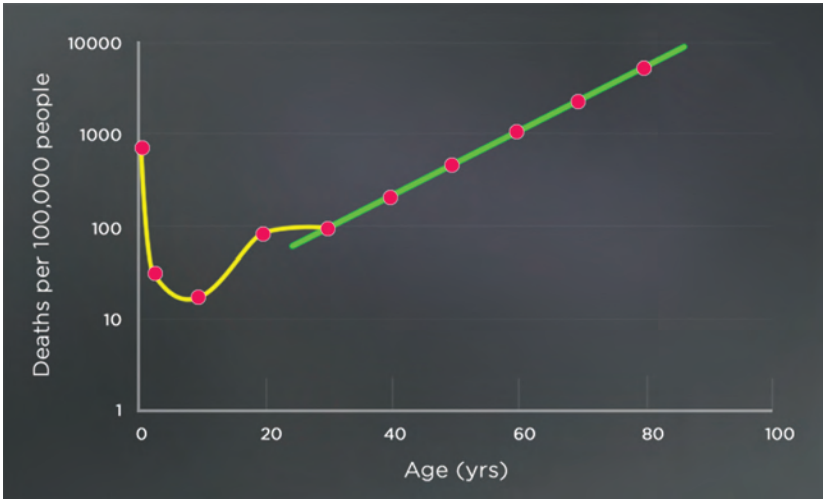
The Aging Mind: What Changes?

In this course, you'll discover that normal aging is associated with some types of neural and cognitive decline, as well as with an increased risk for certain brain diseases. But you'll also learn that for many people, age-related changes in the brain are fairly subtle and don't undermine their ability to lead stimulating and fulfilling lives. And many aspects of our mental life actually tend to remain stable or even improve with age. Furthermore, by adopting a few strategies that have been scientifically demonstrated to improve brain health, you may be able to delay or even avoid many age-related impairments. In this lecture, you'll learn that our brains age, but in very specific ways.

The Science of Aging

- When scientists talk about aging, they usually don't mean a simple increase in chronological years; they usually mean what's called senescence, or the accumulation of harmful effects that make us more fragile and vulnerable to disease and death as we get older. This increase in vulnerability is typically estimated by modeling mortality as a function of chronological age.

- After controlling for external causes such as being hit by a car or killed in a war, the chance of dying doubles every eight years after we reach adulthood. This exponential increase in mortality rate is sometimes called the Gompertz law of mortality, after British mathematician Benjamin Gompertz, who first discovered the relationship in the early 1800s. And that increasing vulnerability and deterioration is what scientists usually mean by aging.



- The number of older people in the U.S. population has been growing dramatically. In 1900, only about 4 percent of the U.S. population was aged 65 or older, whereas today more than 13 percent of our population is. Likewise, only about 3 million Americans were aged 65 or older in 1900; today, that number is more than 40 million.

- The last 150 years have also seen a dramatic increase in life expectancy, or the number of years that a newborn baby can be expected to live on average. In 1850, life expectancy was less than 40 years. By 1930, it was around 60 years. Today, it's almost 80 years. So, the average life span has roughly doubled in the past 150 years.

- The main reason that life expectancy has increased is not because we age more slowly, but rather because we've gotten so much better at treating diseases that have nothing to do with age, particularly in infants and children. For example, infant mortality rates today are more than 25 times lower than they were in 1900.

The average life span has roughly doubled in the past 150 years.

- And the evidence suggests that the aging process hasn't changed. For example, the probability of dying doubles every 8 years after we reach adulthood. That's called the mortality rate doubling time, and it hasn't changed much over the last century. In fact, the original estimate was calculated in 1825, and it has remained very similar ever since.

Analyzing Three Types of Memory

- Unfortunately, the brain ages—it also experiences senescence. It deteriorates and becomes more vulnerable to damage and disease as we get older. For example, aging is associated with significantly higher risk for many brain diseases. In fact, age is the single greatest risk factor for Alzheimer's disease, Parkinson's disease, and stroke.

- But aging is also associated with cognitive declines even in the absence of significant disease. However, it turns out that those declines are often restricted to a few specific cognitive processes, and for many people, even those declines are relatively subtle.

- Some of the best work on age-related changes in cognition has been done by Dr. Denise Park at The University of Texas at Dallas. In 2000, she and her research team recruited nearly 350 healthy people ranging in age from 20 to 92 and gave them all a battery of cognitive tests, assessing everything from processing speed, to different types of memory, to vocabulary. Then, they compared those abilities in each decade of life.

- Specifically, they found that some aspects of cognitive function declined, but many others didn't. In particular, they identified three specific areas of mental function in which aging seemed to have a detrimental effect: processing speed, executive function, and episodic memory.

- Participants in the study performed three different tasks that assessed processing speed. For all three tasks, they found the same results: 20-year-olds were the fastest, 30-year-olds were a little slower, and 40-year-olds were slower still. And with each passing decade, processing speed declined a little bit more. In fact, it declined by a roughly constant amount every decade. And this decline actually started in the 20s.

- Dr. Park's team also found that aging affected what's often called executive function, which refers to our ability to oversee and manage our more basic cognitive processes, such as recognizing a face or moving an arm. The executive functions of the brain include processes such as setting goals and deciding what to pay attention to and what to ignore. Dr. Park and her colleagues found that such executive functions tend to deteriorate a little as we get older.

- Perhaps the most important ability that depends on executive functions is what psychologists call working memory. Working memory refers to our ability to store information temporarily, maintain it over brief periods of time, and then retrieve it later on in the service of some mental

computation. It requires the ability to rehearse information that you want to remember, to update what you're trying to remember, and to retrieve information that you previously stored away. In short, it requires the ability to exert executive control over your memory system.

- Dr. Park's team asked their participants to perform a number of working memory tasks. And when they looked at performance as a function of age, they found a relatively constant, linear decline in performance with each passing decade, just like what they found with processing speed. Like processing speed, the decline started in the 20s. And this was true for all of the working memory tasks that they tested.

- Dr. Park and her colleagues also identified one other type of memory that sometimes declines with age: episodic memory, which is memory for specific episodes from your life. For example, your memory of a conversation, social event, or memorable trip that you took are episodic memories.

- Episodic memories are tied to a specific time and place and are remembered from a first-person perspective. Unlike working memories, which are short-term memories, episodic memories can last for a long time and are therefore considered to be long-term memories. For example, you may still have episodic memories from your childhood. But episodic memories can also be from just a few minutes ago.

- Dr. Park's team gave all of their participants four different tests of episodic memory. The results for all of the episodic memory tests looked very similar to each other. In fact, they looked almost identical to the working memory and processing speed results. Once again, there with a gradual, but relatively constant, decline with each passing decade.

Other Types of Memory

- But episodic memory isn't the only kind of long-term memory. In addition to memories for personal episodes, there are memories for facts, which are referred to as semantic memories. Unlike episodic

memories, semantic memories aren't tied to a specific time and place and are not remembered from a first-person perspective.

- Dr. Park's team also tested this kind of knowledge-based semantic memory. To do so, they used three different kinds of vocabulary tasks. The results for these tasks were very different than what they found for processing speed, working memory, and episodic memory. In fact, the older groups tended to perform better than the younger groups. In other words, we typically know more information when we're old compared with when we're young, which makes a lot of sense.

- Other types of memory are also preserved in normal aging. In particular, many types of unconscious, implicit memory don't seem to decline much at all. For example, people are typically faster and more accurate at processing information if they've processed that same information in the recent past.

- This is what psychologists call priming, and it's a very general memory phenomenon that applies in a variety of different domains. And it turns out that healthy older people show exactly the same kinds of priming effects as younger people do.

- Another type of memory that's preserved in normal aging is your memory for skills and habits, or what's sometimes called procedural memory. You may not be able to explain exactly how you perform these skills; you just have an unconscious memory for how to do so.

- Muscle memory for motor skills, such as riding a bike or tying a shoe, are good examples, but you also have procedural memories for cognitive skills, such as reading or speaking a language.

- Studies have repeatedly found that procedural memory doesn't normally decline as we get older. Although our strength and coordination may get a little worse, the underlying memory for how to perform motor skills that we've acquired seems to remain intact

as we age. Likewise, normal aging doesn't impair our memory for cognitive skills.

- There's also substantial evidence that emotional life gets better for most people with age. Older people report greater life satisfaction and fewer negative emotions than young adults do. They're also better at resolving interpersonal problems and at sidestepping social conflict.

- Dr. Park's results are consistent with a distinction between fluid intelligence and crystallized intelligence that was proposed by Dr. Raymond Cattell at the University of Illinois in the 1940s. Cattell showed that if you look at the performance of a large group of people across a wide range of tasks, you can typically identify two major factors that influence how well people do.

- The first is what he called fluid processing ability, or fluid intelligence, which refers to cognitive abilities that are relatively independent of what you know. Brain teasers and puzzles that depend more on your ability to think in creative ways than on how much you know emphasize fluid processing ability.

- The other factor is what Cattell called crystallized intelligence, which refers to cognitive abilities that depend critically on knowledge, experience, and acquired skills. For example, crossword puzzles place significant demands on crystallized intelligence because they depend a lot on how much you know about the world.

- Cattell showed that older people tend to do a little worse on fluid processing tasks than younger people do. But he also showed that older people tend to do better on tasks that rely on crystallized knowledge. And that's exactly what Dr. Park and her colleagues found.

- Declines in processing speed may actually underlie age-related declines in other fluid processing tasks, including tests of working memory and episodic memory. Likewise, problem solving and other fluid processing abilities might suffer.

- Consistent with these intuitions, there's now quite a bit of evidence that declines in processing speed may underlie a lot of the subtle cognitive declines associated with aging. For example, Dr. Park's team found that processing speed was a key predictor of how well people did on their fluid processing tasks, specifically their working memory and episodic memory tasks.

- Processing speed, working memory, and episodic memory definitely do decline with age. However, exactly when that decline starts is a little more controversial. Furthermore, there are substantial individual differences in how aging affects cognition, and experiencing cognitive impairments is not an inevitable consequence of aging.

Muscle memory for motor skills, such as riding a bike or tying a shoe, is classified as procedural memory.

Suggested Reading

Arkowitz and Lilienfeld, "Memory in Old Age."

Craik and Salthouse, *The Handbook of Aging and Cognition*.

Irving, *The Upside of Aging*.

Park and Schwartz, *Cognitive Aging*.

Salthouse, *Major Issues in Cognitive Aging*.

Questions to Consider

1. This lecture explained that scientists typically think of aging as increasing frailty and vulnerability (senescence). What do you see as the pros and cons of that way of defining it?
2. In this lecture, you learned a lot about how aging does, and doesn't, affect behavior. What surprised you the most? What did you find most predictable?
3. Do the results you learned about match your own experience? Do you think your own processing speed, working memory, and episodic memory have declined more than other cognitive processes?

LECTURE 2

Why Don't We Live Forever?

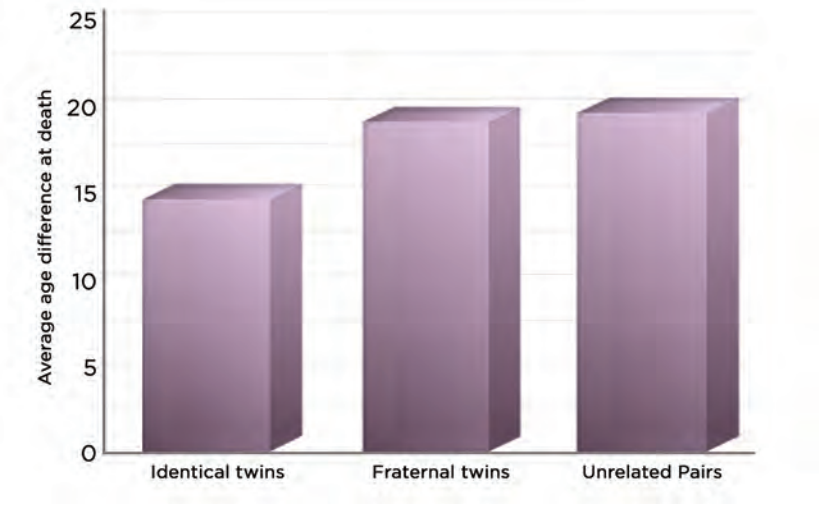
There's enormous diversity in how different species age, but there's also substantial consistency in life span within each species. Together, these facts suggest that aging might be part of a species' genetic program. This lecture will address three questions: Is it true that some aspects of aging are genetic? Why is aging influenced by genetics? What are some of the genetic mechanisms that lead to age-related deterioration?

Is Aging Genetically Programmed?

- A number of scientific studies suggest that some aspects of aging are genetically programmed. One piece of evidence comes from the study of twins. Identical twins have virtually the same genetic makeup, which is why they look so much alike and share so many traits. Fraternal twins, on the other hand, are no more similar genetically than any other siblings, so they tend to share a family resemblance, but they don't look identical.

- The same is true for any trait that is influenced by genetics. If a trait varies from person to person and is significantly influenced by genetics, then that trait should be more similar in identical twins than it is in fraternal twins. In particular, if our genes really do influence our life span, then we would expect the life spans of identical twins to be more similar than the life spans of fraternal twins. And it turns out that they are.

- Dr. James Vaupel and some of his colleagues in Denmark and Minnesota analyzed the life spans of 2,872 Danish twin pairs who were born between the years 1870 and 1900. They found that the correlation between age at death in siblings was higher in the identical twins than it was in the fraternal twins. Based on their data, they estimated that about 25 percent of the variability in life span could be



attributed to genetic factors. Apparently our genes really do influence how long we live.

- But scientists have gone much further than that. By now, they've identified dozens of specific genes that influence aging in different animal species. One of the first studies was published in 1988 by Thomas Johnson and David Friedman at the University of California, Irvine. They studied life span in a small roundworm called *C. elegans*.

- They separated worms that lived a long time from worms that didn't. By selectively mating the long-lived strains, they were able to show that a single genetic variant, which they named age-1, was associated with a roughly 50 percent increase in average life span and that it almost doubled maximal life span.

- When this discovery was first reported, many scientists assumed that the age-1 gene was not regulating aging itself. Rather, they thought that it was making the animals less fertile and that the animals were

Research on identical twins has shown that some aspects of aging are genetically programmed.

compensating for their reduced fertility by living longer to increase their chances of reproduction.

- However, in 1993, Cynthia Kenyon and her colleagues at the University of California, San Francisco, provided evidence for a genetic influence on aging that wasn't due to reduced fertility. They demonstrated that mutations in a different gene, called daf-2, caused worms to live more than twice as long as normal worms. These old mutant worms behaved a lot like young worms—for example, they were still very fertile.

- Furthermore, this research team was able to show that destroying the reproductive cells in normal worms, and therefore eliminating their fertility, did not actually increase their life span. These findings suggested that the rate of aging itself was under genetic control, independent of fertility.

- Inspired by these results in invertebrates, many scientists started looking for similar genes in humans that might be related to healthy aging. And although the jury is still out, there are some promising early results.

- For example, in 2008, Dr. J. David Curb and his colleagues at the University of Hawaii looked at the form of five hypothesized longevity genes in a few hundred Japanese men who were at least 95 years old—a relatively rare population. They also looked at the form of the same genes in a few hundred other subjects whose average age was 77—a population common enough to act as a control group.

- The very old men tended to have a different form of one of the genes compared with the control group. Since then, this same gene, called the FOXO3 gene, has been linked to human longevity in at least six other human cohorts around the world.

- A final piece of evidence for the hypothesis that some aspects of aging are genetically programmed comes from the study of patients with genetic disorders. In very rare cases, genetic anomalies can lead to what looks like extremely rapid aging.

Why Is Aging Influenced by Genetics?

- Why would we be genetically programmed to age and ultimately die? Aren't our genes supposed to be helping us survive?

- In the late 1800s, a famous German evolutionary biologist named August Weismann proposed an answer that is often referred to as the programmed death theory. According to Weismann, although aging is obviously not good for the individual, it is good for the species as a whole. In particular, if individuals in a species didn't age and die, then they would compete for food and other natural resources with the younger generations. Therefore, aging and death are necessary for a species to thrive.

- But a very significant problem for Weismann's theory is that animals in the wild don't usually die of so-called natural causes. They usually die from predation, disease, lack of food, or other external factors.

- So, it doesn't seem like there's any need for a genetic time limit on life span, because nature is dangerous enough that most individuals won't die of old age anyway. Most theorists, including Weismann himself, therefore abandoned the programmed death theory of aging.

- Recognizing this key problem, British biologist Sir Peter Medawar proposed an alternative theory in 1952 called the mutation accumulation theory of aging. The basic idea is that natural selection has less and less of an effect as we get older, and that's why genetic variants that lead to deterioration and death in old age don't get weeded out.

- There are two reasons why the impact of natural selection would get smaller as we get older. First, given that nature is dangerous and that individual animals are getting killed off all the time, there simply won't be that many old animals around. Therefore, if a genetic variant exists that causes old animals to become frail and die, it won't make much difference, because the animal isn't likely to reach that age anyway.

- The second reason is that genetic variants that have harmful effects late in life will have already been passed on to offspring. They therefore won't be selected against as strongly as variants that have harmful effects before reproduction.

- Genetic variants that lead to deterioration and death simply won't get selected against if their effect isn't felt until old age. As a result, they tend to accumulate, causing the kind of deterioration that we associate with aging. That's mutation accumulation theory.

- Medawar's theory has been very influential, but it does have at least one significant problem: Many of the harmful effects of aging begin relatively early in life, often before reproduction. For example, physical

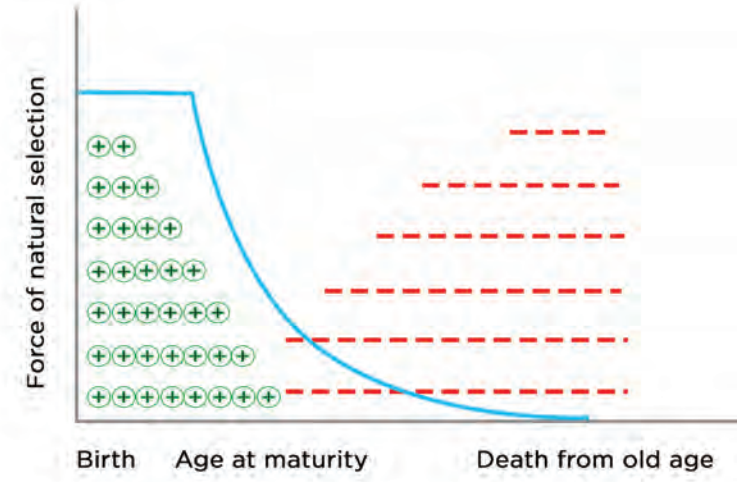
abilities tend to start declining around age 20. This seems inconsistent with Medawar's hypothesis.

- In particular, mutation accumulation would predict that harmful effects of age that appear during youth, when reproductive capacity is still high, should be selected against and eliminated. But apparently they aren't. Why not?

- In 1957, George Williams at Michigan State University proposed a variant of Medawar's theory that addresses this question. His theory has come to be known as antagonistic pleiotropy. Pleiotropy refers to the well-established fact that a single gene can have different effects within the same organism. Williams proposed that sometimes these effects could be antagonistic—that is, one effect of the gene might be beneficial to the organism while another effect is harmful.

- Williams argued that age-related impairments could be seen as examples of this kind of antagonistic pleiotropy. Specifically, he suggested that a genetic variant that is beneficial during youth might

Antagonistic Pleiotropy



actually be harmful during old age. And following Medawar, Williams assumed that the effects of natural selection would get smaller and smaller as we get older. Consequently, a genetic variant that leads to deterioration in old age could still be selected for if it increases fitness and reproductive success during youth.

- One specific mechanism by which antagonistic pleiotropy could explain aging was proposed by Dr. Tom Kirkwood at the National Institute for Biological Standards and Control in London. He argued that our body is constantly deteriorating at a molecular level and must be repaired. However, making those repairs requires energy—energy that could be used for other functions, such as reproduction.

- There is therefore an inherent trade-off, or antagonism, between energy invested in reproduction and energy invested in maintenance and repair of the body. Consistent with the idea that natural selection cares more about reproduction than it does about living for a long time, maintaining the body gets sacrificed. This view is often called the disposable soma theory of aging.

How Do Our Genes Control Aging?

- One question these theories don't address is how our genes control aging. In particular, what are some of the biological mechanisms that make us grow old and die?

- In 1961, a young microbiologist at The Wistar Institute in Philadelphia named Leonard Hayflick compared older cells, which had already divided a lot, with young cells, which had only divided a few times, and found that the older cells stopped dividing long before the young cells did.

- What is it about the cells that limited their life span? One possibility is simply the passage of time. But another possibility is that the limitation is based on the number of previous cell divisions independent of time.

- Through his research, Hayflick discovered that the fundamental constraint is on the total number of cell divisions, or replications, and is independent of time. In fact, it's now well established that most human cells are only capable of about 50 to 70 divisions before they enter what is often called cellular senescence and can no longer divide. This specific limit is now referred to as the Hayflick limit.

- Why is there an inherent limit on the number of times a cell can divide? About 10 years after Hayflick's original experiments, Russian biologist Alexey Olovnikov proposed a theoretical possibility that was subsequently shown to be correct.

- Whenever a cell divides, both new cells need a copy of the genetic material. The enzymes that create new DNA molecules are called DNA polymerases, and they work by stringing together subunits of DNA, which are called nucleotides, one at a time, in a single direction.

- Olovnikov proposed that if the DNA polymerase can't copy the DNA all the way to the very end, then the DNA would become shorter with every replication. He suggested that once the DNA becomes too short, then the cell would enter cellular senescence and would no longer be able to divide.

- But why does it take around 50 replications before problems start to arise? There are disposable, protective caps at both ends of every DNA molecule called telomeres. They don't contain any genes; they just consist of the same six nucleotides repeated thousands of times.

- Just as Olovnikov predicted, these telomeres become shorter with every cell division because the very end doesn't get copied. But they protect the genes themselves and prevent them from getting truncated. With enough divisions, the telomeres get completely used up and can no longer protect the genes. And that's when cells reach the Hayflick limit, enter cellular senescence, and stop dividing.

- However, it turns out that some cells aren't subject to the Hayflick limit. For example, cancer cells can divide indefinitely and are often considered to be biologically immortal. What's going on in these seemingly immortal cells that allows them to bypass the Hayflick limit?

- In 1984, Dr. Elizabeth Blackburn and her graduate student Carol Greider discovered an enzyme that can rebuild telomeres after they've been shortened. They named this enzyme telomerase, and it has since been found to be active in about 90 percent of all human tumors. Furthermore, human cells that were genetically engineered to express telomerase were found to continue dividing long past the normal Hayflick limit. These findings led to a huge number of studies investigating the extent to which telomerase could slow or even reverse aging.

Suggested Reading

Arking, *Biology of Aging*.

Barzilai, Guarente, Kirkwood, Partridge, Rando, and Slagboom, "The Place of Genetics in Ageing Research."

Goldsmith, *Introduction to Biological Aging Theory*.

Hayflick, *How and Why We Age*.

Shay and Wright, "Hayflick, His Limit, and Cellular Ageing."

Questions to Consider

1. Based on what you learned, why do you think humans age? Which theory did you find most convincing?
2. This lecture considered evidence from other species (e.g., roundworms). What do you see as the pros and cons of studying other species to understand human aging?

Is Aging a Disease?

Is aging a disease? This question is a topic of considerable debate. Regardless of your opinion on it, it is clear that normal aging is associated with detrimental disease-like effects. And understanding the mechanisms behind those effects could potentially lead to treatments that address the many health problems associated with aging. Although scientists are still a long way from having a complete understanding of how aging produces its detrimental effects, research over the last few decades has identified a number of mechanisms that seem to play an important role. This lecture will discuss three of them: energy consumption, free radicals, and damage to DNA.

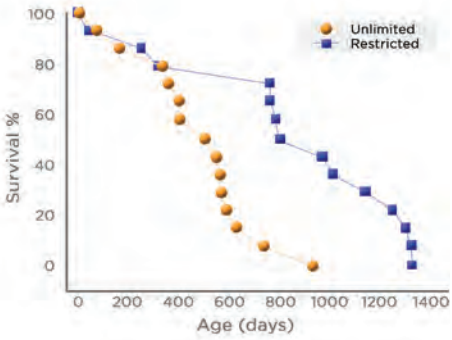
Energy Consumption

- The first scientific experiments on restricted diets weren't done until the mid-1930s by Clive McCay, Mary Crowell, and Leonard Maynard at Cornell University. Their experiments were inspired by the observation that animals that develop more slowly tend to live longer overall.

- McCay and colleagues therefore tried to slow down the growth of experimental rats by severely restricting the number of calories that they ate, while ensuring that they got all the vitamins and minerals that they needed to remain healthy. The rats on the restricted diet did grow more slowly, and they also lived roughly twice as long as the animals that ate as much as they wanted.

- Similar results have now been reported in a number of other short-lived species, including worms, flies, and even yeast. Furthermore, restricting caloric intake has also been found to decrease the incidence of cancer and other late-life diseases. So, it's not just that they live longer than control animals; these animals also seem to stay healthy longer.

Caloric Restriction and Life Span



- But will it work in long-lived species such as primates, particularly humans? Well-controlled human studies are almost impossible to do because they would involve carefully controlling many people's diets for most of their adult lives.

- There are, however, two studies on caloric restriction in monkeys that started in the late 1980s: one at the National Institute on Aging (NIA) and one at the University of Wisconsin. Unfortunately, after 25 years of following the animals, the two studies found conflicting effects on longevity.

- The Wisconsin study reported that caloric restriction significantly improved their monkeys' survival rate. In contrast, the NIA study did not find an effect of caloric restriction on longevity. They did report that the monkeys on the restricted diet were healthier than their control monkeys, but they didn't find any effect on survival rates.

- The authors of the Wisconsin study suggest that one possibility for the difference in results is how the control animals in the two studies were fed. In the Wisconsin study, the control monkeys were allowed to eat as much as they wanted. In the NIA study, the control monkeys ate more than the restricted animals, but the NIA scientists did put a limit on how much they ate.

- The Wisconsin team argued that the NIA control animals may have been on a restricted calorie diet themselves. If so, it could explain why they didn't see a significant difference in longevity between the groups. If both groups were experiencing caloric restriction, then both might be expected to live longer.

- Consistent with this interpretation, the NIA control monkeys weighed significantly less than the Wisconsin control monkeys and also less than comparable monkeys in a national database. Furthermore, five of the male NIA control monkeys lived more than 40 years, which is a very long time for monkeys.

- The jury is still out, but there's reason to believe that caloric restriction might extend life span in monkeys like it does in shorter-lived species. That certainly raises the hope that it might work in humans, too. In fact, many scientists interested in treating age-related deterioration are now trying to develop drugs that mimic some of the effects of caloric restriction.

- So, a lot of evidence suggests that, done right, caloric restriction without malnutrition can delay the effects of aging. But why would reducing caloric intake keep us healthy longer? We don't know for sure, but there are some promising possibilities.

- One theory is that when food is scarce, our cells reprogram their metabolism and enter a kind of standby mode in which more energy is devoted to cellular maintenance and repair. The thought is that such a mechanism helps animals survive periods of starvation. But a side benefit is that it also reduces the deterioration associated with aging.

Free Radicals

- Free radicals are atoms or molecules that contain unpaired electrons. Chemical species are more stable when their electrons are paired with other electrons, so free radicals are often unstable and prone to react with other molecules. In particular, when a free radical encounters another molecule, it may grab one of that molecule's electrons to pair with its unpaired electron and increase its own stability.

- There are many kinds of free radicals, but the ones most related to biology and aging are based on oxygen, and they're collectively referred to as reactive oxygen species. They are normal and are generated all the time in every cell in our body, and they're known to perform some

critical biological functions. For example, most white blood cells make reactive oxygen species and use them to fight infection.

- But reactive oxygen species can also be harmful. In particular, they can lead to chain reactions that ultimately damage molecules such as proteins and lipids that perform important functions. The body has a number of built-in mechanisms to try to keep free radicals under control, but those mechanisms can sometimes get overwhelmed, leading to a condition known as oxidative stress.

- In 1955, Dr. Denham Harman at Berkeley suggested that aging might be caused by the accumulation of this kind of free radical damage and oxidative stress. He was looking for a progressive mechanism that was present in every living thing and that was capable of causing deterioration and ultimately death.

- Harman was inspired by data suggesting that the speed of aging was directly related to the speed of metabolism. In particular, an animal like a mouse that has a fast metabolism tends to be small and age and die relatively quickly. In contrast, an animal like an elephant that has a relatively slow metabolism tends to be bigger and age more slowly.

- The idea of free radical damage seemed to fit well with these findings. Reactive oxygen species are universal enough to potentially explain why age-related deterioration is also so widespread. Furthermore, free radicals are a natural by-product of metabolism, so it makes sense that animals with a fast metabolism would age and die more quickly than animals with a slow metabolism. The faster metabolism leads to more free radicals, which in turn cause faster age-related deterioration.

- Harman's theory took a long time to catch on, but a growing body of evidence suggests that free radicals probably do play an important role in aging—specifically, in many types of deterioration associated with aging.

- Because antioxidants, such as vitamin C, vitamin E, and beta-carotene, can mitigate the effects of oxidation by free radicals, one might hope

that they could serve as effective anti-aging medicines. Unfortunately, the experimental results are not very promising. In particular, taking antioxidant supplements hasn't been found to reduce the risk of heart disease, stroke, or cancer.

- On the other hand, eating lots of antioxidant-rich foods, such as fruits and vegetables, does reduce your risk for many of the age-related diseases that have been associated with oxidative stress. Figuring out how to reconcile all these findings is a topic of current debate and research.

Damage to DNA

- DNA is crucial to life. The DNA in our chromosomes represents the master instruction set for all of our cells. It tells them how to make the thousands upon thousands of proteins that underlie all of the biological

Eating lots of antioxidant-rich foods, such as fruits and vegetables, has been shown to reduce your risk for many of the age-related diseases that have been associated with oxidative stress.

processes in our bodies. And if our DNA gets damaged, then that could undermine a cell's ability to make some of the proteins it needs to make, or it could cause the cell to make defective versions of the proteins. DNA damage can even lead cells to commit cell suicide in a process called apoptosis.

- Obviously, we want our DNA to be in good shape for as long as possible. Unfortunately, the DNA in our cells is under constant siege. Free radicals regularly damage our DNA. Ultraviolet rays from the sun or tanning beds can also damage DNA. Tobacco smoke is another well-documented cause of DNA damage.

- DNA damage happens a lot. In fact, scientists estimate that the DNA in each individual cell experiences tens of thousands of insults every day. The DNA strand gets broken, additional molecules get attached, a bend or kink can get introduced by the formation of an undesirable bond, and different chromosomes can get bonded together. These types of DNA damage are happening all the time in all of our cells.

- Fortunately, animals are equipped with sophisticated DNA repair systems that can usually detect damage to the DNA and fix it. However, although these repair mechanisms are very good, they're not perfect. Occasionally, mistakes slip through unnoticed, or the damage doesn't get repaired for some other reason.

- And the DNA repair mechanisms themselves are part of the DNA instruction set, so imagine what happens if that part of the DNA gets damaged. Then, more mistakes will slip through and the damage will only get worse. The end result is that DNA damage inevitably accumulates progressively as we age, and studies in a variety of different species have now confirmed that fact.

- Given how important DNA is to all aspects of biological function, it's probably pretty clear how accumulating DNA damage might contribute to age-related deterioration. Essentially, as the DNA instruction set becomes more and more defective, the cells have an increasingly

difficult time performing the biological functions that they need to perform. And this is happening throughout the body, in all kinds of cells—and the result is deterioration.

- That's the DNA damage theory of aging, sometimes called the somatic mutation theory. This theory was first proposed in the 1950s but has received a lot of new empirical support since then.

- For example, the theory predicts that species that repair their DNA faster and more effectively should age more slowly than species that repair their DNA more slowly and less effectively. And that prediction turns out to be true.

- Even stronger evidence comes from studies with mice that have been genetically engineered to do a bad job of repairing their damaged DNA. These mice seem to age faster than normal and also die much sooner.

Mice that have been genetically engineered to do a bad job of repairing damaged DNA seem to age faster than normal and also die much sooner.

- On the other hand, scientists have also tried to genetically engineer mice that do an extremely good job at repairing their damaged DNA, with the expectation that such mice would age more slowly and live longer. Unfortunately, a number of such attempts have failed to find evidence of increased life span, which poses a problem for the theory.

- A third piece of evidence comes from progeria syndromes, in which a genetic abnormality can sometimes lead to extremely accelerated aging. It turns out that many of these diseases are caused by genetic defects that undermine DNA repair, and that supports the idea that the accumulation of DNA damage may play an important role in aging.

Suggested Reading

Austad, *Why We Age*.

Brown, "A Radical Proposal."

Cornaro, *How to Live 100 Years*.

Selkoe, "Aging Brain, Aging Mind."

Stipp, "Is Fasting Good for You?"

Questions to Consider

1. Based on what you learned, do you think aging is a disease?
2. Based on what you learned, do you think caloric restriction would actually work in human beings?

Aging and Brain Structure

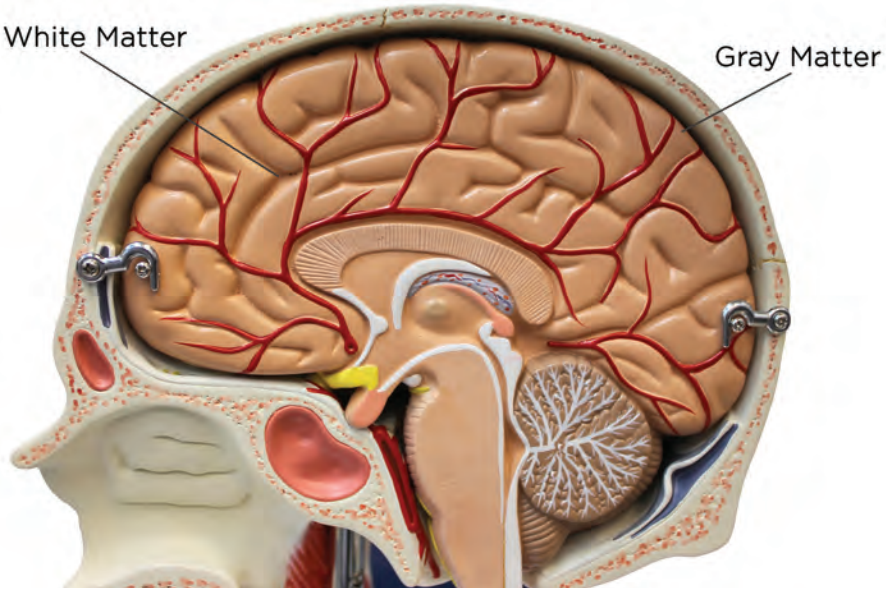
Why do some cognitive functions—such as executive function, episodic memory, and processing speed—decline with age, while many others—such as world knowledge, procedural memory, and emotional processing—remain stable or even improve? The brain regions that support executive function, episodic memory, and processing speed are the brain regions that are most susceptible to deterioration with age. This lecture will explore these regions and how they change. Specifically, this lecture will focus on three major brain changes that neuroimaging research has discovered: age-related changes in the prefrontal cortex, the hippocampus and medial temporal lobes, and white matter.

The Prefrontal Cortex

- If you look at a cross-section through a real brain, you'll see what looks like a ribbon of slightly darker tissue running around the outside of the brain. That is the cerebral cortex, and it's also called gray matter because of its slightly darker color.

- But if you look inside the outer ribbon on the cross-section, you'll see tissue that's significantly lighter in color. That's the white matter. Gray matter and white matter correspond to different parts of brain cells, which are called neurons.

- Neurons are specialized cells in the nervous system that can send and receive information using electrical and chemical signals. A neuron consists of three major parts: the cell body, the dendrites, and the axon.
  - The cell body is the central component of the neuron, and it contains the cell's nucleus, including its DNA.



- The dendrites are treelike branches that project out of the cell body and function like the neuron's antenna or ears. The dendrites receive signals from other neurons and propagate those signals to the cell body.
- In addition to dendrites, each neuron also has a long, slender projection that it uses to send signals to other cells. That's the axon. At the far end of the axon, it might typically connect with the dendrites of other neurons and thereby communicate with them. And these connections between neurons are called synapses.

◆ Dendrites are rarely longer than one to two millimeters, but axons can be much longer. But the length of axons poses a problem. We want to send information through the nervous system very quickly. Unfortunately, signals don't move down bare axons very quickly. Many

axons are therefore covered in a sheath of fatty insulating material called myelin that significantly speeds up neural transmission.

- Gray matter mainly consists of the cell bodies of neurons and contains relatively few myelinated axons. On the other hand, white matter mainly consists of myelinated axons, and it contains relatively few cell bodies.

- With the development of neuroimaging techniques, such as magnetic resonance imaging (MRI), scientists were able to start examining people's brains noninvasively while they were still alive. And when they started looking carefully at the cerebral cortex and white matter in individual people, they noticed that it looked different in older people compared to younger people.

- Naftali Raz and his colleagues at Wayne State University in Detroit have done some of the most systematic measurements of brain changes in aging. They discovered that the overall volume of gray matter declines with age. But the shrinkage is not uniform. Some brain regions shrink significantly faster than others. Two of the regions that shrunk the most were the prefrontal cortex and the hippocampus.

- The cerebral cortex is usually divided into four major lobes.
  - The cortex at the back of the brain is called the occipital lobe, which is where the age-resistant visual cortex is.
  - The cortex on the back half of the top of the brain is called the parietal lobe, which is particularly important in spatial processing and our sense of touch.
  - The cortex on each side of the head, behind the ears, is called the temporal lobe.
  - The cortex at the front of the brain is called the frontal lobe, and the front-most part of the frontal lobe is where you'll find the prefrontal cortex.

- The prefrontal cortex is the brain region we use to set goals. It also controls what we pay attention to and what we ignore, and it monitors and controls activity in other lower-level brain regions. And it plays a

crucial role in working memory. These are so-called executive functions, which are well known to decline as we get older.

- These functions depend on our prefrontal cortex, and our prefrontal cortex shrinks significantly as we age. So, it makes sense that these kinds of functions, but not others, would be significantly affected by age.

- Studies have shown that people who have greater prefrontal cortex volume tend to perform better on tests of executive function compared with people who have less, and this is true even after accounting for age.

The Hippocampus and Medial Temporal Lobes

- In addition to the prefrontal cortex, the hippocampus is another region that exhibits significant decline with age. It is also significantly smaller in older people.

- There are two hippocampi: one in the left hemisphere and one in the right hemisphere. They're located in the medial temporal lobes, which just means toward the midline of the temporal lobes, which are behind your ears.

- Numerous neuroimaging experiments have confirmed that medial temporal lobes, and the hippocampi in particular, are crucial to episodic memory. Age-related shrinking of the hippocampi might explain why our episodic memory abilities get worse as we get older. If these structures are crucial to episodic memory, and if they tend to get smaller as we get older, then it is not surprising that episodic memory abilities decline with age.

- And there's now substantial scientific evidence to support that hypothesis. Some of the best evidence comes from a 2011 study published by Jonas Persson, Lars Nyberg, and their colleagues at the Stockholm Brain Institute.

- As part of a large longitudinal study of aging called the Betula project, they measured hippocampal volume and performance in the same older individuals but years apart. They found that individuals who exhibited the most hippocampal shrinkage also exhibited the greatest decline in episodic memory performance. Using a technique called functional MRI, they also showed that the people whose memory performance declined the most also exhibited the greatest reduction in hippocampal activity during an episodic memory task.

White Matter

- If you compare MRI scans of younger and older people, one of the most striking differences is in the white matter. In particular, older people tend to have spots on their white matter that look brighter than normal in MRI images, whereas young people don't. These spots, referred to as white matter hyperintensities, reflect areas of damage to the white matter. They tend to show up around age 50 to 55 and often multiply and get bigger as we age, even in healthy older people.

- Another recent neuroimaging technique called diffusion tensor imaging (DTI) has discovered other important changes in white matter as we age. DTI measures the movement, or diffusion, of molecules in the body—particularly water molecules.

- In some tissues, water molecules can move in any direction relatively freely. But in other tissues, their motion is restricted, and they can move in some directions but not in others. DTI detects the directions that the molecules can, and can't, move, and it uses that information to construct an image of structural pathways.

- We can use DTI to map out white matter paths in the brain. Specifically, the motion of water molecules in axons is restricted. The molecules can move down the length of the axon, but they can't move outside the axons. So, by imaging the movement of water molecules in axons, we can get a picture of the where the axons go in the white matter tracts.

In MRI scans of the brain, older people tend to have spots on their white matter that look brighter than normal in MRI images, whereas young people don't. These spots reflect areas of damage to the white matter.

- Furthermore, if all the nearby water molecules are moving in the same direction, then you'll get a strong DTI signal, indicating that there is a very clear, coherent structure in the underlying white matter. On the other hand, if the water molecules in a given region aren't all moving in the same direction, then the DTI signal will be weaker, indicating less coherence in the underlying white matter.

- Well-myelinated, coherent white matter tracts lead to very coherent diffusion and high DTI signal, whereas poorly myelinated and incoherent white matter leads to lower DTI signal.

- Using this technique, scientists have found that white matter integrity or coherence tends to decline with age. Specifically, if you compare the DTI image of a young person with that of an older person, you'll see the same white matter tracts, but they won't be as bright in the older person, particularly in the front of the brain.

- So, white matter changes as we get older. In addition to white matter hyperintensities that reflect damage in specific areas, the overall integrity and coherence of white matter declines as we get older.

- The white matter is the communication network of the brain, sending signals back and forth between different brain areas. Furthermore, white matter is white because of the insulating myelin surrounding the axons. As our white matter declines with age, our myelin sheaths aren't what they used to be.

- The primary function of myelin is to speed up neural transmission. So, white matter decline should also make neural communication slower and less efficient. Naturally, if our neural communication gets slower, then our mental processing speed is likely going to suffer. And declines in processing speed are one of the hallmark features of the aging brain.

- Declines in processing speed may contribute to declines in other types of fluid processing, such as executive function and episodic memory. Recent studies have also found a clear relationship between white matter deterioration and these cognitive processes.

- Faith Gunning-Dixon and Naftali Raz examined the relationship between white matter hyperintensities and cognitive performance in 2000 at the University of Memphis and found that the top three aspects of cognition that were most strongly related to white matter hyperintensities were processing speed, executive function, and episodic memory. And these are the functions that tend to decline most with age.

- Studies of white matter using DTI are finding similar relationships. For example, David Madden and his colleagues at Duke University identified significant associations between white matter decline and impairments in executive function, processing speed, and to a lesser extent episodic memory.

Suggested Reading

Bloom, ed., *Best of the Brain from* Scientific American.

Fields, "White Matter Matters."

Haier, "What Does a Smart Brain Look Like?"

Jagust and D'Esposito, *Imaging the Aging Brain*.

Raz and Rodrigue, "Differential Aging of the Brain."

Questions to Consider

1. Why do you think the volume of a brain region would be related to behavior?
2. Based on what you learned, do you think damage to prefrontal cortex would be more or less debilitating than damage to the hippocampus? Why?

Aging and Brain Function

The structural changes that happen in the brain as we get older affect how the brain functions, and that's the topic of this lecture. Often, the structural deterioration that occurs is associated with a corresponding deterioration in neural function, and you will learn about some of the ways that the brain's function declines with age in this lecture. However, as you will also learn, there's now substantial evidence that our brains can reorganize themselves, and that reorganization can sometimes compensate for structural deterioration, allowing us to perform significantly better than we otherwise would.

Neural Specificity

- Research conducted by Dr. Thad Polk as a postdoctoral fellow at the University of Pennsylvania showed that people use very different parts of their brain to read letters and numbers. In particular, an area near the back and on the bottom of the left hemisphere seemed to respond selectively when people were processing letters and words, but not numbers.

- Other research has reported evidence for similar kinds of selectivity in neural response. For example, Nancy Kanwisher and her colleagues at the Massachusetts Institute of Technology found that a nearby brain area responded selectively to faces, while another area responded selectively to outdoor scenes. Yet another area responded selectively to body parts.

- Together, these studies demonstrate a fair degree of neural specificity in the brain's visual system, with different categories of stimuli being processed in different brain regions.

- But these studies were done in young adults, so a natural question is whether that kind of neural specificity changes as we get older. One possibility is that as we gain more and more experience, our neural representations become more and more specific. Or maybe neural specificity declines as we age, reflecting structural deterioration in the brain. Yet another possibility is that neural specificity doesn't change much after we reach adulthood.

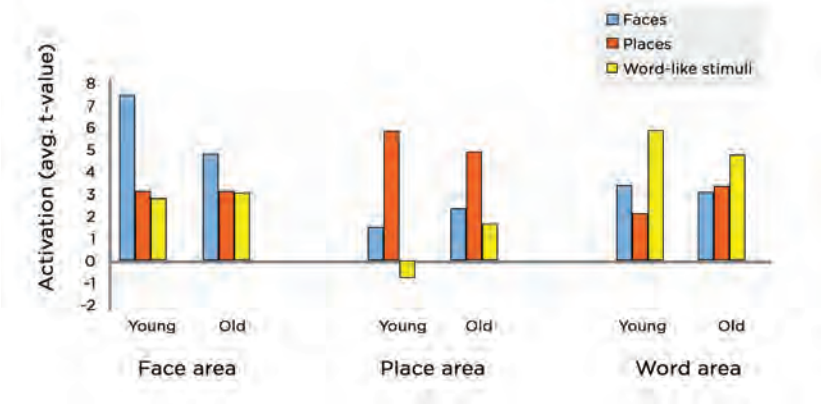
- A study conducted by Dr. Polk and Dr. Denise Park at the University of Michigan used functional magnetic resonance imaging (fMRI) to investigate how aging affects neural specificity. They scanned 13 college-aged young adults and 12 older adults whose average age was 70. Everyone read words and looked at pictures of faces and of places while neural activity was estimated with fMRI.

- Their findings in the young adults looked a lot like the previous findings demonstrating neural specificity. In virtually every young subject, they found an area that responded selectively to words, another that responded selectively to faces, and another that responded selectively to places.

- In contrast, the neural responses in the older participants were much less selective. The region that responded most to words also responded a lot to faces and places. The region that responded most to faces also responded a lot to words and places. And the region that responded most to places also responded a lot to words and faces.

- In short, the differentiation between neural responses was significantly reduced in the older people. This phenomenon is now often referred to as age-related neural dedifferentiation.

- Neural representations seem to get more confusable and less distinctive as we age. But does it make any difference? In particular, do older people who exhibit the most neural distinctiveness perform better than older people who exhibit the least?



- A study was conducted by Dr. Polk and Dr. Park, along with their graduate students, to investigate that question. They scanned 19 participants who were in their 60s and 19 others who were in their 20s. Everyone performed a simple visual matching task on pictures of faces and pictures of buildings. They then measured the distinctiveness of the neural activation patterns associated with faces and buildings in each individual participant.

- Consistent with their previous study, many of the older participants exhibited neural dedifferentiation—that is, the neural activation patterns evoked by faces and buildings weren't nearly as distinctive as they were in the young adults. On the other hand, some of the older participants looked a lot like young adults; their neural activation patterns were still quite distinctive and easy to tell apart.

- They also asked all the participants to perform a bunch of cognitive tasks that typically decline with age, such as executive function and processing speed tasks. But they also gave them a task that typically doesn't decline with age—a vocabulary task. Finally, they analyzed the relationship between neural distinctiveness and cognitive performance.

- They found that older people who showed the most neural distinctiveness also performed the best on measures of executive function and processing speed. Conversely, people exhibiting the least neural distinctiveness performed the worst on these tasks.

- But this relationship was only observed for the tasks that decline with age. For the vocabulary test, how distinctive a person's neural representations were didn't make any difference. So, neural distinctiveness affects performance on tasks that tend to decline with age, but it doesn't affect tasks that don't. And that supports the idea that changes in neural distinctiveness may be an important factor underlying age-related cognitive deficits.

Signal Variability

- An fMRI machine takes a picture of blood oxygen levels every few seconds, so the blood oxygen level is the signal that is being measured. Each image of the blood oxygen signal throughout the brain provides a snapshot of which parts of the brain are most active at a given point in time. By stringing these images together, you get a movie that shows changes in brain activity.

- Suppose that you zoom in on one cubic millimeter of the brain and watch the blood oxygen levels over time. You will find that the signal will vary, even if the participant is just resting and doing nothing. That's signal variability. The blood oxygen signal is variable over time. And that's true everywhere you look in the brain.

- But why does the blood oxygen signal vary even when someone is at rest and isn't doing anything? One natural assumption is that the signal is just noisy. After all, no instrument is perfect, and fMRI is no exception. So, you might expect to see variability in the fMRI signal even if the blood oxygen levels are perfectly constant.

- But in 2010, Doug Garrett, Cheryl Grady, and their colleagues at the University of Toronto demonstrated that that assumption is wrong.

Research has shown that a person's age can be predicted pretty accurately from the variability in his or her fMRI signal.

They measured fMRI signal variability throughout the brain in about 50 people while they did nothing but stare at a fixation point.

- They reported that signal variability declined with age in a number of brain areas. And these results were fairly consistent across the participants: Most of the older participants showed decreased variability in the same regions relative to the young participants.

- Apparently, fMRI signal variability is conveying important information that's relevant to aging. It isn't just noise. In fact, Dr. Garrett and his colleagues found that they could predict a person's age pretty accurately just by looking at the variability in his or her fMRI signal. Furthermore, variability-based predictions of age were far more accurate than predictions based on average blood oxygen levels—that

is, the variability of neural activity may be more relevant to aging than average activity levels are.

- In 2011, these same researchers showed that signal variability was strongly associated with behavioral performance. They found that people who exhibit greater variability in their fMRI signal tend to be faster and more consistent in their performance on speeded tasks. Younger people tend to have the most signal variability, so perhaps their increased neural variability contributes to their behavioral speed and consistency.

- An important open question is why increased variability would help performance. One possibility is that it prevents us from getting stuck in a mental rut. Neural variability might improve our mental flexibility. But we don't know for sure.

Communication between Different Brain Areas

- One of the classic studies in the area of how age affects communication between different brain regions was carried out by Adam Gazzaley, Mark D'Esposito, and their colleagues at the University of California, Berkeley, in 2005. They were looking for a neural mechanism that could explain age-related memory deficits, specifically in the ability to remember a picture after a delay, despite distraction.

- They showed a group of people in their 20s and another group in their 60s intermixed pictures of faces and outdoor scenes, and they asked them to remember one group of pictures while ignoring the other. They also used fMRI to estimate neural activity while people did this.

- Because of neural specificity, different parts of the brain respond selectively to different categories of visual stimuli. In particular, faces tend to activate a different part of visual cortex than outdoor scenes do. When Gazzaley's group tracked neural activity in the scene-selective region, they found that when young people were trying to remember scenes, neural activity in the scene-selective region was enhanced, but

when they were trying to ignore scenes, activity in the scene-selective region was suppressed.

- A natural explanation is that the scene-selective region was being modulated by another part of the brain and that this other brain region was exciting the scene-selective region when scenes needed to be remembered and was inhibiting that region when scenes needed to be ignored.

- The prefrontal cortex exerts that kind of executive control. Numerous studies have demonstrated that the prefrontal cortex excites and inhibits other parts of the brain depending on task demands—at least in young adults. What about in older adults?

- Gazzaley and colleagues found that their older participants exhibited the same kind of enhancement effects as the young people did. So, when the older people were trying to remember scenes, activity in the scene-selective region increased. However, the older adults did not exhibit the normal suppression effect—that is, when they were trying to ignore scenes, activity in the scene-selective region didn't decrease.

- So, the older participants had a selective deficit in neural inhibition. Although their prefrontal cortex could turn on relevant parts of the brain when necessary, it didn't do a good job in turning irrelevant brain areas off.

- Dr. Gazzaley and his collaborators found that this kind of deficit in neural inhibition contributes to age-related problems with memory. Specifically, older people whose neural inhibition was intact did better on the memory task than did older people whose neural inhibition was impaired. This experiment suggested that the ability to inhibit neural processing might be a crucial component of successful memory.

- More generally, a number of studies have found that as we get older, we tend to have a more difficult time turning off brain systems compared with when we were young.

Neural Reorganization

- There's now a lot of evidence that our brains don't take age-related declines lying down. Rather, our brains reorganize their processing in an attempt to compensate for these impairments and maintain our cognitive abilities for as long as possible.

- Some of the first evidence for neural reorganization came from Cheryl Grady, James Haxby, and their colleagues at the National Institutes of Health in 1994. They measured neural activity while older and younger people performed a face-matching task and a location-matching task.

- They found that young people activated posterior areas near the back of the brain more than older people did, while older people activated anterior regions near the front of the brain more than younger people did. This kind of posterior-to-anterior shift in aging has now been replicated in imaging studies of attention, visuospatial processing, working memory, and episodic memory.

- Furthermore, Simon Davis, Roberto Cabeza, and their colleagues at Duke University reported evidence that this reorganization actually helps cognitive performance. In particular, older adults who exhibited more activation in anterior regions such as the prefrontal cortex also performed better on an episodic memory test and a visual perception test.

- One natural interpretation of these results is that older adults compensate for impaired processing in posterior areas by increasing activity in anterior brain regions.

- Additional evidence for age-related neural compensation comes from studies of the lateralization of brain activity—that is, the extent to which brain activation is restricted to a single hemisphere versus both hemispheres. Roberto Cabeza, Patricia Reuter-Lorenz, and a number of other researchers have repeatedly found that cognitive tasks that evoke activity in a single brain hemisphere in young adults often evoke activity in both hemispheres in older adults.

- Many scientists have endorsed the compensation interpretation, although it's still a topic of ongoing debate.

Suggested Reading

Cabeza, Nyberg, and Park, eds., *Cognitive Neuroscience of Aging*.

Grady, "Cognitive Neuroscience of Aging."

Hedden and Gabrieli, "Insights into the Ageing Mind."

Park, Carp, Hebrank, Park, and Polk, "Neural Specificity Predicts Fluid Processing Ability in Older Adults."

Polk, Stallcup, Aguirre, Alsop, D'Esposito, Detre, and Farah, "Neural Specialization for Letter Recognition."

Questions to Consider

1. What do you see as the major strengths and limitations of functional MRI?
2. The lecture discussed age-related declines in neural specificity, in neural variability, in neural inhibition, and in the regulation of the brain's default network. Which do you think would have the biggest impact on cognitive performance, and why?
3. If older people perform better by recruiting brain regions that young people aren't using, why do you think younger people don't also recruit those same regions? Do you think they could perform even better if they did?

LECTURE 6

Emotional Aging

How do our outlooks change as we age? In particular, how do our emotions and mood change? As you will learn in this lecture, in many ways, our emotional life gets better as we get older. But this seems counterintuitive, because normal aging is associated with many kinds of deterioration. This is sometimes referred to as the emotion paradox of aging, and this lecture will introduce you to theories about what's going on. Finally, you will learn about depression in the elderly—specifically, about some of the signs and symptoms of depression in older people and what treatments are available to help.

How Our Emotions and Mood Change as We Age

- In 2013, the Substance Abuse and Mental Health Services Administration interviewed more than 65,000 Americans to examine the frequency of mental health problems and substance use in the country. When they looked at depression as a function of age, they found that 18- to 25-year-olds were 70 percent more likely to have experienced a major depressive episode in the past year compared with people over the age of 50.

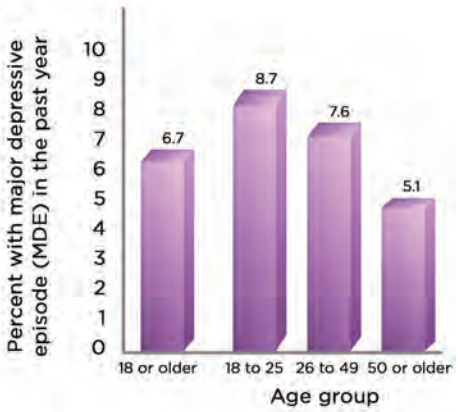
- Another study investigated how measures of life satisfaction changed with age. Daniel Mroczek at Fordham University and his colleague Avron Spiro at Boston University analyzed data from about 2,000 men who had completed mail surveys every few years that asked about satisfaction with their life. It turns out that life satisfaction peaked at age 65.

- A recent study found that older married couples rated their spouse more positively after a disagreement compared to middle-aged couples. Furthermore, relative to young adults, older adults report

fewer social conflicts, less anxiety, less anger, fewer regrets, and even less buyer's remorse.

- Why do so many people report higher levels of emotional well-being as they get older? One possibility is that these findings represent what's called a cohort effect—that is, the impact of being born at a particular time in history.

Prevalence of Depression as a Function of Age



- You can make a case that life is easier today than it was when our oldest generations were growing up. The standard of living and the average level of education have both increased substantially over the past 50 to 75 years, and health care has also improved dramatically during that time.

- Maybe older people aren't really any happier or more positive than younger people—it's just that their cohort went through tougher times. This explanation is based on the assumption that the older cohort has had very different experiences than the younger cohort, and it's these experiences that lead to differences in positivity and emotion, not their age.

- Cohort effects are a significant issue in aging research. In particular, many aging studies compare a group of older people with a separate group of younger people who were born in a completely different era. The hope is to gain insight into the effect of age on some process of interest, but it can often be difficult to distinguish whether an observed effect is due to age or to the different experiences of the two cohorts.

- That's why aging scientists often prefer studies in which the same people are followed over time as they age, rather than comparing people of different ages. This is the distinction between longitudinal studies and cross-sectional studies. Although following people longitudinally as they age takes a long time and is much more difficult, it's the only way to be sure that differences across age aren't simply a cohort effect.

- It turns out that the increased positivity observed in older generations is not due to a cohort effect. Although many of the original studies reporting increased positivity were cross-sectional, a number of longitudinal studies have also been done, and they've found the same thing: If you follow a bunch of people longitudinally, most people experience more positive emotions as they get older.

- One cynical possibility is that older people's positivity is actually another type of impairment. Maybe positive emotions are easier to process than negative emotions, so when you're impaired, you switch to processing mainly positive emotions. Or maybe aging selectively impairs brain regions that are involved in processing negative emotions.

- If that hypothesis were correct, then you would expect that older adults who are most cognitively impaired would be the most positive, while the most intact individuals would be the least. But in fact, the opposite is true: The sharpest older people are typically the most positive. The positivity seen in older adults seems to be a strategic choice, not a pathological impairment.

- Probably the most successful explanation for this is called socioemotional selectivity theory, which was developed by Laura Carstensen at Stanford University. One way of summarizing this theory is to say that older people realize that life is too short to focus on the negative.

- Socioemotional selectivity theory was proposed around 1990, and since then, a number of studies have found empirical support for it. In one of the first studies, Dr. Carstensen analyzed interviews that had been conducted with the same 50 people four times over the course

of their lives. The interviews asked planned questions about social relationships, relationship problems, patterns of interactions, and satisfaction with the relationships.

- Consistent with socioemotional selectivity theory, the subjects narrowed their social networks as they got older and focused more on family. So, apparently, as people get older, they do appear to spend more time with those closest to them, just as socioemotional selectively theory assumes. You can even see this starting to happen between young adulthood and middle age.

- And this narrowing appears to continue into old age. For example, a similar analysis of Germans in the Berlin Aging Study found that the number of social partners declined fairly steadily from age 70 up to age 100. Furthermore, the number of peripheral acquaintances declined a lot as these people got older, but the size of the inner circle of very close relationships didn't change much. As socioemotional selectivity theory assumes, we see evidence that people tend to narrow their social networks and focus on intimate relationships as they get older.

- But a key assumption of the theory is that it's not age per se that leads people to focus on emotional goals and to be more selective about who they spend time with. Rather, the claim is that older people have a more limited time horizon, and it's the realization that time is short that leads them to be selective.

- So, the theory predicts that even young people who realize that time is short will emphasize emotional goals and intimate relationships, just like older people do. To test this prediction, Dr. Carstensen collaborated with Barb Fredrickson at the University of Michigan. They compared gay men who were HIV positive and living with AIDS with other gay men who were HIV negative. They predicted that the men living with AIDS would have the shortest time horizon and would therefore put more emphasis on emotional goals and less emphasis on future-oriented, knowledge-based goals. And they did.

Many depressed older people claim that they don't feel sad, but rather that they just feel very unmotivated, hopeless, or empty.

Depression in the Elderly

- Clinical depression is a potentially serious mental illness that's typically characterized by pervasive and persistent feelings of sadness, hopelessness, or emptiness. Everyone feels sad sometimes, especially after experiencing traumatic events, but usually those negative feelings fade over time. And even during tough times, most people experience periods of happiness and joy.

- In contrast, in clinical depression, the negative feelings persist for weeks, months, or even years; they pervade all areas of life; and victims have a difficult time taking pleasure in anything. People suffering from depression often feel racked by guilt and a sense of worthlessness and

sometimes become preoccupied with thoughts of suicide. They may feel listless or exhausted and may lack the motivation to get out of bed and take care of personal hygiene, much less engage in challenging activities at work or school.

- Depression also often leads to significant changes in appetite and in sleeping patterns, and it's sometimes accompanied by increased use of alcohol or other drugs. It can even lead to cognitive problems such as indecisiveness and impairments in thought and concentration.

- Depression in older adults often looks somewhat different than it does in younger people. In particular, many depressed older people claim that they don't feel sad, but rather that they just feel very unmotivated, hopeless, or empty. They may complain about unexplained aches and pains and lose interest in socializing and hobbies. Depression in the elderly is also often associated with significant anxiety, irritability, slowed movement or speech, and memory problems.

- Unfortunately, perhaps because of these differences, depression in the elderly often goes unnoticed and untreated. Older people may not realize that their low energy, lack of motivation, and physical symptoms may be signs of depression, especially if they aren't experiencing overwhelming feelings of sadness.

- Other people mistakenly believe that depression is just a normal part of aging and may therefore not seek treatment. But depression is definitely not normal and should be treated.

- The significant life changes that are often associated with old age can sometimes trigger bouts of depression. Significant health problems that lead to disability or chronic pain are also a very common cause. Furthermore, some older people live alone and have very few social interactions, which can lead to loneliness and increase the risk of depression. There are also some prescription medications that have been associated with the disorder.

- Even retirement can lead to depression. Some older people feel a reduced sense of purpose and value, especially if they retired from a job from which they derived a lot of self-worth.

- But probably the most common cause is bereavement. The death of friends and family members is tough for anyone, and the death of a spouse has to be among the most difficult challenges anyone will ever face. It's only natural to feel profound pain and sadness at such a loss. And such grief is normal. But it can also trigger bouts of major depression that are neither normal nor healthy.

- There's also recent evidence that some of the age-related changes in the brain may contribute to depression in older people. Many cases of late-life depression may actually be caused by brain lesions rather than psychological trauma. This kind of depression is referred to as vascular depression, because the lesions are thought to arise from dysfunction in the vascular system that supplies blood to the brain.

- Because vascular depression is based on dysfunction in the vascular system and the white matter, it has some unique characteristics. In particular, it often arises out of the blue late in life, even in people who have no prior history of depression, and it typically doesn't respond as well to antidepressant medications as other forms of depression do.

- Treatment can help. Unfortunately, many older people with depression are not getting treatment, either because they don't realize that they have depression or because they feel uncomfortable about getting help. But depression is an illness, and like most other illnesses, getting the right treatment can make a world of difference. Furthermore, research has found that getting treatment earlier can reduce the length of time treatment is needed.

- The first step is getting a physical examination by a doctor to rule out other possible causes of the symptoms. If depression is diagnosed, the two most common forms of treatment are psychotherapy and antidepressant medication.

- Often, the most effective approach is to combine antidepressant medication with psychotherapy. In fact, a number of studies have found that combining the two treatments leads to significantly better results than either treatment alone.

- In cases of severe depression that don't respond to psychotherapy or medication, electroconvulsive therapy (ECT) can sometimes be very effective. Contrary to what you might imagine about ECT, modern ECT is a very safe procedure. Patients are anesthetized and given a muscle relaxant, and electrodes are placed on the scalp. Electricity is then passed between the electrodes while the patient is unconscious to generate a seizure. In many cases, these electrically induced seizures seem to reset the brain and can lead to dramatic improvements in patients with severe depression.

Suggested Reading

Carstensen, *A Long Bright Future.*

Charles and Carstensen, "Social and Emotional Aging."

Gross, ed., *Handbook of Emotion Regulation*.

Mather, "The Emotion Paradox in the Aging Brain."

Zaraska, "The Positivity Effect."

Questions to Consider

1. Do you think socioemotional selectivity theory captures the main reason older people report greater well-being and life satisfaction than younger people? What other factors do you think are important?
2. Why do you think the symptoms of depression typically look different in older people compared with younger people?

LECTURE 7

Strategies for an Aging Memory

Certain types of memory deteriorate as we age, and understanding how our memory works can help us use it more effectively. This lecture will emphasize four key points about memory. First, we tend to remember interesting information that we process deeply. Second, we remember visuospatial information better than verbal information. Third, we remember information that is connected to things we already know. Fourth, we remember information that we test ourselves on. As you'll learn, exploiting these principles can help us improve our memory.

We remember interesting information that we process deeply.

- Early models of memory assumed that repetition was the key to getting information into long-term memory. The assumption was that if you want to remember something, then it needs to be transferred from short-term memory into long-term memory. And the more you rehearse a piece of information, the more likely it is to get transferred into long-term memory.

- This assumption underlies the standard strategy that most people use when they try to remember new information: Just repeat it over and over in the hopes that it will get burned into long-term memory. But simple repetition doesn't always work.

- In 1972, Gus Craik and Robert Lockhart at the University of Toronto proposed an alternative framework based on depth of processing rather than number of repetitions. The basic idea is that you remember information that you think hard about and process deeply much better than information that you only process superficially. So, rather than just repeating information over and over, you're better off elaborating on the information and thinking about its associations and implications.

- In one famous experiment, participants were asked one of three questions about a bunch of different words. One question asked about the physical appearance of the word, such as whether the word was in italics. For that type of question, you don't even have to think about how to pronounce the word, much less what it means. Just a quick, superficial level of processing is sufficient to answer the question.

- Another question asked about the sound of the word, such as whether it contains the "B" sound or what it rhymes with. This type of question requires an intermediate level of processing. You do have to read the word and think about what it sounds like, which is deeper processing than the physical appearance question. But you still don't have to think about what the word means or how that meaning relates to other ideas.

- A third question required thinking about the word's meaning, such as whether you would be likely to see the word in the street or what a synonym of the word is. Those types of questions require the deepest level of processing. You can't answer them based simply on the physical appearance of the word, or even based on the sound of the word. You have to think about what the word means.

- Participants were given a long list of words, and for each word, they had to answer one of these three questions: a physical appearance question, a sound question, or a meaning question. Then, after a delay, they were asked to try to remember the words they had seen.

- Memory for words associated with the meaning questions was the best, memory for words associated with the sound questions was intermediate, and memory for words associated with the physical appearance questions was the worst.

- Note that all the words were presented equally often, so if memory strength were just based on repetition, then you wouldn't expect to find a difference. The bottom line is that deeper, more elaborate processing leads to stronger memory.

- It helps if the information we're trying to remember is interesting or strange. When we encounter information that's unusual or particularly interesting to us, then we naturally pay more attention to it and process it more deeply. Accordingly, we also remember it better. In fact, if you can transform the information you want to remember into a form that is strange, quirky, or funny, then you're much more likely to remember it.

We remember visuospatial information better than verbal information.

- We remember visual and spatial information much better than verbal information. In fact, there's evidence that our long-term memory system was designed to remember information about the locations of visual objects.

- The hippocampus is the brain area most associated with episodic memory, and it tends to shrink as we age, which might explain why episodic memory tends to get worse as we get older. The hippocampus is also the region typically damaged in patients with amnesia.

- Neuroscientists have begun to explore how the hippocampus works at the level of individual cells. Specifically, a number of experiments have recorded data from individual neurons in the hippocampus to investigate what makes those neurons fire. What makes many of those cells fire is spatial location.

Deeper, more elaborate processing of something you're trying to remember leads to stronger memory.

- In particular, scientists have discovered what are now called place cells and grid cells in the hippocampus of different species of animals. Place cells got their name because they tend to fire when the animal is in a particular place in their environment. In human terms, you might have some place cells that fire when you're in your living room and other place cells that fire when you're in your kitchen, and so on.

- Grid cells are similar to place cells, except they respond to multiple locations throughout the environment in a kind of grid. Imagine a tennis net laid out on the floor. But instead of small square holes, this net has large, triangular holes. A grid cell might fire whenever the animal is at one of the vertices where the cords in the net cross. Conversely, it might not fire when the animal is in the holes between the cords.

- These studies demonstrate that at a very fundamental level, our hippocampus is designed to process spatial information. And this makes sense if you think about it. Before the development of writing and math, it seems likely that remembering spatial locations was the most important function of memory. Do you remember where to find shelter? Do you remember where the water and food are?

- Furthermore, consistent with the neuroscience findings, a number of psychological experiments have demonstrated quite convincingly that we're much better at remembering visual and spatial information than we are at remembering verbal information.

- In 1967, Roger Shepard at Harvard University showed people about 600 pictures for six seconds each. Afterward, people had to indicate which of two alternative pictures they had actually seen. He found that people were correct 98 percent of the time.

- A few years later, Lionel Standing at Bishop's University in Canada showed people 10,000 color photographs for just five seconds each. Just displaying that many pictures took a few days. But despite only seeing each picture once and often days previously, people could indicate which of two images they had actually seen 83 percent of the time. Memory for verbal information was much worse.

We remember information that is connected to things we already know.

- Individual memories are not isolated—or at least strong memories aren't. Instead, strong memories are associated with lots of other information that we have stored away. Your memory of your kitchen is strongly associated with your memory of items in the kitchen, as well as with events that happened there, people who have been there, and so on.

- When you remember your kitchen, doing so naturally triggers related memories and brings them to mind. So, your kitchen can serve as a cue to help you remember the associated information.

- In general, if we can associate new information that we want to remember with existing information that's already stored in our long-term memory, then we can use the existing information as a cue to help us remember the new information.

We remember information that we test ourselves on.

- When most people think of testing, they think of a stressful exam that assesses how well you learned something. But a lot of recent research has found that testing is actually one of the most powerful ways to learn. It turns out that being tested on information often helps you remember it better than would studying the material again.

- Unfortunately, it's only recently that scientists have begun to appreciate the power of testing as a method to improve learning. One particularly powerful demonstration was conducted by Henry Roediger and Jeffrey Karpicke at Washington University in St. Louis. They asked 120 undergraduates to study and try to remember as much as they could about an article that you might read in an encyclopedia.

- One group of students studied the article in four different sessions for a total of 20 minutes. Another group of students only studied it once for five minutes but were then immediately tested three times. Specifically, they were given a blank piece of paper and were asked to write down

as much as they could remember. After that piece of paper was taken away, they were given another blank sheet and again asked to write down as much as they could remember. They then got a third blank sheet and did it one more time.

- They were not given any feedback about the accuracy of their memory and were never allowed to look back at the article.

- Both groups were also asked to guess how well they would remember the article a week later.

- The next week, everyone came back and tried to recall as much information from the article as they could. The students who studied the article for 20 minutes, but were never tested, remembered about 40 percent of the ideas from the original article after a week.

- The students who had been tested did much better. They managed to remember more than 60 percent of the original ideas. These were the students who had only studied the article once for five minutes, while the other group had studied it for 20 minutes. Despite not getting any feedback about what they wrote down on the three pieces of paper, the group that was repeatedly tested did much better.

- Incidentally, the students in the experiment expected the opposite: The people who studied the article for 20 minutes predicted that they would remember more than the people who only studied it for five minutes and then got tested. But they were wrong.

- The effects of testing on learning have important real-world implications for how we should study new information that we want to remember. Rather than passively reading and absorbing information, we should constantly be testing ourselves to see if we can generate the information.

Suggested Reading

Carey, *How We Learn*.

Foer, *Moonwalking with Einstein*.

Lorayne and Lucas, *Memory Book*.

Mishkin and Appenzeller, "The Anatomy of Memory."

Questions to Consider

1. In the age of smartphones, is having a good memory still important? Why?
2. Are there any other memory strategies that you find particularly helpful in your daily life?
3. What are some specific ways that you can use the memory principles you learned about in this lecture?

LECTURE 8

Dementia and Alzheimer's Disease

In this lecture, you'll explore what dementia is, what causes it, and what we can do about it. You'll learn about different types of dementia, some of the characteristic symptoms associated with dementia, and how we can distinguish dementia from the subtler cognitive impairments that we all experience as we age. Then, you'll learn about the most common cause of dementia in older people, Alzheimer's disease, including steps you can take to reduce your risk and research aimed at understanding the underlying mechanisms and finding a cure.

Dementia

- Dementia refers to a loss in mental abilities that is severe enough to interfere substantially with the normal activities of life. To be diagnosed as dementia, the mental impairment should not have been present from birth, should not be associated with any alteration in consciousness, and should last for more than six months.

- Dementia is usually progressive, meaning that the mental impairments get worse over time. Often, the first signs are significant memory problems, such as forgetting where you live or the names of close friends and family members. Reasoning abilities may get worse, making it difficult to plan activities, perform straightforward computations, or follow the storyline of a book or television show.

- People with dementia may also have trouble with language and may find it difficult to follow directions or put thoughts into words. They may become restless, agitated, or disoriented and start behaving inappropriately, or

even aggressively. They often lose interest in activities that they once enjoyed and may become passive or depressed. Ultimately, they may experience hallucinations, paranoid delusions, and personality changes that make them almost unrecognizable to their friends and family.

- Dementia is different than occasional mental lapses. Most older people experience memory problems from time to time. Perhaps they forget where they put their glasses or keys or where they parked their car. Many people experience problems like these as they age, and they aren't normally a cause for concern.

- However, if the mental lapses become severe enough to disrupt daily life, then it might be the beginnings of dementia. For example, temporarily forgetting the word for toothbrush probably doesn't indicate a problem, but forgetting what a toothbrush is for might.

- Warning signs include symptoms like repeatedly asking for the same information, finding it difficult to complete mental tasks that used to be easy, or forgetting what season it is. Other early symptoms could include getting lost in a very familiar environment, having trouble carrying on a simple conversation, or failing to take care of basic personal hygiene. Significant changes in personality or mood are also potential warning signs. If you notice symptoms like these in yourself or in someone else, then it's worth consulting with a doctor.

- There are a variety of different types and causes of dementia. Some types are reversible and will improve if the underlying condition is treated. For example, depression can occasionally produce dementia-like symptoms, which will often improve if the depression is treated. Other potentially treatable causes include a vitamin B_{12} deficiency and Lyme disease.

- Even commonly prescribed medications can produce symptoms associated with dementia. These symptoms can often be reversed by treating the underlying condition or by switching to a different medication. If you notice dementia-like symptoms in yourself or in a loved one, be sure to see a doctor.

Often, the first signs of dementia are significant memory problems, such as forgetting where you live or the names of close friends and family members.

- But dementia can also be caused by brain diseases. For example, more than 50 percent of patients with Parkinson's disease eventually develop symptoms of dementia, although it typically takes about 10 years after the onset of Parkinson's for such symptoms to appear.

- Progressive loss of neurons in the frontal and temporal cortex can also produce a dementia called Pick's disease, or frontotemporal dementia. This disorder is characterized by significant personality changes, apathy, and problems understanding and producing language.

- One fairly common type of dementia in older people is vascular dementia, or multi-infarct dementia. An infarct is a localized area of tissue that dies because of a lack of oxygen. When this happens in the brain, it's called a stroke.

- The victim of a major stroke may experience weakness or paralysis on one side of the body. The person may also exhibit abnormal speech, particularly if the stroke involves the brain's left hemisphere, which controls spoken language in most right-handed people.

- But it's also possible to experience minor strokes that only affect a very small part of the brain and don't lead to any outward symptoms. In fact, the victim may not even be aware that he or she had a stroke. These so-called silent strokes are probably much more common than major strokes that produce significant symptoms.

- Furthermore, silent strokes produce infarcts—that is, localized brain damage. And if someone experiences a series of multiple infarcts, the accumulation of brain damage can lead to dementia. That's why it's called multi-infarct dementia.

Alzheimer's Disease

- By far the most common cause of dementia is Alzheimer's disease. In fact, Alzheimer's disease accounts for 50 to 75 percent of cases of late-life dementia.

- Alzheimer's disease is named after Dr. Alois Alzheimer, a German psychiatrist who identified the first published case in a mental hospital in Frankfurt. On November 25, 1901, a railway worker named Karl Deter brought his wife Auguste to the hospital because she was becoming demented. Her memory was failing, and she was often delusional.

- Dr. Alzheimer describes his patient forgetting about objects she was just shown a few minutes before, misidentifying cauliflower and pork as spinach, and being unable to write her complete name.

- What interested him about Auguste Deter's case was her age. She was only 51 years old. In 1900, even doctors thought that dementia was a result of aging. Why would someone develop dementia at age 51?

- Alzheimer followed her case closely for the next five years. After she died in 1906, he carefully examined her brain. When he looked at her brain under a microscope, Alzheimer found two significant abnormalities that are now considered to be the defining features of Alzheimer's disease.
  - He found unusual clumps between neurons that turned out to be composed largely of protein fragments called amyloid beta. These clumps are now referred to as amyloid plaques.
  - He also found what looked like tangled strands inside many of the neurons. These tangled strands are now called neurofibrillary tangles.

- When scientists started examining the brains of other patients who had been demented before they died, they found these same kinds of plaques and tangles in many of them. In fact, finding these microscopic abnormalities in patients who had dementia is the only way Alzheimer's disease can be definitively diagnosed.

- Physicians and scientists can often be fairly confident of an Alzheimer's diagnosis based on behavioral symptoms, the patient's history, and brain scans, but they can never know for sure until they can look at the brain with a microscope after autopsy. That's why they often refer to their diagnosis as dementia of the Alzheimer's type or as probable Alzheimer's disease.

- The disease progresses at different rates in different people, but no treatments have yet been found that can slow or halt the disease. It usually has a late onset, meaning that it's diagnosed after age 65. When it's diagnosed before age 65, it's referred to as early-onset Alzheimer's disease, but that's much less common. On average, people live about four to eight years after their initial diagnosis, although some patients live significantly longer.

- There's currently no cure. There are, however, some palliative treatments that help relieve some of the symptoms as the disease develops.

- For example, the drug donepezil is often prescribed, especially during the early and middle stages of the disease. Another commonly prescribed drug is called memantine, which has been found to improve cognitive function in some moderate to severe Alzheimer's patients.

- Both genetic factors and environmental factors influence risk of contracting Alzheimer's disease. Most studies suggest that genetic factors may actually be more important. In fact, some genetic variants virtually guarantee that a person will develop Alzheimer's disease early in life, but these variants are very rare.

- A much more common genetic factor is the so-called APOE gene, which encodes the information necessary to make apolipoprotein E, which influences how likely it is for amyloid plaques to form. In particular, 40 to 80 percent of people with Alzheimer's disease carry at least one copy of the e4 version of this gene. If you carry two copies of that version, you're more than 10 times more likely to contract the disease late in life.

- There's nothing we can do about genetic risk factors, but there are nongenetic factors over which we do have some control. There are no guarantees, but research has shown that a number of behavioral changes can reduce the risk of contracting Alzheimer's disease. Most of these can be summarized in two pieces of advice: stay active and eat right. These two pieces of advice are important for everyone as they get older, even people who won't ever develop Alzheimer's.

- In 2005, Miia Kivipelto and Suvi Rovio at the Karolinska Institute in Stockholm, along with a number of their colleagues, examined the relationship between leisure-time physical activity during middle age and the subsequent development of Alzheimer's disease. They found that four to five percent of people who were sedentary during middle age developed Alzheimer's disease when they got older, while only two percent of the people who were active did. Similar results have been reported for people who regularly engage in cognitive and social activities.

Research has shown that staying active and eating right can reduce the risk of contracting Alzheimer's disease.

- A number of studies have found that eating a lot of fruits and vegetables, especially green leafy vegetables, can reduce your risk of Alzheimer's disease. Omega-3 fatty acids, which are found in salmon and certain other fish, have also been found to reduce the accumulation of amyloid plaques in experimental animals and may therefore reduce the risk of developing the disease. These foods are featured prominently in the so-called Mediterranean diet.

- A study out of Columbia University found that people who eat a Mediterranean diet are less likely to develop Alzheimer's disease than other people. Furthermore, people eating diets like these are less likely

to be obese and are also less likely to develop diabetes, both of which significantly increase risk for Alzheimer's disease.

- Most of the Alzheimer's studies investigating diet and activity are correlational—that is, physical activity and a healthy diet are correlated with reduced risk. But a correlation does not imply causation, so we can't say with certainty that diet and exercise cause a reduction in risk. Nevertheless, it seems quite plausible that they could help.

- Although there's still substantial debate about the key biological mechanisms that lead to Alzheimer's disease, most researchers today believe that the accumulation of amyloid plaques initiates a cascade of molecular events that lead to the appearance of neurofibrillary tangles within cells, to compromised neural function in the hippocampus and association cortices, and ultimately to Alzheimer's disease.

- This so-called amyloid cascade hypothesis has led to a number of promising directions to pursue to try to stop the disease. One idea is to try to slow down the accumulation of amyloid plaques. The core of these plaques is composed of protein fragments called amyloid beta that are part of a much longer protein but only accumulate into plaques when they get snipped off into shorter fragments.

- There are two enzymes that do the snipping: beta-secretase and gamma-secretase. Many scientists are exploring ways to inhibit these enzymes in the hopes of preventing the formation of amyloid beta fragments, thereby reducing the level of amyloid plaques.

- Another very promising approach is called immunotherapy. The basic idea is to try to use a person's own immune system to attack the amyloid plaques. These are just a few of the many approaches that scientists are exploring in their efforts to fight this disease.

Suggested Reading

Cayton, Graham, and Warner, *Dementia*.

Genova, *Still Alice*.

Mace and Rabins, *The 36-Hour Day*.

Magnusson, *Where Memories Go*.

Wolfe, "Shutting down Alzheimer's."

Questions to Consider

1. What was the most surprising fact that you learned about dementia from this lecture?
2. If you've known someone with Alzheimer's disease, how did their symptoms compare with the symptoms discussed in the lecture?
3. Why do you think interventions that improve cardiovascular health (such as diet and exercise) would reduce the risk of Alzheimer's disease?

Parkinson's Disease and Stroke

In this lecture, you will learn about two brain problems that typically attack late in life: Parkinson's disease and stroke. What's going on in the brain during Parkinson's disease? What about during a stroke? How do these problems affect our behavior? How can they be treated, and is there anything we can do to reduce our risk? What is the latest research telling us? These are the questions that will be addressed in this lecture.

Parkinson's Disease

- Parkinson's disease is associated with a number of motor symptoms, and two of the most prominent are shaking and rigidity. The shaking, or tremors, are often the first signs of the disease. They typically start in one of the hands or feet and then spread to other parts of the body as the disease progresses. One characteristic type of tremor is an involuntary back-and-forth rubbing of the thumb and forefinger, which is referred to as a pill-rolling tremor because that's what it resembles. The tremors are usually most severe at rest and might even disappear during voluntary movement.

- Rigidity, or stiffness, is another very common symptom. Muscles often contract involuntarily and stay that way for an extended period, making it difficult to move. The rigidity might be constant or might be an intermittent resistance that gives way in little jerks, which is sometimes called cogwheel rigidity. These sustained muscle contractions can also be quite painful. In fact, significant pain in the neck or back is often the problem that brings patients to the doctor initially.

- In addition to tremors and rigidity, Parkinson's is also associated with a slowing of movement, which is sometimes called bradykinesia. Sometimes external stimuli can help the patient move more quickly than they would otherwise.

- The other core motor symptom associated with Parkinson's is a difficulty with balance and posture, especially during the late stages of the disease. As a result, people with Parkinson's often fall a lot, which can lead to significant injuries.

- In addition to these four core motor symptoms, patients sometimes exhibit a so-called Parkinsonian gait when they walk. They tend to take small, shuffling steps and lean forward at the waist. Facial expressions also often become less expressive because of reduced control of the facial muscles, producing what's sometimes called a stone face or a

The motor symptoms that are associated with Parkinson's disease typically start in one of the hands or feet and then spread to other parts of the body as the disease progresses.

poker face. They might start speaking more softly, and their writing might get smaller.

- For a long time, scientists thought that Parkinson's only had significant effects on motor control, but more recent evidence has shown that it can also impair cognition and mood. The most common cognitive impairment is in executive control, which includes planning, problem solving, and other higher cognitive functions. A significant percentage of Parkinson's patients also develop dementia during the late stages of the disease.

- The most common emotional problems are depression and anxiety. Other common symptoms are sleeping problems, including difficulty sleeping at night and/or excessive sleepiness during the day. Many patients complain about an impaired sense of smell. Others complain about excessive sweating. Constipation and urinary incontinence are also very common.

- Given this wide range of symptoms, the disease affects different people in different ways. It can be a very idiosyncratic disease.

- What's going on in the brain that leads to these kinds of symptoms? The motor problems have long been known to arise mainly from the death of cells in a region of the brain stem called the substantia nigra. Neurons in the substantia nigra communicate with movement centers of the brain using the chemical neurotransmitter dopamine, so dopamine is crucial for voluntary movement.

- As we age, cells in the substantia nigra slowly begin to die off, usually at a rate of about four percent every decade. And although the loss of these cells may contribute to subtle declines in motor function as we age, this very gradual loss doesn't normally lead to major problems.

- But in Parkinson's disease, the neurons in the substantia nigra die much more quickly than normal. Once about 70 percent of the cells have died, the motor problems associated with the disease begin to appear.

- There's currently no cure for Parkinson's, but there are some treatments that have been demonstrated to help alleviate the symptoms. The most common treatment is based on trying to replace the dopamine that is being lost because of the deterioration of the substantia nigra.

- But you can't just take dopamine itself, because there's a protective barrier around the blood vessels in the brain that prevents harmful molecules from getting from the blood into the brain. Unfortunately, dopamine isn't able to cross this blood-brain barrier, so even if you get dopamine into the blood, it won't be able to help the brain.

- In the 1960s, scientists found a way to get around this problem with a drug called levodopa, or L-dopa for short, which can cross the blood-brain barrier and get to the dopamine neurons in the substantia nigra. Furthermore, once it gets there, those neurons are able to convert it into dopamine that they can then use.

- L-dopa is still the most effective medicine in the treatment of Parkinson's major symptoms. It's almost always used in combination with another drug called carbidopa, which helps prevent the breakdown of L-dopa before it reaches the substantia nigra. Combining the drugs allows patients to get the same benefits from much smaller doses of L-dopa, significantly reducing the likelihood of nausea and vomiting, which are common side effects of higher doses.

- There are still some problems, though. As the disease progresses, patients typically need to take larger and larger doses and also develop more significant side effects, such as involuntary movements and motor tics. They also often experience so-called off periods when they don't respond to the drug and have a difficult time moving. Doctors therefore often try to delay the use of L-dopa for as long as possible.

- Another approach to treatment, especially during the early stages of the disease, is to use what are called dopamine agonists. Rather than trying to replace dopamine itself, these drugs mimic some of dopamine's

effects. They therefore can help improve motor function that depends on dopamine.

- But they can also have side effects, including drowsiness, increased risky behavior, and even hallucinations. Many doctors begin treatment with dopamine agonists to delay the use of L-dopa until later in the progression of the disease.

- For patients whose symptoms can't be controlled by medications or who experience severe side effects from the medications, doctors will occasionally resort to surgery. Patients who undergo surgery can often decrease the amount of medication they take, which can significantly reduce the unpleasant side effects they experience.

- But it's important to remember that L-dopa, dopamine agonists, and even surgery only treat the symptoms of Parkinson's, not the underlying cause. Therefore, the disease will continue to progress at the same pace it was progressing before the treatments. In particular, once enough neurons die in the substantia nigra, these treatments will lose their effectiveness.

- We don't yet know what causes these dopamine neurons to die, but research on Parkinson's has made substantial progress in the last few years, so there's now optimism that we might able to beat this disease in the not-too-distant future.

- Scientists have tried using stem cells—special types of cells that are capable of differentiating into more specific cell types—to make new dopamine neurons. Another promising recent approach is based on what's called gene therapy. The idea behind gene therapy is to insert genes into specific brain cells so that those cells can then make a protein that might prevent, or at least slow down, the development of Parkinson's disease.

- Although we don't yet know what causes Parkinson's, scientists have identified a number of factors that can increase your risk. For example, extensive exposure to pesticides, as well as significant head injury, are associated with a higher chance of developing Parkinson's. Avoiding

these risk factors can reduce your chance of getting the disease. Exercising and eating right are also simple measures you can take that may reduce your risk.

Stroke

- A stroke happens when the blood supply to a part of the brain is interrupted for some reason. The blood provides brain cells with oxygen and nutrients that they need to survive. So, if a region of the brain doesn't receive any blood for more than a short period of time, then the neurons in that region will eventually die, and the functions they support will be compromised. That's a stroke. People who have had a stroke therefore often experience deficits in cognitive, motor, or sensory functions, depending on which part of the brain is affected.

- One characteristic feature of strokes is that the symptoms are often lateralized to one side of the body. Symptoms that are lateralized to one side of the body are therefore a telltale sign of stroke.

- You can also develop stroke-like symptoms that are temporary and resolve before brain damage occurs. That's referred to as a transient ischemic attack (TIA). Although they're less serious than strokes, TIAs should nevertheless be taken very seriously, because they indicate that a stroke is likely to occur if nothing is done. It's still important to see a doctor right away.

- Unfortunately, strokes are quite common. But they are often preventable. In fact, experts estimate that up to 80 percent of strokes could be prevented by appropriate management of the risk factors.

- Strokes are often treatable, especially if treated within the first few hours. It's therefore critical to be able to recognize the signs and symptoms of a stroke to get treatment as soon as possible.

- One easy way to recognize a stroke is to use the so-called FAST test, which was developed by stroke experts in England in 1998. FAST is

a simple acronym that reminds you to look for symptoms in the *face*, in the *arms*, and in *speech*, and if you notice any symptoms, then you need to react in a short period of *time* by calling 911.

- To check the face, you can ask the person to try to smile. If one side of the face droops or appears weaker, that's a danger sign. For the arms, you can ask the victim to put both arms straight out and keep them there. If he or she has trouble raising an arm or if one arm drifts down involuntarily, that's a sign of a potential stroke. Finally, you can check whether the person suddenly has difficulty understanding or producing speech. That, too, is a danger sign.

- If you do notice any abnormalities in the face, in the arms, or in speech, then you should call 911 right away, because the faster you get treatment, the better the outcome. Symptoms like this suggest the possibility of a stroke and constitute a serious medical emergency.

Reducing Your Risk of Stroke

- The National Stroke Association released a list of 10 ways to reduce the risk of stroke.
  1. Know your blood pressure. If it's high, work with your doctor to control it.
  2. Ask your doctor to check if you have an irregular heartbeat called an atrial fibrillation. If you do, ask how best to manage it.
  3. If you smoke, quit. Smoking doubles your risk of stroke.
  4. If you drink, do so in moderation. Small amounts of alcohol may actually reduce your risk of stroke, but if you don't drink, you certainly shouldn't start.
  5. Find out if you have high cholesterol, and if you do, work with your doctor to manage it.
  6. If you're diabetic, follow your doctor's recommendations carefully to keep it under control.
  7. Include exercise in your daily routine.
  8. Don't eat too much sodium or too much fat.

9. If you have circulation problems, work with your doctor to improve your circulation.
10. If you experience any symptoms of stroke, call 911 right away. Every minute matters!

If you follow these guidelines, you can significantly decrease your risk of stroke.

Suggested Reading

Fox, *Always Looking Up*.

Kringelbach and Aziz, "Sparking Recovery with Brain 'Pacemakers.'"

Okun, *Parkinson's Treatment*.

Taylor, *Stroke of Insight*.

Zivin and Choi, "Stroke Therapy."

Questions to Consider

1. Why do you think older people are more vulnerable to Parkinson's disease than younger people? Likewise, why do you think stroke is more common later in life?
2. Head injuries are associated with the subsequent development of Parkinson's disease. But correlation does not imply causation, and some scientists have raised the possibility that early stages of Parkinson's disease (before diagnosis) might lead to head injuries rather than the other way around. Which hypothesis do you find more plausible?
3. Do you know any victims of Parkinson's disease or stroke? If so, what symptoms were discussed in this lecture that you see reflected in their behavior? What symptoms do you not see?

Aging Well: Staying Active

In this lecture, you will learn about the effects of physical activity on the mind and brain, and especially whether exercise can forestall some of the effects of aging. Then, you will learn about the effects of social activity and whether interacting with other people can improve your health and lengthen your life span. Finally, you will learn about mental activity. Is there any science to support the idea that training your brain can keep you sharp as you age? What about intense intellectual engagement, such as learning a second language or taking a Great Course?

Physical Activity

- Physical activity is good for you, so it's no surprise that people who are physically active tend to live longer. Physical activity promotes a healthy cardiovascular system and therefore protects against heart disease.

- A lot of evidence suggests that physical exercise also makes your brain healthier. It sharpens your cognitive abilities and perhaps even protects you from some of the cognitive declines that are associated with normal aging.

- A number of large longitudinal studies—which follow the same people over a period of time—have found a correlation between physical activity and a healthy mind. In one famous study at Harvard's School of Public Health, called the Nurses' Health Study, researchers mailed questionnaires asking about walking and other physical activity to nearly 20,000 older nurses starting in 1986.

- Then, they called those same nurses 10 to 15 years later and asked them to perform some cognitive tests over the phone. They found that

the nurses who had been more physically active did better on the cognitive tests. The more-active nurses also exhibited less of a drop-off in their cognitive performance as they got older. And it wasn't just vigorous exercise that helped; nurses who walked at least 15 minutes a day showed the same benefits.

- Another large longitudinal study called the Canadian Study of Health and Aging followed more than 4,000 people who had been cognitively normal five years earlier to see who had developed cognitive impairments and dementia. The most physically active people were about 40 percent less likely to have developed cognitive impairments compared with people who were not active.

- Likewise, the most physically active people were about 50 percent less likely to have developed dementia of the Alzheimer's type. And it wasn't just high levels of physical activity that helped; even low levels of activity reduced the risk of cognitive impairments and of Alzheimer's disease by about 33 percent compared to no activity.

- These studies demonstrate an association between physical activity and healthy aging. But these results are correlational, so we can't tell definitively whether physical activity actually causes improvements in cognition and health.

- One influential study, in which scientists experimentally manipulated who exercises and who doesn't, was conducted by Kirk Erickson and Arthur Kramer at the University of Illinois, along with a number of their colleagues. They randomly assigned 60 older people to one year of aerobic exercise and another 60 older people to one year of stretching and toning as a control condition.

- Both groups had their brains scanned before and after the training. They also had their memory tested. And the scientists found that aerobic exercise reversed the normal age-related shrinkage in the hippocampus and led to improved memory performance.

Research has suggested that physical exercise might protect you from some of the cognitive declines that are associated with normal aging.

- A large number of animal studies have also demonstrated significant benefits from physical activity, both at a cognitive level and at a neural level. Although these studies don't involve humans, they can often be more informative than human studies, because they can be more carefully controlled. They also can make it possible to explore the biological mechanisms involved in much more detail than is possible in humans.

- One of the most important animal studies was done by Mark Rosenzweig at Berkeley, William Greenough at the University of Illinois, and their colleagues. They found that rats that are raised in enriched environments, with new toys every day and lots of other rats,

learn faster than rats raised in standard cages. Furthermore, these rats also have more connections between brain cells and an overall increase in cerebral cortex volume.

- One hypothesis for this is that rats in enriched environments are more physically active than rats in normal cages. But can physical activity alone produce those kinds of brain changes?

- Fred Gage and his colleagues at the Salk Institute for Biological Studies near San Diego began investigating that question in the mid-1990s and found that the answer is yes. In fact, they found that making rats exercise leads to the growth of new brain cells in the hippocampus, the brain area that is crucial for memory. Before then, most neuroscientists assumed that we can't grow new brain cells in adulthood, but Gage's work proved that that assumption was wrong.

- Subsequent animal studies have shown that physical activity also leads to new blood vessels in the brain, higher levels of chemicals that trigger growth in the brain, increased resistance to brain damage, and improved learning and cognitive performance.

Social Activity

- In a large longitudinal study at the Karolinska Institute in Stockholm, Laura Fratiglioni and her colleagues tried to address whether frequent social interactions help people live longer, healthier lives. They found that people with strong, positive social networks were 60 percent less likely to develop dementia compared with people with a poor or limited social network.

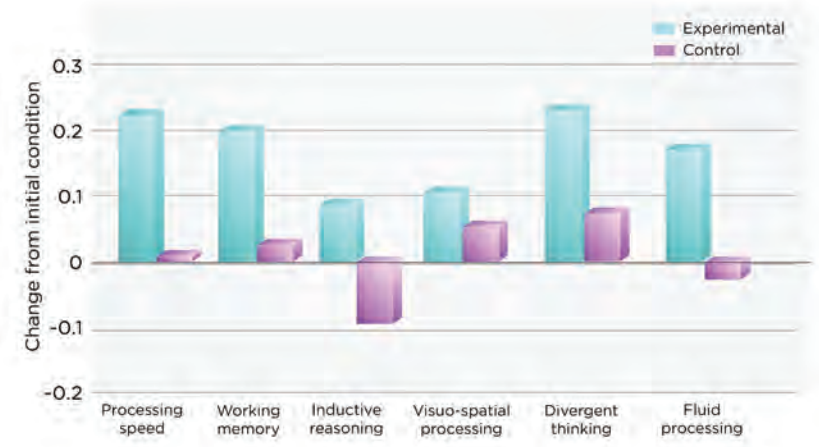
- Furthermore, social support may also improve recovery after brain injury. Maria Glymour at Columbia University and her colleagues investigated the effect of social support on recovery after a stroke. Stroke victims who had more social ties and stronger emotional support tended to perform better on cognitive tests six months after their stroke.

- Living alone versus with other people has also been shown to have a significant effect on cognition in older people. One study followed more than 1,000 European men over the age of 70 for 10 years. Men who lost a partner, were unmarried, or lived alone exhibited more than twice as much cognitive decline over the 10-year period compared with men who lived with someone.

- It's also important that the social interactions be positive rather than negative. In fact, people who report less satisfaction with their social network tend to exhibit greater cognitive decline than people who are more satisfied.

- But all of these studies are correlational, and correlation does not imply causation. To infer causality, we need experimental studies that randomly assign some people to more social interaction and some people to less. So far, there aren't very many of these studies.

People who report less satisfaction with their social network tend to exhibit greater cognitive decline than people who are more satisfied.



- One study that comes close was conducted by Elizabeth Stine-Morrow at the University of Illinois and her colleagues. They randomly divided a large number of older people into an experimental group and a control group. The people in the experimental group worked with five to seven other participants on a long-term project that involved 20 team meetings over a period of about six months. The control group just continued life as normal.

- The researchers tested a number of cognitive abilities both before and after the intervention, and the experimental group showed greater improvement on all of them compared with the control group.

- It's impossible to know whether it was the social interaction that led to the observed improvements in cognitive function. In addition to greater social interaction, the experimental group also engaged in more mental activity. It's even likely that they engaged in more physical activity than the control group, because they had to physically get to and from the 20 group meetings. So, although engaging in this group activity helped, we don't yet know why.

Mental Activity

- A number of websites, computer programs, and apps are now being marketed that claim that they can keep your brain sharp and improve your memory and attention. But do these products actually work?

- In 2014, the Stanford Center on Longevity and the Max Planck Institute for Human Development in Berlin gathered leading scientists in the field to discuss the effectiveness of these kinds of brain games and to prepare a statement summarizing their consensus about the existing science. They reached a number of important conclusions.

- First, claims promoting the advantages of brain games are often exaggerated and sometimes misleading. In particular, although cognitive training can definitely improve your performance on the specific task that you're practicing, there isn't convincing evidence that it will improve your performance on cognitive tasks that you engage in every day.

- Cognitive training has been shown to produce improvement in specific practiced skills, and that improvement sometimes extends to other closely related tasks, but in general the gains are typically very narrow.

- The scientists' consensus statement also pointed out the importance of considering opportunity costs when evaluating the benefits of cognitive training. In particular, if you're spending time playing brain games or solving crossword puzzles, then you're typically not spending that time being physically active or socializing, even though evidence suggests that physical activity and social interactions do help brain health.

- The scientists concluded their statement with the following five recommendations.
  1. Try to lead a physically active, intellectually challenging, and socially engaged life.

2. Try to incorporate physical exercise into your routine, because it has been shown to be an effective way to improve your health, including your brain health.
3. Be skeptical about claims based on the results of a single study or on the recommendation of a single scientist; many claims are based on fairly narrow findings that didn't generalize to real life and that haven't been replicated.
4. Remember that no studies have demonstrated that playing brain games will cure or prevent the development of Alzheimer's disease or other types of dementia.
5. Don't expect the benefits of mental training to last for extended periods of time after you've stopped the training. Mental training is not a vaccine that can prevent age-related cognitive decline.

- Even though there isn't strong evidence that brain-training games lead to general improvements in cognitive function, that does not that mean we don't need to stay cognitively engaged and keep our minds active. There's solid evidence that intense cognitive training that specifically targets processing speed, episodic memory, and executive function can improve our abilities in those domains. Given that these are the domains that tend to decline with age, that's very good news.

- More traditional intellectual engagement, such as learning a second language or taking a Great Course, has also proven to be helpful. A large number of studies have investigated the relationship between formal education and cognitive vitality late in life, and the consistent finding is that higher levels of education are associated with less cognitive decline during old age.

- Likewise, learning a second language has also been associated with improved cognitive function in older adults, particularly improved executive function. Neuroimaging studies have even found greater white matter integrity and prefrontal cortex volume—both of which tend to decline with age—in bilinguals compared with monolinguals.

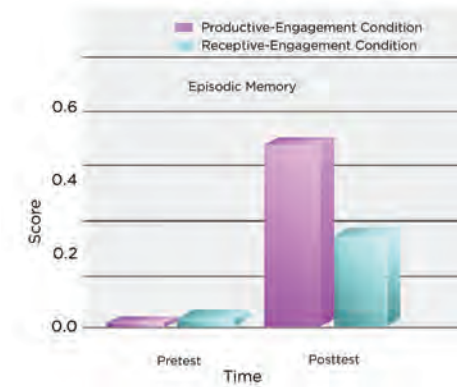
- These kinds of associations are just correlations, and they don't allow us to infer causality. So, scientists have vigorously debated how to interpret the observed associations. What was needed was an experimental study that randomly assigned some older people to a control condition and other older people to a condition in which they were seriously intellectually engaged.

- In 2014, Denise Park, Jennifer Lodi-Smith, and their colleagues at the University of Texas at Dallas did just that. Specifically, they recruited about 220 older adults and randomly assigned groups to different conditions. Three of the groups were assigned to what they called a productive-engagement condition, in which they took an intense 14-week course that required active learning.

- The control groups were assigned to what they called a receptive-engagement condition, in which they spent the same amount of time pursuing an activity, but the activity did not require the intense intellectual engagement that taking a course involves.

- The researchers found that people in the productive-engagement conditions improved significantly more on measures of cognitive function than did the people in the receptive-engagement conditions. In particular, episodic memory improved quite substantially.

Intellectual Engagement



Suggested Reading

Buettner, *The Blue Zones*.

Crowley and Lodge, *Younger Next Year*.

Hertzog, Kramer, Wilson, and Lindenberger, "Fit Body, Fit Mind?"

Restak, *Think Smart*.

Schmiedeskamp, "Preventing Good Brains from Going Bad."

Questions to Consider

1. What specific things can you do to be more active physically? Socially? Intellectually?
2. Why do people who are physically, socially, and mentally active live longer, healthier lives?

Aging Well: Diet and Stress

What else can we do to keep our brains in good shape as we age? This lecture will focus on eating right and avoiding stress. As you will learn, diet and stress have both been shown to have a significant effect not only on our health in general, but specifically on the health of our brains. In this lecture, you will learn about how diet plays a critical role in how successfully we age. You will also learn how stress can influence how we age.

Diet

- Does consuming fewer calories lead to a longer, healthier life? We don't know for sure because human experiments on calorie restriction are very difficult to perform, but there have been a number of animal experiments that have found that significantly restricting the number of calories that an animal eats does significantly extend their life span—sometimes by a lot.

- In addition, there are a number of scientific studies suggesting significant health benefits from eating the way people living around the Mediterranean Sea in the 1960s did. The Mediterranean diet focuses on fruits and vegetables, nuts and legumes (such as beans, peas, and lentils), olive oil, fish and whole grains, and moderate amounts of alcohol (particularly red wine).

- One of the most famous studies was the so-called Seven Countries Study, which was started in the late 1950s by Ancel Keys at the University of Minnesota and a number of other scientists around the world. This study investigated the diets and lifestyles of more than 10,000 men in

seven different countries and followed them longitudinally to examine associations with cardiovascular disease.

- The study found that dietary patterns in Japan and the Mediterranean in the 1960s were associated with lower rates of heart disease and longer life. When they looked specifically at the elderly in the sample, they found that older people eating a Mediterranean-style diet lived the longest and also suffered the least cognitive decline and depression.

- The study also found that over time, the lifestyle and diet of the people in the Mediterranean countries began to change. They began to eat a diet that was more similar to people in the United States and became less physically active. As their lifestyle changed, their risk of heart disease began to rise.

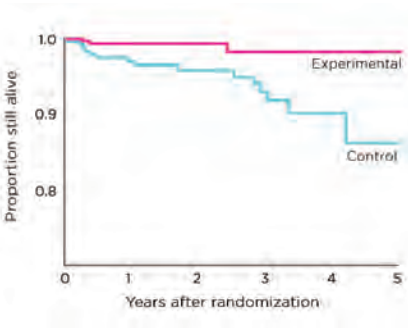
- Similar results have been reported in a number of other studies, including the much larger European Prospective Investigation into Cancer and Nutrition (EPIC) study in Europe and the NIH-AARP Diet and Health Study in America. Both studies found that people who ate a Mediterranean-style diet tended to live longer, healthier lives than people who didn't. The Diet and Health Study also reported that eating a Mediterranean diet was associated with less cardiovascular disease and cancer.

- These studies are correlational, so if we want to infer causality, then we need a randomized control trial in which some people are randomly assigned to a Mediterranean diet while others are not. Fortunately, there have been a few such trials.

- The first study, called the Lyon Diet Heart Study, investigated whether eating a Mediterranean diet could improve survival after a heart attack. About 300 heart attack victims were randomly assigned to eat a Mediterranean diet, and another 300 were assigned to receive the standard dietary advice provided by their physicians. The plan was to follow the people for 5 years to see if eating a Mediterranean diet would lead to better outcomes.

- But they stopped the study after just 27 months, because it was already apparent that the people in the control group were dying at a significantly higher rate than the people eating the Mediterranean diet. In fact, four years after the study started, the benefits of the Mediterranean diet were still apparent.

Lyon Diet Heart Study



- A second randomized control trial, called the PREDIMED Study, randomly assigned more than 7,000 people to three different diet conditions. One group ate a Mediterranean diet that was supplemented with free extra-virgin olive oil. Another group ate a Mediterranean diet that was supplemented with free nuts. The third group ate a standard low-fat diet.

- They actually had to stop this study, too, and for the same reason. After about five years, both of the Mediterranean diet groups were doing significantly better than the control group. This study also measured cognitive performance in the three diet groups, and the two groups who ate a Mediterranean diet performed significantly better than the control group.

- Similar results have been reported for a related style of eating known as the DASH (Dietary Approaches to Stop Hypertension) diet, which was specifically designed by doctors in an attempt to prevent and control high blood pressure.

- Compared with a typical American diet, the DASH diet involves a lot more fruits and vegetables, low-fat dairy products, whole grains, fish, poultry, and nuts. It's also significantly lower in red meat, sweets, and sugary drinks.

- The DASH diet was tested in a large multicenter randomized control trial in the 1990s. The DASH diet led to significantly lower blood pressure than the control diet. In fact, differences in blood pressure were starting to be seen after just two weeks on the diet. A subsequent experiment found that reducing the sodium content in the DASH diet led to even greater reductions in blood pressure. Like the Mediterranean diet, the DASH diet has also been shown to improve cognitive function.

- Recently, a group at the Rush University Medical Center in Chicago studied a related diet called the MIND diet, which is a hybrid of the Mediterranean and DASH diets. The researchers found that people eating a MIND-like diet were more than 50 percent less likely to develop Alzheimer's disease than people who ate other diets. And even people who only followed the diet moderately well were still about 35 percent less likely to develop the disease.

- Most scientists agree on some parts of why these diets work but not others. For example, scientists often point out that fruits and vegetables contain lots of vitamins and minerals and are high in antioxidants, which can help neutralize free radicals, which are thought to cause a lot of the cellular damage associated with age.

- But what's undoubtedly more important is what people following these diets don't eat. Most Americans eat a lot of processed food. Eating this way is associated with heart disease, stroke, diabetes, and cancer. Naturally, it's also associated with a shorter life.

- There are things that we can do to change our environments so that they nudge us to eat in healthier ways. One of the most important changes is based on what we bring home from the grocery store. If we bring home soda, potato chips, and ice cream, then that's what we'll tend to eat; conversely, if we bring home fresh fruits and vegetables, fish, beans, and other healthy foods, then we'll tend to eat better.

- Another idea is to make only as much food as you want to eat at each meal. Americans often make more food than they need and then save

Most Americans eat a lot of processed food. Eating this way is associated with heart disease, stroke, diabetes, and cancer. Naturally, it's also associated with a shorter life.

the rest for leftovers. But doing so also makes it easy to eat more than you actually want. You might also consider using smaller plates at meals.

- One of the most important ideas might be the most basic: Eat when you're hungry, but then stop eating when you're full. And don't eat when you're not hungry.

Stress

- Low levels of stress could translate into longer, healthier lives. Long-term stress could have detrimental effects on the brain and could lead to premature aging.

- When we experience stress, we activate a biological system called the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis consists of three main components: the hypothalamus, the pituitary gland, and the adrenal glands.

- The hypothalamus is a small region near the base of the brain. When we're under stress, the hypothalamus signals the brain's master gland, the pituitary, and causes it to release a hormone into the bloodstream. That hormone travels to the adrenal glands on the kidneys and triggers the release of adrenaline and glucocorticoids, which are often referred to as stress hormones. The release of these hormones produces what's often called a fight-or-flight response.

- The fight-or-flight response is the body's way of quickly preparing you to deal with a dangerous situation. For example, if you're walking down the street and someone appears out of an alley, pulls a gun, and demands your purse or wallet, you'll get a sudden jolt of adrenaline and your senses will be heightened. Your pupils will dilate, your heart will start to race, and your mouth will go dry.

- The glucocorticoids also quickly make glucose available so that you'll have the energy you need. They also turn off body systems that aren't essential for fighting or fleeing. All of these biological effects prepare you to be aggressive and fight if that's necessary, or to run away with extra speed if that's the better option.

- In a life-or-death situation, this kind of fight-or-flight response is a very good thing, because it increases our chances of survival. But chronic activation of the HPA axis in day-to-day life can be very bad for us, both mentally and physically.

- Some of the health problems associated with chronic stress are weight gain, digestive problems, and heart disease. It can also lead to mental health problems, such as anxiety and depression. And chronic stress can speed up aging.

- Chronic stress and abnormally high glucocorticoid levels have also been found to impair brain function. As we age, we tend to lose neurons in the hippocampus, which is the key brain structure involved in long-term memory.

- Rats also experience neuron loss in the hippocampus as they get older. But if you remove their adrenal glands and prevent the production of glucocorticoids, then you don't see the normal age-related loss of hippocampal neurons. Conversely, repeatedly injecting rats with glucocorticoids speeds up the loss of these neurons.

- There's even evidence that chronic stress can speed up aging at the molecular level. Telomeres, which are the caps at the end of chromosomes that protect the DNA from getting cut off during cell division, become shorter with every cell division, and once they get used up, the cell can't divide anymore. As a result, there's a limit on how many times most cells can divide, the so-called Hayflick limit, which might play a role in how long we can live.

- In 2004, Elissa Epel and Elizabeth Blackburn at the University of California, San Francisco, along with a number of their colleagues, published a study on the effects of stress on telomere length. They analyzed the telomeres in mothers of normal children and in mothers of chronically ill children.

- As expected, the mothers of sick children reported significantly higher stress levels than the other mothers. And the women who reported the highest levels of stress had much shorter telomeres than women who reported the lowest levels. In fact, their telomeres were shorter by an average of about 10 years' worth of cell divisions.

- Is there anything we can do to control our stress levels to live longer, healthier lives? There is indeed. One proven method for stress reduction

is meditation. It lowers heart rate, reduces blood pressure, and has even been found to lower levels of bad cholesterol.

- Furthermore, three of the most effective approaches to reducing stress are physical activity, social activity, and a healthy diet—all of which have been repeatedly shown to reduce stress and the health problems associated with stress. In fact, it's quite likely that one of the reasons that exercising, socializing, and eating right tend to extend our life span is precisely because they all reduce our stress levels.

Suggested Reading

Buettner, *The Blue Zones*.

Emmons and Alter, *Staying Sharp*.

Sapolsky, *Why Zebras Don't Get Ulcers*.

Questions to Consider

1. What specific things can you do to improve your diet? What about to reduce your stress?
2. What do you think are the main reasons many Americans eat a less healthy diet than people in some other countries?
3. Why do you think humans are more susceptible to stress than other species?

The Science of Immortality

Human beings have dreamed of finding a way to overcome aging since ancient times. This lecture will review two cutting-edge approaches that are now being investigated in the fight against aging: gene therapy and stem cell therapy. As you will learn, some scientists today believe that techniques like these may one day not only be able to slow the aging process, but potentially be able to stop it—or maybe even reverse it.

Gene Therapy

- Many aspects of aging are influenced by genetics. Some species age very quickly, while others age much more slowly—and some don't appear to age at all. So, presumably, there are genetic differences between species that influence how quickly they age.

- Twin studies, animal studies, and studies of genetic diseases that speed up aging have confirmed that our DNA plays a major role in the aging process. Likewise, many age-related diseases, including Alzheimer's disease and cancer, are strongly influenced by our DNA.

- Many people assume that our DNA is fixed and can't be changed, but it turns out that that's not true. For example, some viruses, such as HIV, replicate themselves by changing DNA.

- Scientists have now discovered ways to modify DNA intentionally and in very specific ways. They can turn genes on so that they start making their proteins. They can also turn genes off or knock them out entirely. They can even insert new genes, which the host cell will dutifully use to make proteins that that person has never made before. Many times, scientists use viruses to make these changes.

- Often, these studies are done to understand how genes work and what functions their proteins serve. For example, scientists sometimes knock out a specific gene in a worm or a mouse and then investigate how that affects the organism—or they might add a new gene and examine its effects. That kind of work is called genetic engineering, and it's a key technology that scientists use to figure out what human genes and proteins do.

- But this technology is also sometimes used to treat genetic diseases, in which case it's called gene therapy. For example, consider severe combined immunodeficiency (SCID), in which certain types of white blood cells that play a key role in the body's immune system don't work correctly because of harmful mutations in one or more genes.

- As a result, babies born with SCID typically develop multiple severe and recurrent infections that they can't fight off, so they usually die within a year if they're not treated. The typical treatment for SCID is to transplant the bone marrow from a matched brother or sister into the patient. The transplanted bone marrow can then make new blood cells that can fight off infection. Unfortunately, many victims don't have a matched sibling who can donate.

- Scientists have now begun inserting a gene into the bone marrow cells of SCID patients who have no other options. They extract cells from the patient's own bone marrow and then use a carefully designed virus to insert a new gene into the DNA of those cells. Finally, they inject the modified cells back into the patient. This work is still in the early stages, but dozens of children who might have otherwise died from SCID have now been successfully treated with this kind of gene therapy.

- Gene therapy has also seen some recent success in the treatment of hereditary blindness, hemophilia, and a serious blood disease called beta-thalassemia. It's also being explored as a potential treatment for several age-related diseases, including age-related macular degeneration, Parkinson's disease, Alzheimer's disease, and a few types of cancer.

- Could gene therapy be used to slow down or even reverse some of the debilitating effects of aging? We're still a long way off, but it certainly seems possible in principle. In fact, some studies have dramatically influenced aging in animals by experimentally manipulating the age-1, daf-2, and FOXO3 genes. As we discover other genes that influence aging and learn about how they work, those genes could become targets for gene therapy, too.

- Our DNA is under constant siege and accumulates more and more damage as we age. Many scientists see accumulating DNA damage as the main culprit in the physical deterioration associated with aging. Gene therapy offers the hope of fixing our damaged DNA.

- One possibility is replacing damaged genes as needed. But an even more promising possibility is ensuring the health of the genes that oversee the repair of DNA. If we could use gene therapy to keep these repair genes functioning well, then they could take care of repairing the rest of the genome. And maintaining a healthy genome may allow us to live much longer, healthier lives.

- While these possibilities are very promising, there are some very substantial barriers that need to be overcome before gene therapy could ever become a viable treatment for aging.

- One problem is that current approaches can only deliver relatively small segments of DNA into cells. In particular, there's only so much genetic material that you can cram into a virus. At the moment, it's therefore only possible to make small, localized changes to DNA, and it's very likely that we'll need to be able to make more substantial changes if we want to make a dent in aging.

- A second problem is that we need to be able to deliver new genes to millions of cells in the affected tissue while also not delivering the genes to all the other cells in the body, where they might do more harm than good. And even if we get the genes into all the target cells, we still need to be able to turn the genes on and keep them on. We're still a long way

from having complete control over gene delivery and activation, but both are very active areas of current research.

- Gene therapy also faces the problem of getting past the body's immune defenses. Introducing viruses into the body often triggers an immune response, and sometimes those immune responses can be very serious.

- Another problem is that if genes get inserted into the wrong place in the DNA, it can disrupt the operation of existing genes and lead to cancer.

- The commercial viability of gene therapy is also an issue, because many of the diseases for which it would be most effective are quite rare. As a result, drug companies are reluctant to make the huge financial investment needed to develop the technology and see it through the required clinical trials.

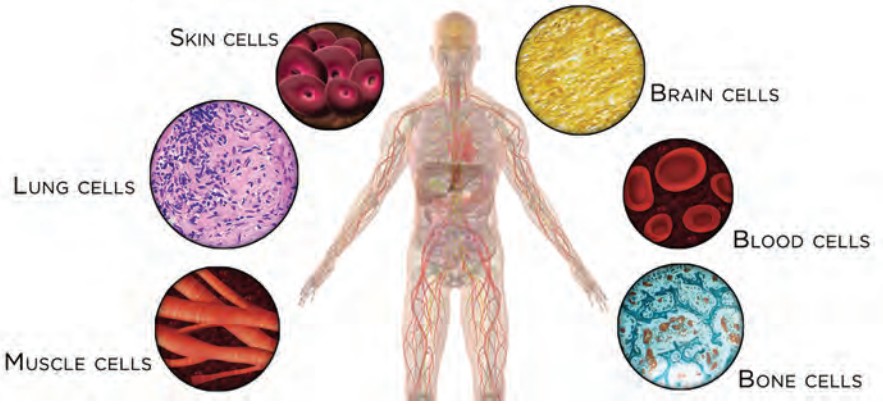
- These are all substantial obstacles, and only time will tell if we'll ever be able to overcome them and make gene therapy a safe and effective approach to treatment. But if we do, it could certainly be life-changing.

Stem Cell Therapy

- Every tissue in your body is made of cells, but the cells in different tissues are very different. You have muscle cells, skin cells, bone cells, brain cells, lung cells, blood cells, and the list goes on and on. But we all start as a single undifferentiated cell when a sperm fertilizes an egg. How does a single cell develop into such a bewildering variety of different cell types?

- The answer is stem cells. Stem cells are very special cells that have the ability to turn into other cell types. Stem cells can divide to produce more stem cells and can also differentiate into the specialized cells needed in a particular tissue.

- When many people think of stem cells, they think of embryos. But there are also many different kinds of adult stem cells. Like all stem



cells, adult stem cells are undifferentiated, but they have the ability to differentiate into different types of cells. However, they're found in specific tissues and normally only differentiate into the cell types found in that tissue.

- Adult stem cells are therefore called multipotent, which means that they can differentiate into multiple different types of cells, but the range of potential cell types is limited. Embryonic stem cells, on the other hand, are pluripotent, meaning that they can differentiate into any of the major cell types in the body—from hair, to muscle, to brain, to bone. They therefore have the potential to replace almost any cells in the body, at least in principle.

- Embryonic stem cells are derived from very early-stage embryos, which were created by in vitro fertilization for couples trying to get pregnant. Embryos that weren't used for that purpose were then donated for research, and embryonic stem cells were extracted from them. However, extracting the stem cells destroys the embryo, and that's led to significant controversy about whether research using embryonic stem cells is ethical.

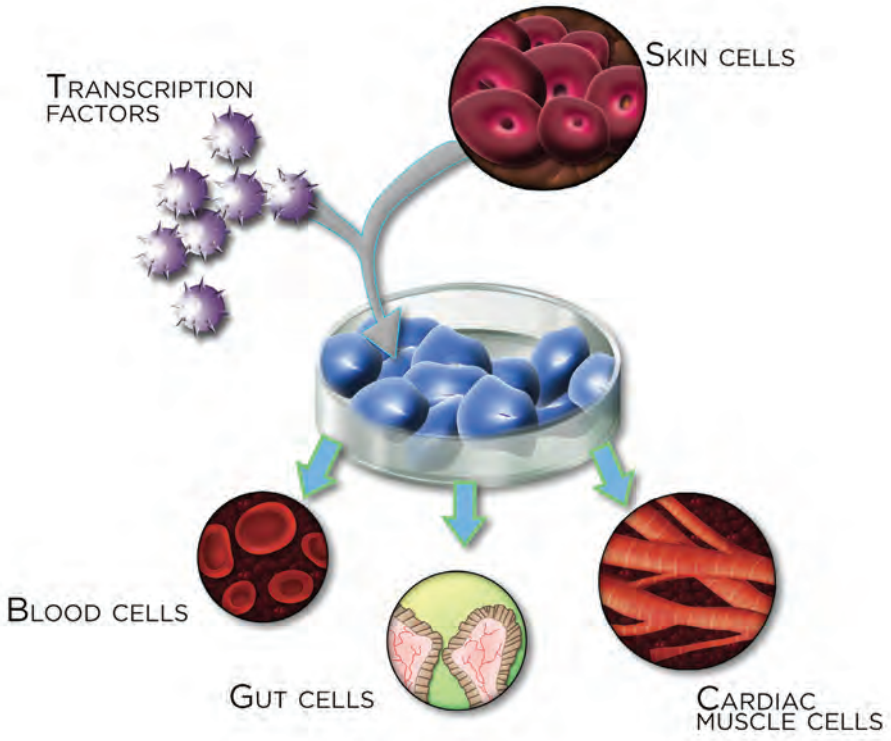
- Fortunately, scientists have discovered a few ways to create pluripotent stem cells without having to use a fertilized embryo. One approach is called nuclear transfer, which starts with a normal cell from an adult, transfers its nucleus into an egg cell, and then stimulates the egg to start dividing.

- But nuclear transfer has its problems. Cloning is controversial, and the idea that this approach could lead to human cloning raises ethical issues for many people. Furthermore, although this approach does create pluripotent stem cells, extracting those pluripotent stem cells still requires destroying a viable embryo that has the potential to develop into a normal adult organism, so some people also have ethical concerns about that aspect of the procedure.

- Finally, on a more practical level, nuclear transfer is a very inefficient process, at least so far. In particular, the vast majority of time it doesn't work. It therefore has to be repeated many times, using many eggs, before a viable embryo happens to be produced.

- However, in 2006, Shinya Yamanaka at Kyoto University in Japan discovered an alternative approach to making pluripotent stem cells that doesn't suffer from these problems. He showed that by introducing a handful of so-called transcription factors, which are chemicals that turn genes on or off, you can induce a normal adult skin cell to revert back into a pluripotent stem cell. These so-called induced pluripotent stem cells can then differentiate into any of the hundreds of different cell types in the body. They can also replicate to make more pluripotent stem cells. And an embryo is never involved at any stage in the process.

- Because pluripotent stem cells can differentiate into any cell type in the body, in principle they could be used to replace any cells that die or that no longer work like they used to. This approach is sometimes called therapeutic cloning, and the possibilities are staggering.



- Imagine replacing heart cells that have died after a heart attack, thereby restoring the heart to complete health, or imagine replacing the insulin-producing pancreas cells that have died in patients with type 1 diabetes. These are both very active areas of research today.

- Likewise, scientists are currently exploring stem cell therapy as a treatment for macular degeneration in the retina, spinal cord injury, burns, arthritis, and many diseases.

- Stem cells could also potentially be used to replace damaged cells in the brain. All of the major age-related brain diseases, including stroke,

Parkinson's, and Alzheimer's disease, lead to the death of brain cells. If stem cells could be triggered to differentiate into the appropriate cell types and replace the dying cells, then we might finally cure these devastating diseases.

- Stem cell therapy even offers the hope of growing entire organs that could then be transplanted, replacing diseased or failing organs. Furthermore, if the stem cells were derived from the patient's own cells, then the replacement organ would be genetically identical to the original, which would eliminate the possibility that the body's immune system would reject it.

- In fact, if we manage to develop a routine and cost-effective method for generating induced pluripotent stem cells from adult cells, then it's conceivable that everyone could have their own personalized line of stem cells waiting to be used whenever they're needed. You could even imagine replacing different tissues as they age, potentially expanding life span dramatically. The possibilities are almost limitless.

- Although these kinds of applications are still only possibilities, there are already some very promising research results. For example, recent studies have shown that young blood can activate previously dormant adult stem cells and cause them to restore certain organ systems in old animals to a younger, healthier state.

- These kinds of effects have also been observed in the brain. Human trials are now underway to test whether administering young blood to older people helps to rejuvenate the human brain like it seems to do in animals. Research on stem cells holds a lot of promise for the future.

Suggested Reading

De Grey and Rae, *Ending Aging*.

Lewis, *The Forever Fix*.

Newman, "Must We Grow Old?"

Park, *The Stem Cell Hope*.

Rando, "Stem Cells, Ageing and the Quest for Immortality."

Questions to Consider

1. Suppose that we figured out how to cure aging. Should we? What are some of the pros and cons?
2. Which approach do you think is more promising: gene therapy or stem cell therapy?
3. Would you impose any restrictions on stem cell research? If so, what would they be, and why?

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