ON THE BRAIN

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The Wonders of the Middle-Aged Brain

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As if people reaching their middle years didn't have enough to keep them awake at night—mortgage payments, job demands, the angst of teenage children—a study by French and British researchers last year concluded that our brains start to decline around age 45, smack in the prime of middle age. Although the study did find that certain innate skills, like memory and reasoning speed, begin to slow between our forties and sixties, the news was not all bad: the study also found that, compared with brain performance in Gen Xers and millennials, middle-aged adult brains perform certain functions better.

According to this study, published in the *British Medical Journal*, our memory, reasoning, and comprehension skills—collectively known as cognitive function—begin to worsen as we enter middle age, not around age 60 as previous studies concluded. Bruce Yankner, an HMS professor of genetics and neurology, notes there is indeed evidence from formal testing that short-term memory starts to decline in our forties and fifties. What's not clear, however, is whether that decline has an impact on day-to-day functioning.

In a 2004 *Nature* study, Yankner examined how human brains change between ages 26 and 106. From ages 26 to 40, brains showed similar patterns of wear and tear, as well as low levels of gene damage. As expected, more genetic damage appeared in the brains of individuals in their seventies. The finding that surprised Yankner appeared in some people between ages 40 and 70, the heart of middle age. The brains of some individuals had gene patterns similar to those found in younger people, while the brains of other individuals were more like those of older people and thus more susceptible to damage. That, says Yankner, suggests that some people's brains age more quickly during middle age.

"Our study showed that genes involved in memory start to fall in expression around age 40," says Yankner. "It's very gradual and very individual, but there are biological changes in gene regulation that start in middle age due, in part, to stress and damage."

Damaging stress

The hormone, cortisol, is produced by the adrenal gland and released during the "fight-or-flight" response to stress. It has positive effects—providing a quick burst of energy for survival or decision making—and negative effects, especially concerning memory. When too much cortisol is released, it

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can prevent the brain from laying down new memories or from accessing memories that already exist. Cortisol also interferes with neurotransmitters, the chemical messengers that help brain cells talk to one another. And, excess cortisol can make it difficult to respond to stimuli or retrieve the stored memories needed to guide us in certain situations, a condition that may account for our being bewildered when stressful situations arise.

Studies by neuroscientist Robert Sapolsky of Stanford University also show that constant stress can damage the hippocampus, the part of the brain where learning and forming memories starts. When released, stress hormones shunt blood glucose to muscles instead of to the brain. This redirection creates a type of energy crisis in the hippocampus, compromising its ability to create new memories. Scientists think that may be why short-term memory is among the first casualties of chronic stress.

Better than ever

It's hard to demonstrate scientifically that middle-aged people are more stressed than people in other age groups. Research shows, however, that the brain may be more resilient during our middle years than at other times in our lives. In her book *The Secret Life of the Grown-Up Brain: The Surprising Talents of the Middle-Aged Mind*, Barbara Strauch, science editor at *The New York Times*, concedes there are obvious issues with short-term memory in this age group, but that middle-aged brains are "better than ever during that period." Among other things, middle-aged people are better at inductive reasoning, which allows them to make broad generalizations from specific observations, and at problem solving. They tend to be more in control and are often in a better position to influence what happens in their lives. For example, David Laibson, the Robert I. Goldman Professor of Economics at Harvard University, found that adults in midlife have a better understanding of economics and make better financial decisions.

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One reason for this increased resilience, many researchers believe, is that those who reach middle age have learned to accentuate the positive, rather than dwell on the negative. In a brain imaging study, University of Wisconsin neuroscientists compared the brains of younger adults with those of middle-aged adults. The latter group appeared to have a greater ability than their younger counterparts to screen out negative emotions when they viewed disturbing pictures. The amygdala, or emotional center of the brain, of the younger group lit up when they looked at both negative and positive images. The older group's amygdala activated only when they saw positive images.

Yankner says the middle-aged brain has learned from experience, as well as from social connections, which also helps to strengthen cognitive function. The brain at midlife also appears capable of rewiring itself and generating new neurons in response to physical activity and new experiences.

Scientists also believe the process of myelination helps the middle-aged brain strengthen its cognitive abilities. Beginning in infancy, a fatty layer, called myelin, begins to accumulate around nerve cells in the brain, enabling neurons to transmit information faster and allowing for more complex brain processes to take place. Researchers used to think that the buildup of myelin ceased in young adulthood, when the prefrontal cortex (where executive functions such as planning and decision making reside) fully matured. Now, there is evidence that the process of building up myelin may continue into our fifties and sixties, particularly in the temporal lobe, which processes visual and emotional memories and encodes long-term memories.

Maintaining overall health will contribute to the health of our brain, as it moves through age-related changes.

"I believe the most important things for middle-age brain health," says Yankner, "are mental health, particularly satisfaction with our lives, diet, and physical exercise."

If we take care of those things, the decline of our brain function may be one midlife crisis we can avoid.

Chemotherapy and the Brain

This article is part of a series on the internal and external forces that affect the brain.

During world war II, scientists who worked with nitrogen mustards, a family of compounds used in chemical warfare agents, knew the compounds could damage rapidly growing blood cells. That knowledge led some to speculate whether the agents might have a similar destructive effect on cancer cells. This line of investigation led to the range of treatments known collectively as chemotherapy, the single or combination drug therapies used to slow tumor growth, keep cancer cells from spreading, and, in some cases, destroy cancers altogether.

Chemotherapy has extended the lives of millions of patients with cancer and is now the most common treatment for just about every type of malignancy. The treatment, however, is not without its costs. Traditional chemotherapeutic agents act by killing cells that divide rapidly, for such cellular activity is the hallmark of malignant growth. Acting in this manner, however, also means these agents can harm cells that divide rapidly under normal circumstances, for example, cells lining the digestive tract and those in hair follicles. Such indiscriminate action results in common side effects such as mucositis, the inflammation of the digestive tract lining that can lead to nausea and vomiting, and alopecia, or hair loss. Chemotherapeutics can also cause cognitive side effects—short-term memory loss, difficulty concentrating, and even dementia—which have come to be known collectively as "chemo brain."

"We know that chemotherapy has toxic effects elsewhere in the body," says Jorg Dietrich, an HMS assistant professor of neurology in the Massachusetts General Hospital Cancer Center. "Why not the brain? The brain is a dynamic organ and its degree of vulnerability to chemotherapy has long been overlooked."

Scientific proof

According to Dietrich, in the 1990s there were a number of neuropsychology studies describing cognitive decline during and after cancer treatment. These were mostly descriptive studies that revealed an association between cancer treatment and cognitive dysfunction, but they fell short in offering a scientific explanation for the observed neurologic deficits. These early reports, however, provided the basis for subsequent preclinical studies to investigate the effects of chemotherapy on brain function.

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Dietrich was part of a research team at the University of Rochester Medical Center that reported in the *Journal of Biology* in 2008, that a commonly used chemotherapy caused healthy brain cells to die long after treatment had ended. They linked the drug 5-fluorouracil (5-FU) to a progressive collapse of specific cells in the central nervous system (CNS). This drug acts by blocking cell division; it has been used for more than 40 years to treat breast, ovarian, stomach, colon, and pancreatic cancer. The team showed that 5-FU damages certain types of neurons in the brain and, in some cases, kills them.

In 2012, a West Virginia University study found that chemotherapy can cause brain changes that

Scientists at UCLA showed a significant correlation between poor performance on neuropsychological tests and memory complaints in early-stage breast cancer patients, particularly those who had undergone treatments that combined chemotherapy with radiation therapy. More than 20 percent of patients in the study reported memory problems or difficulties with higher-level cognitive tasks such as problem solving and reasoning.

affect memory and concentration. Researchers performed pre- and post-chemotherapy PET scans on female cancer patients and found that after treatment there was decreased brain activity in areas involved with long-term memory, problem solving, organization, and prioritizing.

More recently, scientists at UCLA's Jonsson Comprehensive Cancer Center showed a significant correlation between poor performance on neuropsychological tests and memory complaints in early-stage breast cancer patients, particularly those who had undergone treatments that combined chemotherapy with radiation therapy. More than 20 percent of patients in the study reported memory problems or difficulties with higher-level cognitive tasks such as problem solving and reasoning.

Before this study, many researchers had considered such patient-reported complaints to be suspect because there had been no scientific link between chemotherapy and cognitive difficulties. The UCLA study, however, analyzed specific components of the patients' cognitive complaints and linked them to relevant abnormalities in neuropsychological function.

Reversing the trend

As we learn more about chemo brain and what contributes to its development, scientists may also get closer to understanding who is likely to suffer from these chemotherapy-related cognitive deficits. "The million-dollar question is how to identify patients who are more susceptible to this," says Mary-Ellen Meadows, an HMS assistant professor of psychiatry and a neuropsychologist at Brigham and Women's Hospital. "But we have no answer yet."

The good news is that one can recover from these cognitive shortfalls. Cancer patients who suffer from chemo brain can strengthen their brain by doing repetitive cognitive exercises such as crossword puzzles or Sudoku, activities that will also help control other causes of memory problems. These activities can help repair broken neural connections that lead to cognitive impairment. Studies in pediatric brain tumor patients show that neurofeedback, a noninvasive treatment that measures brain-wave activity, will not only help the brain reorganize itself, but also has the potential to reduce or even reverse the cognitive deficits that can follow chemotherapy.

Several centers around the country are integrating cognitive remediation into their treatment plans during and after chemotherapy, according to Meadows. Through this form of rehabilitation, patients learn to develop compensatory strategies to improve their neurocognitive abilities, including attention, memory, and executive functions.

Cardiovascular exercise may be the "strongest factor in enhancing brain repair," says Dietrich. In fact, he believes that everyone undergoing toxic treatments like chemotherapy should engage in some sort of physical exercise, despite the fact that they are often very sick. Exercise promotes the endogenous repair potential of the brain, he notes. It also keeps patients active and engaged, so side effects may be perceived as less onerous.

As the scientific community learns more about the biology of chemo brain, it becomes incumbent upon clinicians to acknowledge the very real possibility of debilitating cognitive impairments following chemotherapy treatment. "That's really not on the minds of many oncologists," says Dietrich. "We tell patients about hair loss, nausea, and other side effects, but we also should tell them what to expect in terms of cognitive issues. Unfortunately, many patients are caught by surprise."

Shining a Light on Concussions

CONCUSSIONS have been in the news a lot lately: football players have sued the National Football League for concealing information linking impact-related head injuries to long-term brain damage, and some school systems have banned football because of its potential for exposing the developing brains of adolescent players to injury.

Preventing such injuries is one thing. Diagnosing and treating those who have experienced traumatic brain injuries (TBIs) presents another challenge, one that researchers have been tackling in several ways. One novel approach involves the use of light.

Researchers at Harvard Medical School are finding that the therapeutic application of red or near-infrared light-emitting diodes (LEDs) may improve cognitive function in patients with TBIs, including concussions. Until this discovery, therapies, especially for injuries such as concussions, have emphasized rest and the avoidance of both physical exertion and the mental concentration required by activities such as office work, schoolwork, videogames, and reading.

"Right now, there is nothing that will fix the biological problems caused by concussion," says William Meehan, an HMS assistant professor of pediatrics and director of the Sports Concussion Clinic at Boston Children's Hospital. "We think light therapy might do that, and that would be revolutionary."

Supply and demand

Concussions result from forces delivered directly to the head or neck, causing the brain's mass to accelerate and decelerate within the skull. When the head is hit, two types of forces are exerted on the brain: linear (straight on) and rotational (twisting). Many experts believe that the rotational forces, because they cause the brain to rapidly spin, cause greater damage. In addition, concussive force causes brain cells to be flooded with sodium and calcium ions at levels that damage neurons.

Because the brain is translucent, shining the right spectrum of light on it, even to a depth of only about 1 centimeter, can reach neurons and other critical brain structures, such as mitochondria, the cellular structures that generates ATP.

"When you spin the brain rapidly, as happens in a concussion," says Meehan, "potassium and calcium ions move to the wrong areas of the brain. It requires a protein pump to move the ions back into the right locations. This pump is fueled by ATP and, after a concussion, the brain needs more ATP."

ATP, or adenosine triphosphate, is a high-energy molecule that stores the energy we need for just about everything we do; it also triggers glucose metabolism in the brain. The disparity between glucose supply and demand after a concussion, however, creates a sort of biochemical energy crisis in the brain, resulting in the well-recognized symptoms of headache, nausea, dizziness, and impaired coordination.

Research has found that light therapy can help ensure that ATP is available to do this job. Because

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Road to recovery

In 2011, researchers from HMS, Massachusetts General Hospital, Boston University, and the VA Boston Healthcare System, led by Margaret Naeser, a research professor at BU School of Medicine, published a study in *Photomedicine and Laser Surgery* reporting that transcranial LED treatment reduced symptom severity and improved the cognitive function of two patients with chronic traumatic brain injury. One patient had suffered a TBI as a result of a motor vehicle accident. Prior to LED therapy, this patient could perform computer–related work for no more than 20 minutes. After eight weekly LED treatments, the patient's attention span had increased to three hours. The other patient was on medical disability following multiple concussions received during recreational activities and military deployment. Following treatment with LED therapy, the patient recovered and was able to return to work full time.

The therapy uses LED light to alter cellular functions in the brain. One way it does this is by increasing the activity of cytochrome c oxidase, an enzyme used in ATP production. Meehan says that shining light on brain cells grown in culture increases their ATP production, a finding that correlates with the functional MRI results of humans treated with LED therapy after suffering TBIs. This may help improve patients' memory and ability to learn after a concussion.

At Boston Children's Hospital, Meehan is studying transcranial LED therapy in children who have suffered concussions. They receive light therapy for 20 minutes three times a week for six weeks. Meehan and his colleagues repeatedly measure the children's performance on various tests for memory and concentration. Naeser and Ross Zafonte, the Earle P. and Ida S. Charlton Professor of Physical Medicine and Rehabilitation at HMS and chief of physical medicine and rehabilitation at Spaulding Rehabilitation Hospital, are conducting similar studies with adult TBI patients.

Since many athletes recover from a concussion in days or weeks, Meehan thinks light therapy may best be used in people who need a month or more to recover. In addition, he's interested in determining whether the treatment can speed up the recovery of those who have only recently been injured, but may be facing a long recovery.

"If our hypothesis proves to be correct," Meehan says, "I would immediately begin treating patients with light therapy. There would be no reason not to."

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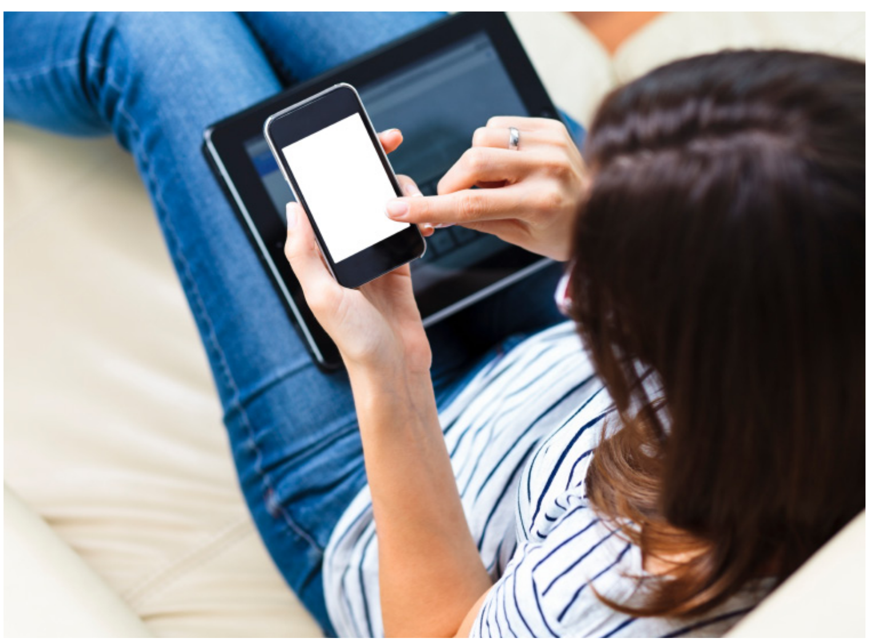
Are Smartphones Killing Our Brains?

"If you do things that stop the right side of the brain from keeping up with the left side, there will be a developmental disadvantage," says David K. Urion, an HMS associate professor of neurology and director of the Learning Disabilities and Behavioral Neurology Program at Boston Children's Hospital. "Electronic devices work more with the left side of the brain than the right, so that side develops more in young people who excessively use these gadgets."

Urion's concern links with an increased worry many are expressing about the effects that excessive use of mobile phones and other electronic gadgets may have on brains, particularly the developing brains of adolescents. Recent statistics from the Kaiser Family Foundation suggest that more than 18 percent of teens in this country use mobile phones more than seven hours a day, longer than most of them are in school. In 2010, the Pew Research Center's Internet and American Life Project reported that some teens even keep their mobile phones under their pillows at night so they can receive late-night text messages.

Many neuroscientists believe that frequent unplanned tweets, texts, and e-mails challenge the brain's cognitive control system, which governs our ability to focus on accomplishing a task in the face of competing demands. There is mounting evidence that our brains are sensitive to the distractions that occur during multitasking, and that outside "noise" can erode performance on a variety of cognitive tasks, such as the recollection of details.



In South Korea, a country with the world's highest penetration of smartphone ownership, the problem may be particularly severe. According to the research firm eMarket, 80 percent of South Koreans ages 12 to 19 own a smartphone, and nearly 40 percent of them spend more than three hours a day on it, tweeting, texting, talking, and playing games.

Recent work by Seoul's Balance Brain Center may cast some light on the issue of brain development and mobile phone use. According to their report, the center's researchers say that teenagers and young adults who overuse electronics, including mobile phones, gaming devices, and the Internet, experience short-term memory loss and other cognitive deficits that are more commonly seen in people with head injuries or psychiatric illnesses. They called these cumulative effects, "digital dementia."

Left brain, right brain

Urion's assessment of the effects of such "asymmetric" use of these devices refers to the theory of left-brain/right-brain dominance, called lateralization. This theory stems from the understanding that each hemisphere of the brain controls specific functions: the right side is most often associated with creative and expressive tasks, while the left side is more involved in logical and critical thinking.

Many neuroscientists believe that frequent unplanned tweets, texts, and e-mails challenge the brain's cognitive control system, which governs our ability to focus on accomplishing a task in the face of competing demands. There is mounting evidence that our brains are sensitive to the distractions that occur during multitasking, and that outside "noise" can erode performance on a variety of cognitive tasks, such as the recollection of details. Although teens may say that multitasking saves time, research shows that may not be true. Studies conducted at the MIT and the University of Michigan conclude that the brain's ability to toggle between two or more tasks—reading a chapter in a history textbook while playing the video game

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Call of Duty, for example—actually impairs both time and performance, in some cases doubling the time needed to complete a task and decreasing one's ability to recall information later on. That double-whammy, scientists say, corrupts the quality of learning.

In addition, many fear that electronic interaction, whether through text messaging or Facebook, may affect children's and teens' social and emotional development. The lack of face-to-face communication diminishes their ability to form impressions of others and gauge social reactions—things that are controlled by their still-developing prefrontal cortex. Some psychologists express concern that the ease of electronic communication may make teens less likely to be interested in face-to-face communication. The caution is, however, that it is too soon to know if or how this affects the quality of teens' social relationships.

A matter of balance

Despite the imbalance that overuse can bring to the developing brain, Urion thinks such an imbalance can be actively countered. Kids who suffer from technology-induced cognitive decline should engage in activities that might help develop the brain in a complementary fashion, including participating in conventional forms of communication, creating face-to-face bonds with friends and family, reading a printed book rather than one that is electronically displayed, and committing information to memory rather than peeking at Google. And, most important, he says, put down or turn off mobile phones when doing homework or other critical tasks.

"We know that interaction with technology changes the brain," says Urion, "but we're in the driver's seat and we can determine how we want to use it."

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