ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

The Toll of Attention Deficit Disorder in Adults

Winter 2014
Vol. 20, No. 1

In 2006, Ronald Kessler, the McNeil Family Professor of Health Care Policy at Harvard Medical School, conducted a large epidemiological study for the U.S. government. It was an investigation of adult attention deficient hyperactivity disorder (ADHD) in the nation. Kessler and his research team found that about 4 of every 100 adults manifested ADHD, or, as it's more usually designated for adults, ADD. Moreover, he discovered that all of those with the disorder traced its beginnings to their childhood. "They indicated they'd had the problem since they were about 7 or 8 years old, that it was bad enough that it got in the way of their daily life, and that they continue to have the problem as an adult," Kessler says.

Although most of us know the hardships faced by children who are diagnosed with ADHD, how many of us consider what this disorder means for adults? What are its implications, social and professional?

While children with ADHD are considered distracted and disruptive, adults with ADD are often perceived as chaotic and disorganized, with a high need for stimulation. The disorder does in fact manifest differently in children than in adults. Children with the disorder are often forgetful, especially about the performance of daily activities. They misplace or lose things, like homework, and they have difficulty concentrating, which often leads to their making seemingly careless mistakes. Adults, by contrast, suffer from behavioral problems related to the processing of information by the brain's prefrontal cortex, which governs executive function, including our ability to plan and organize. Adults with ADD tend to avoid tasks that require concentration, to have poor time-management skills, and to be plagued by indecision and doubt. They are also more likely to be easily bored, inpatient, and intolerant.

"Life in general for adults with ADD gets more complex," says Kessler. "They can't keep appointments or meet deadlines. These are not problems that kids, with or without ADHD, typically face."

Something awry

Throughout the past 30 years, research into the causes of ADD has greatly accelerated; however, there is no unified theory that explains the cause of the disorder or why certain children carry the disorder into adulthood. Two studies, however, may shed some light on the disorder's neurobiology.

In 2009, researchers at the National Institute of Mental Health (NIMH) demonstrated a link between attentiveness and brain activity. The investigators asked adult participants to learn a list of words. As they performed this task, their brains were undergoing a PET scan that determined the levels

continued on page 2

HARVARD MEDICAL SCHOOL

CONTENTS

continued from page 1

of glucose, the brain's principal source of energy, in areas of the brain that thwart impulses and control attention. In adults diagnosed with ADD, the attention–control regions of the brain used less glucose than those regions did in participants without ADD. This finding suggested that, in the participants with ADD, these areas of the brain were less active. According to the NIMH researchers, this lower level of activity in certain parts of the brain may contribute to inattention.

Another 2009 study, this one by researchers at the National Institute on Drug Abuse (NIDA), focused on the brain's reward circuit and its relationship to inattention. Again, PET scans were used to measure markers in the dopamine systems of the brains of adults with ADD and of the brains of adults without the disorder. Dopamine is a chemical that helps control the brain's reward and pleasure centers. The NIDA scientists found that participants with ADD had a reduction in dopamine receptors and transporters (proteins that pump dopamine from synapses to surrounding cells) in two regions of the brain involved in processing reward and motivation. The scientists say that these sorts of deficits in the brain's reward pathway lead to the inattention and lack of motivation that often characterizes the behavior of adults with ADD.

Social problems

A 2013 study conducted by researchers at Boston Children's Hospital (BCH) and the Mayo Clinic found that ADHD persists into adulthood for a significant percentage of children with the disorder. Their research added to evidence that adults who suffered from ADHD as children are at greater risk for mental health issues, including anxiety, depression, antisocial behavior, and substance abuse.

The findings, which were published in the journal *Pediatrics*, noted that 29 percent of children with ADHD still had the disorder as adults; 57 percent of children with ADHD had at least one other psychiatric disorder as adults (compared to 35 percent of controls), including substance abuse/dependence, antisocial personality disorder, generalized anxiety, and depression; and 81 percent of children who still had ADHD as an adult had at least one other psychiatric disorder, compared to 47 percent of those who no longer manifested the disorder.

According to the American Psychiatric Association (APA), the ramifications of childhood ADHD may keep adults from reaching their full academic and occupational potential and may limit their satisfaction with themselves and relationships with others. Adults with ADD are three times more likely to suffer stress, depression, or other emotional problems that may cause them to miss work. According to the association, about 24 percent of adults with ADD say they are prevented from participating in normal activities such as work as a result of poor physical or mental health. Only 9 percent of adults without ADD report these types of problems. In addition, within a given 10–year period, adults with ADD changed jobs more often compared with people without the disorder, and 43 percent with ADD lost or left a job in part as a result of difficulties related to their symptoms.

Adults with ADD have residual issues because they had ADHD as kids, says Kessler. For example, many of these adults have difficulty finding a decent job because they didn't do well in school. Kessler says these adults tend to "find places in the world to function where the demands of education and peer pressure aren't as strong."

The effects of adult ADD extend outside of the workplace, as well. The APA says that adults with ADD are twice as likely to divorce or separate than adults without the disorder. Of those who are in relationships, less than half say they are satisfied with those relationships. And these adults are more likely to engage in harmful behavior; more than 60 percent smoke cigarettes and 52 percent report using drugs recreationally. Adults with ADD are also twice as likely as their non–ADD peers to be arrested.

Although it is impossible to discern which children with ADHD will carry the disorder into their adult years, addressing the issue early can help lessen the impact of the condition later. There is no cure, but educational approaches, psychological or behavioral modification, and stimulant drug therapy have all proven successful in treating ADHD in children. The more these interventions succeed in controlling ADHD behaviors in children before they reach their adult years, the better the outlook for these children as they age. That's important, says Kessler because the implications of ADD on adult function are indeed dire.

Seasonal Affective Disorder and the Brain

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

When earth's position in relation to the sun results in shorter periods of daylight and longer periods of darkness, many people experience the often-debilitating symptoms of seasonal affective disorder (SAD).

SAD is a form of depression that occurs at times of the year when the hours of daylight wane. It has been linked to a biochemical imbalance in the brain, prompted by a decreased exposure to sunlight. The higher the latitude, the greater the prevalence of SAD. An estimated 10 percent of people living in New Hampshire, for example, suffer from SAD, while the prevalence in Florida is only about 1.5 percent, according to a study in the journal *Psychiatry*.

Although it is not uncommon for people who live in colder climates with abbreviated daylight hours to experience diminished levels of energy compared with what they experience during summer months, there are individuals who suffer profound symptoms triggered by a limited exposure to sunlight. They may, for example, have difficulty waking up and concentrating; experience daytime sleepiness, irritability, and social unease; and crave quick-energy foods such as carbohydrates and sugars, which may lead to weight gain. Some may even experience anxiety, hopelessness, and depression. A small number of people are so affected by SAD that they are unable to function.

Although the symptoms of SAD usually vanish during months with more hours of daylight, the American Academy of Family Physicians notes that for about 10 percent of people with the disorder, symptoms also appear in the summer, possibly in response to heat and humidity. This relapsing type of SAD is characterized by insomnia, decreased appetite, and weight loss.

A matter of balance

Light acts as a biological regulator: it prompts the brain to decrease its activity for sleep and increase its activity when it's time to wake up. This cyclical regulation involves the suprachiasmatic nuclei (SCN), two tiny structures located above the optic chiasma, where the left and right optic nerves cross. The SCN receives light input from the eyes, and converts that information into sleep/wake rhythms. The SCN also regulates the secretion of melatonin, a neurotransmitter produced by the pinecone-shaped pineal gland. As daylight hours decrease, the duration of melatonin synthesis expands, extending the "biological night." Melatonin levels—the marker of biological night—dissipate spontaneously by morning awakening, with or without actual light.

"Light both suppresses melatonin and sets the relationship of the circadian system to the light-dark cycle," says Robert Thomas, an associate professor of medicine at Harvard Medical School and a sleep medicine specialist at the Beth Israel Deaconess Medical Center Sleep Disorders Clinic. "Production of cortisol, another hormone, starts to increase, our body temperature rises, and we start waking up. However, with not enough morning light during the short days of fall and winter, we are still asleep when that alarm goes off. Our biological night seems to expand in darkness."

Our circadian rhythm, or biological clock, determines our biological night. People who are sensitive to light deprivation have a longer biological night, so they produce greater levels of melatonin. With SAD, this melatonin profile is even longer. "The apparent disruption in melatonin production results in the body believing it is night during the daytime because melatonin normally increases at night," says David Mischoulon, an associate professor of psychiatry at Harvard Medical School and a neuropsychiatric researcher at Massachusetts General Hospital. This disruption causes fatigue and a desire to sleep during the day, hallmarks of SAD.

In addition to melatonin's role, an imbalance in the levels of the neurotransmitter serotonin is believed to be involved in SAD. Many researchers say such an imbalance leads to depression, one of the principal symptoms of SAD. The possible

continued on page 4

continued from page 3

causes of this imbalance may include low serotonin production, a lack of serotonin receptors in the brain, an inability of serotonin to reach these receptors, or a shortage of tryptophan, the chemical from which serotonin is made. Any one of these anomalies could lead to depression.

Researchers have yet to verify the theory that serotonin is involved in depression because there is no way to measure serotonin levels in the brain. Although serotonin levels in the blood can be measured—and are lower in people who suffer from depression—researchers are uncertain whether low blood levels of the neurotransmitter equate to low brain levels of the chemical. Mischoulon says that neuroscientists are now learning more about genetics as a factor in depression and that abnormal genes in the serotonin receptor promoter region of the brain have been associated with SAD.

While medications and cognitive behavioral therapy are appropriate for some patients with seasonal affective disorder, light therapy appears to be the most effective and common treatment.

Light bright

Medications, such as selective serotonin reuptake inhibitors, or SSRIs, can be especially helpful in treating depressive symptoms in SAD patients by affecting naturally occurring serotonin levels in the brain. Prozac, Paxil, and other SSRIs act by blocking brain cells' reabsorption of the neurotransmitter serotonin. This decreases cellular levels of the neurotransmitter, increases neurotransmitter concentrations at the synapse, and allows more communication between neurons, which improves mood. More effective than tricyclic antidepressants and monoamine-oxidase inhibitors, and causing fewer side effects, SSRIs are the first-line treatment for depression.

Another helpful treatment for SAD-related depression is cognitive behavioral therapy, a type of psychotherapy that helps people understand the thoughts and feelings that influence their behavior. "Cognitive behavioral therapy can help people regulate their behaviors; for example, the urge to do nothing and stay in bed," says Mischoulon. A 2009 University of Vermont study found that people with SAD who are treated with this form of psychotherapy have less-severe episodes of depression one year after therapy compared to those undergoing other treatments.

While medications and cognitive behavioral therapy are appropriate for some SAD patients, light therapy appears to be the most effective and common treatment. Increased exposure to light improves symptoms of the disorder. Regular long walks outdoors also can allow exposure to levels of light sufficient to reverse symptoms.

Light therapy also can involve the use of light, especially bright light, to directly activate the SCN and the downstream biological pathways mediating the biological effects of light. Light stimulates retinal ganglion cells containing melanopsin, a visual pigment that synchronizes the circadian cycle to the day-night cycle. Activating these retinal cells with bright light at the same time each day can restore normal circadian rhythm and reduce SAD symptoms. Although scientists don't know the exact mechanism of this process, they think that bright light, particularly blue light, changes brain chemistry in ways that affect its levels of melatonin and serotonin and modulates the circadian rhythm.

The phototherapy process that reduces SAD symptoms involves exposure to bright light for 30 minutes soon after awakening. Light at an intensity of 10,000 lux is generally sufficient. This lux level is about 100 times greater than that produced by typical indoor lighting but about 5- to 10-fold less than the light produced outdoors on a sunny summer's day. While it is not necessary for the patient to look directly into the therapeutic light, it is necessary for those undergoing therapy to be awake during their exposure. About half the people with SAD who are treated with light therapy recover, says Mischoulon. Blue-enhanced light sources, which have intensities in the range of several hundred lux, seem to work as well as higher intensity, full-spectrum light.

Mischoulon advises SAD patients to seek the help of a psychiatrist if their symptoms are so severe that they interfere with daily life. Serious impairment and difficulty functioning likely indicate a depressive disorder, which should be assessed in a full psychiatric evaluation and addressed by a mental health professional. For those whose SAD symptoms are not debilitating, there is phototherapy and, for those who can afford it, Mischoulon recommends traveling to sunny locations. "Even a few days in a warm sunny environment can refuel the batteries, so to speak, and make the rest of the winter more bearable."

Fighting Phobias

More than 15 million people in the United States deal with some sort of phobia, according to the National Institute of Mental Health. These exaggerated—some would say irrational—fears are a type of anxiety disorder in which a person's encounter with a specific object or situation evokes an unusually heightened state of stress. Whether triggered by spiders (arachnophobia) or snakes (ophidiophobia), flying (aviophobia) or darkness (achluophobia), phobias can become so consuming that they interfere with daily life.

"The hallmark of a phobia is the presence of a marked, persistent fear that the person recognizes is excessive and unreasonable," says Edward Pace-Schott, an assistant professor of psychiatry at Harvard Medical School and a psychiatric neuroscientist at Massachusetts General Hospital.

Phobias are divided into three main categories: specific phobias, which involve a disproportionate fear of a particular creature, object, or circumstance (for instance, dogs, blood, and heights); social phobias, which are a response to personally unbearable social situations (public speaking, for example); and agoraphobia or fear of open spaces, which is a heightened fear of being in a situation from which there appears to be no escape.

All phobias are anxiety disorders, therefore, much of what we know about their neurological basis comes from research on more severe disorders, such as social phobia, post-traumatic stress disorder, and panic disorder.

Fear in the deep brain

All phobias are anxiety disorders, therefore, much of what we know about their neurological basis comes from research on more severe disorders, such as social phobia, post-traumatic stress disorder, and panic disorder. Whatever triggers a phobia, says Pace-Schott, activates brain structures that are involved in emotion-based responses. Such structures include the amygdala, the insula, and other deep-brain structures that process

continued on page 6

continued from page 5

emotional and autonomic responses, including those involved with fear and pleasure.

Phobias can elicit any number of physiological reactions, including higher heart rate, increased sweat, chest tightness, dry mouth, confusion, disorientation, and nausea. These symptoms can occur not only when a fearful object or situation is encountered, but also at the mere suggestion of a fear-filled stimulus.

Phobias can form for any number of reasons—some understood and others still mysterious—and usually become seated in an individual by or before early adulthood. A child's phobia may mirror the behavior of another family member with a phobia: A child whose father has a fear of snakes, for example, may develop the same phobia. The causes of complex phobias, such as social phobias or agoraphobia, are less well understood. Neuroscientists say a combination of factors, including genetics, brain chemistry, and experience, are likely to have roles in the genesis of these phobias. Some indicate a possible evolutionary basis for why some phobias are more common than others.

The causes of complex phobias, such as social phobias or agoraphobia, are less well understood. Neuroscientists say a combination of factors, including genetics, brain chemistry, and experience, are likely to have roles in the genesis of these phobias.

"Our ancestors, by natural selection, came to fear dangerous things so there is a propensity to have a phobia to those things," says Pace-Schott. "The most common phobias are to blood, spiders, snakes, and heights, things that, in the past, posed dangers to humankind."

Unlearning fear

Although the evolutionary origin of phobias remains a matter of speculation, Pace-Schott says that today the medical community is well versed in their treatment. If a phobia does not lead to serious problems or interfere with personal or professional life, most people remain in control by simply avoiding whatever induces their fear. For phobias that do interfere with daily life, certain medications, particularly SSRIs (selective serotonin reuptake inhibitors), tricyclic antidepressants, and sedatives, can lessen some of the more common symptoms.

For people whose phobias are debilitating and interfere with daily life, Pace-Schott says exposure therapy is the gold standard of treatment. Exposure therapy relies on a basic learning process called fear extinction, a process whereby one learns that what once signaled danger no longer does so. Learning to extinguish a fear—becoming frightened and realizing that nothing bad occurs—requires experience. He says this type of therapy forms safety memories, which inhibit fear responses triggered in the amygdala and other deep-brain regions. Exposure therapy is most successful if the patient is willing to tolerate the anxiety that is provoked by exposure to the fearful stimulus and experience its natural decline over time.

Unraveling the Mysteries of the BRAIN

In April 2013, when President Obama introduced a bold initiative to comprehensively map signals in the human brain, he said, "As humans, we can identify galaxies light years away, and we can study particles smaller than an atom, but we still haven't unlocked the mystery of the three pounds of matter between our ears." According to the National Institutes of Health, which oversees the initiative, the human brain, with its billions of neurons and trillions of connections, "remains one of the greatest mysteries in science and one of the greatest challenges in medicine."

Some of the new technologies the initiative hopes to spur include tools to support scientists' efforts to show how complex neural circuits interact over time.

The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative is part of an international effort to revolutionize our understanding of the human brain. Some of the new technologies the initiative hopes to spur include tools to support scientists' efforts to show how complex neural circuits interact over time. Such imaging technologies may provide clues to the treatment of brain disorders, including Alzheimer's disease, Parkinson's disease, and psychiatric illnesses.

"We are at the brink of a revolution in understanding how complex patterns of neural activity underlie behaviors and mental activities—thoughts, emotions, perceptions, decisions," says Joshua Sanes, the Jeff C. Tarr Professor of Molecular and Cellular Biology and the Paul J. Finnegan Family Director of the Center for Brain Science at Harvard University. "Once we do that, we will not only understand what it means to be human in a new way, but will also find new ways to treat currently intractable neurologic and psychiatric disorders. The BRAIN Initiative begins with a sharp focus on developing the next generation of technologies needed to achieve these goals."

Better tools for brain science

Recent collaborations, including those for sequencing the human genome and developing tools for mapping neuronal connections, have paved the way for joint scientific projects involving the U.S. government and the nation's scientific community. Three federal agencies—the National Institutes of Health (NIH), the Defense Advanced Research Projects Agency, and the National Science Foundation–will share, with prominent private-sector science organizations, $110 million in fiscal year 2014 to develop a broad range of projects that will investigate the inner workings of the brain's neuronal connections. An NIH advisory committee of 16 leading neuroscientists, including Sanes, is responsible for the initiative's overall goals and future funding decisions.

Several high-priority areas of research for BRAIN funding have been identified. They include:

- A census to characterize all cell types in the nervous system
- Structural maps of the brain that detail interconnected circuits and distributed brain systems
- Large-scale network recording to document dynamic neuronal activity throughout the brain
- Tools that activate or inhibit neuron populations
- Technologies that link neuronal activity to cognition and behavior
- Modeling and statistics to advance our understanding of complex nonlinear brain functions
- Mechanisms to collect human data from brain monitoring and other neurotechnologies
- Education and training in neuroscience for scientists and nonscientists

continued on page 8

continued from page 7

Scientific challenge

The BRAIN Initiative was prompted by a proposal from six scientists, including George Church, a professor of genetics at Harvard Medical School, for an international effort to create a brain activity map that would reconstruct the functional activities and connections involving every neuron in the brain. Church was a key member of the Human Genome Project, a 13-year effort to identify and map all the genes in the human genome. Says Church, the "ability to measure and alter brain activity inexpensively and accurately should help us find ways to prevent or cure neurologic disease in the same way that personal genomics and gene therapy are for genetic diseases."

Like the Human Genome Project, which has provided treatment targets for many types of cancer and other genetic diseases, the BRAIN Initiative is expected to yield insights that will aid scientists in discerning the mechanisms of brain diseases. Many psychiatric disorders, for example, may be so-called connectopathies, diseases in which neurons work well, but are wired incorrectly. "If we can pinpoint such wiring errors," says Sanes, "we should be able to come up with new ways—not necessarily pharmacological ones—to correct these circuit errors."

Although the BRAIN Initiative is years away from the scientific discoveries it will ultimately release, scientists remain committed to the task of unraveling the secrets of the human brain. The effort, says Sanes, is the signal scientific challenge of this century.

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

HARVARD MAHONEY NEUROSCIENCE INSTITUTE

ON THE BRAIN

On The Brain is published electronically three times a year through the Office of Communications and External Relations at Harvard Medical School, Gina Vild, Associate Dean and Chief Communications Officer.

Editor: Ann Marie Menting

Freelance Writer: Scott Edwards

Design: Gilbert Design Associates, Inc.

In collaboration with: Michael E. Greenberg, Nathan Pusey Professor of Neurobiology and Chair, Department of Neurobiology

Harvard Mahoney Neuroscience Institute
Harvard Medical School
107 Avenue Louis Pasteur
Suite 111
Boston, MA 02115

www.hms.harvard.edu/hmni
hmni@hms.harvard.edu

CORRESPONDENCE/CIRCULATION

Harvard Medical School
Gordon Hall
25 Shattuck Street, Room 001
Boston, MA 02115