

# ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

## A Different Voice

Winter 2013  
Vol. 19, No. 1

**J**OAN OF ARC, THE HEROINE who led the French army to victory over the English at the battle of Orléans in 1429, claimed that the voices of saints compelled her to action. She was resolved to obey these messages, she said, because they were sent directly from God. At the time, many believed the voices she heard were divinely inspired. Today, many historians and psychiatric professionals speculate that Joan of Arc experienced auditory hallucinations symptomatic of schizophrenia.

In scientific terms, a hallucination is the perception of an object or event in the absence of an external stimulus. Auditory hallucinations, the most common form, are typically described as the expression of one or more voices—a voice speaking one's own thoughts, one or more voices arguing, or a voice narrating one's own actions.

Because hallucinations are spontaneous, transient, and unpredictable, the neural activity underlying them is difficult to study. A number of what are referred to as symptom-capture studies, however, offer a glimpse of what is happening in the brain during a hallucination. These studies

measure the brain activity associated with the onset of hallucinations and compare it with neural activity during hallucination-free periods. Many of these studies, says Ann Shinn, an HMS instructor in psychiatry who studies auditory hallucinations at McLean Hospital's Schizophrenia and Bipolar Disorders Program, show abnormal activity in the superior temporal gyrus during auditory hallucinations. This region of the brain is involved in auditory processing, including language, and is the location of the primary auditory cortex, a region responsible for processing sounds.

"When you hear real sounds in the world—sounds from the environment—the auditory cortex is activated," says Shinn. "That same area of the brain is stimulated during an auditory hallucination."

### Different causes, different content

Auditory hallucinations are experienced by approximately 70 percent of patients with schizophrenia, a mental disorder characterized in part by an inability to differentiate between what is real and unreal. This type of hallucination also commonly manifests in people with bipolar disorder, certain major depressive illnesses, and post-traumatic stress disorder.

The voices that people with schizophrenia hear often articulate negative or derogatory content. Sometimes the voice is recognized as that of a family member or someone from the person's past; sometimes it is a voice that, although unfamiliar, has recognizable features (a deep, gruff tone, for instance). In extreme cases, the voice commands the person to commit destructive acts, which often causes considerable distress. Many who experience this type of hallucination feel they cannot escape it, a perception that can lead to depression, fear, anxiety, or anger. Some commit suicide to escape the voices.

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Not all auditory hallucinations, however, stem from mental illness, a fact that neurologist Oliver Sacks addresses in his recent book, *Hallucinations*. Some studies, in fact, have found that 10 to 40 percent of people without a diagnosable psychiatric disorder experience auditory hallucinations. For these people, auditory hallucinations are caused by such conditions as temporal lobe epilepsy, delirium, dementia, focal brain lesions including tumors, and infections such as viral encephalitis. Withdrawal from alcohol, cocaine, and amphetamines can also trigger such hallucinations. People without

*Currently, antipsychotic medications like Haldol (haloperidol), which are effective first-line therapies for schizophrenia, can act to calm hallucinations. These drugs block abnormal activity of dopamine, a neurotransmitter involved in regulating mood and behavior.*

mental illness tend to report positive messages from the voices they hear, and, as a result, are less likely to suffer distress or interference with their daily activities than are people with psychiatric illnesses.

According to Shinn, however, hallucinations are not as well studied in nonpsychiatric patients as they are in psychiatric patients. But she notes that scientists are beginning to conduct research on the latter population to determine whether the neural substrate—the set of brain structures that underlie specific behaviors and psychological states—is similar to that found in mentally ill patients who experience hallucinations.

#### **A question of connectivity**

At McLean, Shinn and her colleagues recently completed a study that compared three groups: schizophrenia patients who have had a lifetime of auditory hallucinations, schizophrenia patients who have not experienced auditory hallucinations, and healthy control subjects who have never experienced a hallucination. The study design used fMRI to measure resting brain activity, an uncommon approach: Typically, study participants are asked to perform a discernible task while being monitored by the scanner so that functional brain activity can be assessed.

Instead of looking at brain structure, Shinn's team looked at functional connectivity; that is, the relationship between activity in certain areas of

the brain and specific mental functions. The team targeted an area deep within the auditory cortex called Heschl's gyrus, where the processing of incoming auditory information begins.

In patients who experience auditory hallucinations, Shinn found decreased functional connectivity between the left portion of Heschl's gyrus and the hippocampus, the brain region where coding and accessing memory occurs, as well as decreased connectivity between the left portion of Heschl's gyrus and the medial dorsal thalamus, which plays a role in abstract thinking and active memory. "This suggests there might be some abnormality involved in remembering stimuli," says Shinn, "some breakdown in the ability of those who hallucinate to remember where the sound originally came from."

Shinn also found increased connectivity between Heschl's gyrus and two other brain regions, Broca's area and the cingulate gyrus. Broca's area plays a significant role in language comprehension, while the cingulate gyrus, an important part of the limbic system, helps regulate emotions and initiates the body's response to unpleasant experiences.

"We found evidence of abnormal connectivity between the left Heschl's gyrus and the forebrain thalamocortical regions in patients prone to auditory hallucinations," explains Shinn. "The data highlight the importance of interactions between the left auditory cortex and brain circuitry involved in speech and language, memory, and the monitoring of self-generated events."

Shinn's findings and those of others may help scientists develop new drugs to treat hallucinations. Currently, antipsychotic medications like Haldol (haloperidol), which are effective first-line therapies for schizophrenia, can act to calm hallucinations. These drugs block abnormal activity of dopamine, a neurotransmitter involved in regulating mood and behavior. "These medications aren't perfect," says Shinn. "They don't quite get rid of the hallucinations, but they do quiet them down."

Some consider hallucinations, especially those initiated by psychotropic drugs, to be expressions of a mind freed of ordinary patterns and structures; others who grapple with mental illness, may consider them to be divine expressions or voices of personal doom; still others may find them to be a non-threatening result of a medical condition. Whatever the interpretation, the neural basis for hallucination remains an area of intense study for Shinn and others. ♥

## Neglect and the Brain

**S**HOULD ANYONE NEED another reason for ensuring that children are nurtured and protected, a growing body of evidence suggests that neglect can harm brain development and cause long-term detrimental effects to cognition and behavior.

According to the National Children's Alliance, a nonprofit association dedicated to helping communities fight child abuse, there are more than 3.3 million reports of child abuse in the United States each year, affecting nearly 6 million children. More than 78 percent of these cases are considered neglect, defined by the U.S. Department of Health and Human Services as "a type of maltreatment that refers to the failure of caregivers to provide needed, age-appropriate care."

"In some ways," says Charles A. Nelson III, an HMS professor of pediatrics and director of the Division of Developmental Medicine at Boston Children's Hospital, "neglect is worse than physical abuse. Kids are starved for information. If they

don't get that information, they're in a holding pattern in terms of brain development."

### Pruning the brain

Neurons are created during fetal development. These cells then migrate to various parts of the brain and develop into specialized cells. Among the first to specialize are nerve cells in the brainstem and midbrain, those regions that govern certain autonomic functions that allow a baby to live. Other regions of the brain, ones that regulate emotion, thought, and language, develop after a baby is born. During a child's early years, the development of synapses, which are connections between neurons, occurs at an astonishing rate. By age 3, a child's brain has trillions of synapses, some of which are strengthened and remain intact, others of which are discarded or pruned as part of the normal development of the brain. While

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

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## The David Mahoney Prize Symposium and Dinner—November 8, 2012



Hildegard Mahoney, chairman of the Harvard Mahoney Neuroscience Institute and Ed Rover, chairman and president of the Dana Foundation and HMNI council member



Nobel laureate Eric Kandel, MD, University Professor and Kavli Professor of Brain Science, director, The Kavli Institute for Brain Science, and codirector, The Mind Brain Behavior Initiative, Columbia University Medical Center, and Gerald Fishbach, MD, John E. Borne Professor of Pharmacology and Neuroscience at Columbia University Medical Center and former director of the Harvard Mahoney Neuroscience Institute, take audience questions at HMNI's 2012 symposium, "Progress in Brain Science over the Past 50 Years."



Jeffrey Flier, MD, dean of the faculty of medicine at Harvard University; Louise Mirrer, president of the New-York Historical Society; and Ambassador Alan Blinken



Guy McKhann, MD, professor of neurology and neuroscience at the Center for Mind-Body Research at Johns Hopkins School of Public Health; Barbara de Portago; and Jerome LeWine



Nobel laureates James Watson and Eric Kandel



Ian Robertson, PhD, professor of psychology, Neuroscience Institute, Trinity College, Dublin; Suzanne McDonough; and James Watson



Bob Merrill, H '81 (center), and his trio



Table setting for the dinner honoring Eric Kandel, recipient of the 10th David Mahoney Prize



Liz Watson; William McDonough; and Fiona Robertson, PhD



Missie Rennie Taylor and Sharon King Hoge

*Photos on page 4 and 5 by Stephanie Badini.*

## Eric Kandel Receives 2012 David Mahoney Prize

THE 10TH BIENNIAL David Mahoney Prize was awarded to Eric R. Kandel, Nobel Laureate, author, university professor at Columbia University and Kavli Professor of Brain Science, director of The Kavli Institute for Brain Science, and codirector of The Mind Brain Behavior Initiative at Columbia University Medical Center, at a festive dinner in New York City on Thursday, November 8, 2012.

The dinner was preceded by a symposium—moderated by Edward Rover, Harvard Mahoney Neuroscience Institute council member and chairman of the Dana Foundation—at which Gerald Fishbach, John E. Borne Professor of Pharmacology and Neuroscience at Columbia University Medical Center and former director of HMNI, interviewed Kandel about the progress of neuroscience throughout the past 50 years. A lively question and answer period was followed by a pre-dinner reception with entertainment by Bob Merrill, H'81 and his jazz trio.

Hildegarde Mahoney, HMNI chairman, presented the David Mahoney Prize. Said Mahoney, “Eric, on behalf of everyone connected with the Harvard Mahoney Neuroscience Institute and myself, it is my pleasure to present you with the 2012 David Mahoney Prize, with which I know David would agree you so richly deserve. The plaque reads: Awarded to Eric Kandel for Building a Bridge Between the Public and Scientists Dedicated to Brain Research by HMNI.”

Among those attending the evening event were Jeffrey Flier, dean of the faculty of medicine at Harvard University; James Watson, Nobel laureate; Ian Robertson, founding director of the Neuroscience Institute at Trinity College, Dublin, and the College's dean of research and professor of psychology at the Institute; and Ambassador and Mrs. Alan Blinken. ♥



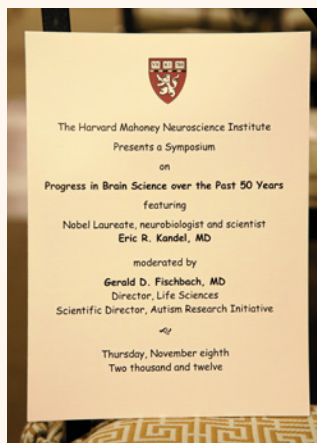
Eric Kandel is presented with the 2012 David Mahoney Prize by Hildegarde Mahoney, chairman of the Harvard Mahoney Neuroscience Institute.



Jeffrey Flier, Hildegarde Mahoney, Eric Kandel, and Gerald Fishbach



Melinda Blinken and Eric Kandel



James Watson and Shirley Rosenthal

synapses are forming, mature neurons become swathed in myelin, a fatty tissue that wraps neurons and helps ensure the clear, speedy transmission of signals along them.

Also by age 3, the brain has almost reached its ultimate physical size. The development of each region of the brain, however, depends on stimulation from the environment: face-to-face talk, repeated sounds, or responses to cries, for example. Scientists think there are critical periods during which the brain has a heightened sensitivity to such stimuli but, compared with their understanding of these periods in non-human

*According to a 2008 study by the American Professional Society on the Abuse of Children, babies who are ignored when they begin to babble, often do not exhibit the rate of language development that children should show between the ages of 18 and 24 months. Other studies indicate that children who suffer severe neglect have smaller brains and fewer neuronal pathways for learning.*

animals, are less certain when and for how long these periods exist in human development. Researchers do know, however, that without experience-dependent learning, the brain is unable to strengthen synapses and neuronal pathways, potentially diminishing its functional capabilities.

### **The price of neglect**

When environmental stimulation is lacking, the brain's development can be altered, resulting in possible cognitive, social, and physical deficits. Experience-dependent learning, for example, is critical for language development. According to a 2008 study by the American Professional Society on the Abuse of Children, a national organization of professionals who serve children and families affected by child maltreatment and violence, babies who are ignored when they begin to babble, often do not exhibit the rate of language development that children should show between the ages of 18 and 24 months. Other studies indicate that children who suffer severe neglect have smaller brains and fewer neuronal pathways for learning, and that some children who do not have a nurturing caregiver have difficulty forming meaningful relationships as they grow older.

Nelson's studies with the Bucharest Early Intervention Project, which examines the effects of institutionalization on the cognitive and behavioral development of Romanian orphans, demonstrate the cascading negative effects that isolation and neglect can have on children. "Our studies show that these kids don't know how to play with others, have no relationships with their caregivers, and have attachment problems that manifest in an inability to form intimate relationships," he says. These problems and others, including diminished cognitive function, low IQ, and executive function deficits, often continue into adolescence and adulthood.

### **A matter of gray and white**

Two recent HMS studies shed some light on what happens to the brains of neglected children and why the lack of a nurturing environment may contribute to abnormal brain development. A recent study by Nelson, published in July 2012 in the *Proceedings of the National Academy of Sciences*, found that children raised in Romania's state-run orphanages developed lower volumes of gray matter and white matter than children who grew up within families. White matter is responsible for the connectivity between different regions of the brain, while gray matter controls sensory perception and other functions.

Nelson's team also found that children who spent their infancy in orphanages but were later transferred to high-quality foster care regained a degree of white matter growth, showing that some of the damage from neglect and social isolation can be reversed.

"What's missing in institutionalized children is the nurturing and interaction required for normal, healthy brain development," says Margaret Sheridan, an HMS instructor in pediatrics and lead author on the *PNAS* paper. "Foster care addresses that specific environment. The kids were still in Romania and their basic needs were still being met, but they had caregivers who were devoted to one-on-one care and to tailoring solid interactions to their needs."

Nelson now plans to study institutionalized children as they enter adolescence to determine how isolation and neglect affect executive function development and risk-taking behavior. "The transition to adolescence is hard anyway," he says. "With a bad early beginning, these kids are at risk for mental health problems as they get older. We need to see what fate awaits these kids." ♥

## The Need to Eat

**A**DMIT IT. You ate too much over the holidays, indulging at parties and family gatherings and, maybe, sneaking a hand—or two—into the cookie tin. For a growing number of Americans, however, the need to eat, to launch that sneak attack on cookies or on food in general, is not a periodic anomaly. It is an addiction, a potentially life-threatening one, that is present year-round.

Although the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*—the foremost reference for U.S. professionals who diagnose psychiatric conditions—does not include food addiction, there is mounting scientific evidence that such a disorder exists. Through animal studies and imaging scans of the human brain, the idea that food can be addictive, like drugs or alcohol, is gaining scientific muscle. In 2011 the National Institute on Drug Abuse awarded grants totaling nearly \$6 million for investigations on the topic.

The nonprofit organization Food Addiction Institute says that people with this type of addiction lose control over their ability to stop eating certain foods. Edward Khantzian, an HMS clinical professor of psychiatry who studies addiction, sees parallels between addiction to food and dependence on drugs or alcohol. “People get hooked on food or drugs,” he says, “because they find it provides temporary comfort and relief, a lifting of some distressing psychological state.”

### The dopamine dance

Experiments in animals and humans show that, for some, the same reward and pleasure centers in the brain that are activated by such addictive drugs as cocaine and heroin are also activated by certain foods, especially those high in sugar, fat, and salt. These so-called highly palatable foods trigger the release of dopamine and similar neurotransmitters that, at certain levels, can induce euphoria. As a person eating these foods experiences the pleasure associated with increased dopamine concentrations in the brain's reward centers, a craving to prolong or intensify the pleasurable feelings takes hold, generating a cycle of overindulging that is hard to break.

In animal studies, researchers have discovered that highly palatable foods cause biochemical changes in the brain. In one experiment, Rockefeller University scientists found that, in response to high-fat food consumption, animals produce certain substances in their brains. Reintroducing these substances by injecting them into test

animals led those animals to crave even more fat. In another study, a team at Scripps Research Institute found that animals that had access to highly palatable foods for an hour a day binged on those foods despite being offered other food options for longer periods of time. When another group of test animals in the Scripps study were offered unlimited access to high-sugar, high-fat foods, they became obese. In addition, when threatened with electrical shocks, the animals continued to prefer the high-sugar, high-fat choices.

Brain scans of compulsive eaters as well as those of obese people reveal chemical surges in the brain's reward circuit similar to those seen in the brains of drug abusers. For example, cocaine floods this reward circuit with 2 to 10 times as much dopamine as is produced by other pleasurable activities such as sex. The brain resets to adjust to the dopamine overload, so, increasingly, more of the drug is needed to achieve a similar result.

In a key study in the early 2000s, a research team at Brookhaven National Laboratory found that the brain scans of obese people show a lack of dopamine D2 receptors, a deficit that mirrors one found in the brains of addicts. Dopamine D2

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inhibits behavior, so an absence of receptors to capture this form of dopamine means the urge to overeat—or to get high—cannot be curbed chemically in the brain. This deficit also decreases a person's sensitivity to the rewards of either eating or using drugs, requiring an ever-greater use of food or drugs to generate the same level of pleasure.

### Packing on the pounds

A hallmark of any addiction is the continued use of a substance regardless of the consequences. “People continue the behavior,” says Khantzian, “despite the costs, despite the harm to relationships, employment, or personal health.”

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And the effects of food addiction, obesity, and overeating, indeed, have consequences: They are taking a toll on our nation's health. Obesity has reached epidemic levels in the past 20 years. Today, nearly two-thirds of U.S. adults are overweight, and 30 percent are obese. These people have a higher death rate than their ideal-weight counterparts and face a greater risk of diabetes, heart disease, and the diminished quality of life that poor health can bring. According to the American Heart Association, a continuation of the current obesity trend could cause total health-care costs to top \$950 billion.

Khantzian says there is hope, however. New drugs are being developed, including ezlopitant, a compound known to suppress cravings for alcohol that may also tamp down the neural pathways involved in food addiction. And programs like Overeaters Anonymous, which models itself on the 12-step programs for people with alcohol or drug addictions, offer hope for those who cannot otherwise stop eating. ♥

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

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*Freelance Writer:* Scott Edwards

*Design:* Gilbert Design Associates, Inc.

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