

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER



The Molecular Underpinnings of Autism

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A STARTLING STATISTIC emerged in recent years: Between 2002 and 2006 the prevalence of autism in children jumped nearly 50 percent, from 1 in 150 to 1 in 100.

According to the Autism and Developmental Disabilities Monitoring Network, the U.S. Centers for Disease Control and Prevention research group that uncovered this increase, the hike in prevalence can be further defined along gender lines. Network investigators also found a 60-percent increase in the number of boys with autism and a 48-percent increase among girls. In other words, in that short period of time, 1 in 70 boys and 1 in 315 girls in the United States were formally diagnosed with autism.

"Better diagnosis is one big reason for the increase, just as it is for other diseases such as prostate cancer," says Christopher A. Walsh, MD,

PhD, the Bullard Professor of Neurology at HMS and chief of the Division of Genetics at Children's Hospital Boston. In addition, some scientists believe that certain children who were originally diagnosed with mental retardation are now being reclassified as autistic.

But scientists such as Walsh and Michael E. Greenberg, PhD, the Nathan Marsh Pusey Professor of Neurology at HMS and chairman of its Department of Neurobiology, are also quite certain that one previously touted link is unfounded. According to these HMS researchers, there is no convincing scientific evidence to support claims that vaccines containing the mercury-based preservative thimerosal are behind the increased

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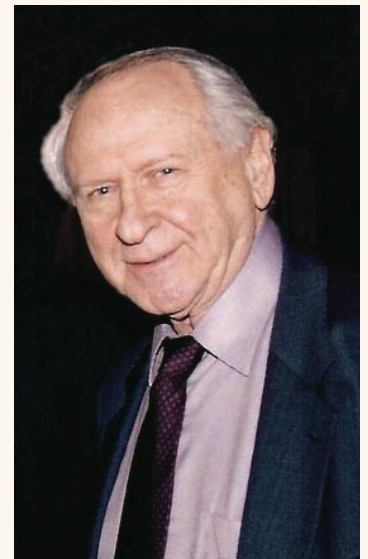
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A Tribute to William Safire, Recipient of David Mahoney Prize

WILLIAM SAFIRE, winner of the 2002 David Mahoney Prize, died on September 27, 2009. Safire was chosen for the prize because of his journalistic efforts to bring neuroscience to the world's attention, which included highlighting the importance of supporting research on the brain and its disorders. At the time of the award, he also was serving as chairman of the Dana Foundation and of the Dana Alliance for Brain Initiatives, where he carried on the programs instituted by his predecessor, David Mahoney.

Safire was a Pulitzer Prize winner honored for his work as a political columnist for *The New York Times*, a role he filled from 1973 to 2005. He was equally well known for his Sunday column, "On Language," which appeared in *The New York Times Magazine* from 1979 until his death, and for his frequent appearances on the television show, "Meet the Press." Prior to joining the *Times* he was a speechwriter for President Richard M. Nixon.

As chairman of the Dana Foundation, Safire expanded its print and web publication programs and was involved extensively in the Dana Press, from guiding its choice of topics and authors to shepherding each publication through editing, production, and distribution. Nearly every title published during his tenure addressed timely topics in neuroscience, including neuroethics, neuroeducation, and neuroimmunology. He was a tireless champion of the outreach efforts of both the Dana Foundation and the Harvard Mahoney Neuroscience Institute. ♥



prevalence. Quite the contrary, they say: Thimerosal was eliminated from vaccines in 1999, yet the prevalence of autism has continued to rise.

Biology, Not Bad Parenting

Autism is a general term used to describe a group of complex developmental disorders characterized by social impairments, communication difficulties, and unusual, repetitive behaviors, such as flapping the arms and hands or snapping the fingers in front of the eyes. This range of disorders, known as autism spectrum disorders, includes the most severe form, autistic disorder, also known as classic autism. At the other end of the spectrum are milder forms such as Asperger's syndrome and the atypical PDD-NOS, or pervasive developmental disorder—not otherwise specified.

Autism was first described as a unique medical condition in 1943 by Leo Kanner, an Austrian psychiatrist. Later, Bruno Bettelheim, a U.S. child psychologist, gained an international reputation for promoting Kanner's theory that uncaring, "refrigerator" mothers caused autism in children. This erroneous, and fortunately short-lived, belief faded as the medical community became aware that autism had genetic roots—that it was a biological disorder, not the result of bad parenting.

While Greenberg teases out the role of MeCP2, Walsh concentrates on identifying genes that, when altered, may lead to autism. Finding autism genes, he says, will help scientists understand its underlying mechanisms and could lead to new studies focused on improving the diagnosis and treatment of the disease.

Although scientists are not certain what causes autism, researchers at HMS and elsewhere who have been investigating possible genetic factors have identified a number of genes associated with this spectrum of disorders. Abnormalities found in post-mortem examinations of the brains of autistic children suggest that autism might result from a disruption of normal fetal brain development caused by defects in the genes that control brain growth and regulate how brain cells communicate with one another.

"It's not yet clear what changes in the brain lead to autism," says Greenberg. "One idea is that

autism is a disorder of the synapses, especially the balance between [activity-promoting] excitatory and [activity-dampening] inhibitory synapses." Synapses are connections between neurons that many consider to be fundamental to the learning process. Information from one neuron to another must move across the synapse, triggering brain activity as it travels.

Because seizure activity is frequently associated with autism, many scientists believe that, as with epilepsy, autism might be caused by an increase in the activity of excitatory neurons.

Out of Balance

To bring greater clarity to autism's root causes, Greenberg is studying the role of a binding protein known as MeCP2. Found in high concentrations in neurons, MeCP2 is involved in the maturation of the central nervous system and in the formation of synaptic connections. MeCP2 acts as a repressor, affecting the expression of genes that regulate the excitatory-inhibitory balance.

Mutations to MeCP2 are known to cause Rett syndrome, a developmental disorder that shares some clinical similarities with autism. The mutations alter the structure of MeCP2 and reduce the amount of the binding protein found in cells. At reduced levels, the protein is unable to control gene expression appropriately. Other research has likewise reported mutations or other changes in MeCP2 activity in some cases of autism.

"Normally, in early life," says Greenberg, "as we engage with the world and learn, signals change within neurons, turning on the genes involved in the maturation of synapses and the development of this excitatory-inhibitory balance. When MeCP2 is mutated, significant defects in this balance between excitatory and inhibitory neurons occur that, in principle, could lead to autism."

Identifying a Common Neural Pathway

While Greenberg teases out the role of MeCP2, Walsh concentrates on identifying genes that, when altered, may lead to autism. Finding autism genes, he says, will help scientists understand its underlying mechanisms and could lead to new studies focused on improving the diagnosis and treatment of the disease.

Last year, Walsh and his colleagues identified five new autism-related gene defects, adding to the dozen or so already known. Walsh says a common pathway seems to be emerging: This



group of genes, including the ones Walsh and his team discovered, work to create, reinforce, or modify synaptic pathways in the brain.

An impaired capacity for synaptic change may be a hallmark of autism, say many neuroscientists. “Of the five genes we found, several have some type of synaptic function,” Walsh says. “With Greenberg’s lab, we also found that some of these genes are regulated by activity in neurons, which causes synapses to change.”

The fact that different genetic causes of autism are tied together through synaptic regulation is a good sign, Walsh says. “Many drugs affect synaptic function,” he says. “We now have a common pathway to look at, so we might not need 1,000 different drugs to treat 1,000 different kids with autism.”

New Opportunities for Answers

This past October, Greenberg and Walsh received a \$4.5 million Grand Opportunity grant from the National Institute of Mental Health, part of the Obama administration’s 2009 stimulus package, to pursue whole-genome sequencing of people with autism using new technologies for rapid DNA sequencing.

The project will focus on 85 Middle Eastern patients who were part of previous studies by Walsh and his colleagues. The parents of these patients share a common ancestry, often as cousins.

These large families, in which several individuals have autism, provide researchers an opportunity to map disease-linked genes; the genetic variability of the disorder, including many of its recessive forms, is often manifested in these families. As technology and informatics techniques are refined, scientists hope to interpret the genetic-sequence information in other groups of related autism patients, including in U.S. families.

In a separate part of the project, Greenberg will examine gene activity in neurons, focusing on genes residing in regions of DNA that have, over many years, been deleted from the genetic material of the Middle Eastern families. His lab will create a map of critical on/off switches in their genomes.

“We’re hoping this study will give us the molecular underpinnings of autism,” says Greenberg. “A lot of genes are implicated. We’re trying to figure out what they’re doing and how they affect synapse development and thus, autism.”

Despite the progress Greenberg, Walsh, and other researchers have made, a cure for autism is by no means around the corner. But Walsh says that along with the new knowledge gleaned from their studies has come a “complete change in our mindset” about autism. In the end, that change is what may lead to better treatments and, ultimately, to a cure for this array of disorders. ♥

Dementia and End-of-Life Care

IT'S HARD TO TALK about dementia, almost as if keeping silent on the subject might help us avoid it altogether. Yet dementia is one of the world's fastest growing medical problems and a leading cause of death in the United States.

But it probably would be wise, even healthy, to break our silence, according to a recent study by Susan Mitchell, MD, MPH, an HMS associate professor of medicine and a senior scientist at the Hebrew SeniorLife Institute for Aging Research in Boston. Her work sheds new light on the clinical

and perception, and produce emotional, social, and cognitive deficits. In the United States today, more than 5 million people suffer from dementia; this number is expected to increase threefold in the next 40 years. Worldwide, an estimated 35 million people have the disease, according to Alzheimer's Disease International.

Mitchell's study, reported in October 2009 in the *New England Journal of Medicine*, is the first to rigorously describe the clinical course of dementia. Previous studies have suggested that a high risk of death is associated with advanced dementia and that patients with the disease all too often receive suboptimal levels of palliative care, a form of care that aims to improve the comfort of the terminally ill rather than treat or cure them.

"Dementia is a terminal illness," says Mitchell. "As the end of life approaches, the pattern in which patients with advanced dementia experience distressing symptoms is similar to that found in patients dying of more commonly recognized terminal conditions, such as cancer."

During her 18-month investigation, Mitchell followed the progress of 323 nursing home residents diagnosed with advanced dementia. In the final stage of their disease, she found all patients had profound memory deficits, including an inability to recognize close family members, speak more than six words at any given time, or walk. Pneumonia, fever, and eating problems also were common and were associated with high six-month mortality rates.

During the study, 177 patients died. Mitchell found that in their last three months of life, nearly 41 percent had undergone at least one intervention she considered to be of questionable benefit to them, including a hospitalization, a visit to an emergency department, intravenous therapy, or tube feeding. Yet when health care proxies, family members, and people with a special interest in the care of these patients learned of the poor prognosis—and expected clinical complications—of proposed interventions, the patients were less likely to undergo an intervention *and* were more likely to receive palliative care in their final days.

"A better understanding of the clinical trajectory of end-stage dementia is a critical step toward improving the care of these patients," says Mitchell. "The findings of this study should give health care providers, patients, and families more realistic expectations about what they will confront as the disease progresses and the end of life approaches." ♥



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course of advanced dementia—and reveals that greater openness about and understanding of the disease could lead to improvements in end-of-life care for patients.

Dementia is an umbrella term that describes a group of symptoms severe enough to interfere with daily function, including language, memory,

Fear and the Brain

In *The Expression of the Emotions in Man and Animals*, the nineteenth-century British naturalist Charles Darwin provided a vivid description of fear:

“Fear is often preceded by astonishment, and is so far akin to it, that both lead to the senses of sight and hearing being instantly aroused. In both cases the eyes and mouth are widely opened, and the eyebrows raised...The heart beats quickly and violently, so that it palpitates against the ribs...The hairs also on the skin stand erect and the superficial muscles shiver. ...”

Fear is an emotional response to a perceived threat in the environment. When we react to a threat, our sympathetic nervous system primes us to either flee from the danger or to stand and defend ourselves, the so-called fight-or-flight response. This response includes the physical reactions Darwin so dynamically described more than a century ago: heightened awareness, increased heart and respiratory rates, and quickened reactions. In addition, the nervous system directs blood toward the muscles that control the movements of our limbs—what Darwin called the superficial muscles—providing them the extra energy resources needed to flee from or confront a fear-provoking stimulus.

The Eyes Have It

In his laboratory at Children’s Hospital Boston, Charles A. Nelson III, PhD, an HMS professor of pediatrics and research director of the hospital’s Developmental Medicine Center, studies how facial expressions relate to fear and other emotions.

“We’re not really sure—no one is—how the brain processes facial expressions of fear,” he says, “but we do know that the eyes react to fearful situations in ways that are sufficiently different from their reactions to other emotions. There’s something about the eyes and fear.”

While it is difficult to describe precisely the messages that the eyes telegraph in response to fear, scientists have found that the eyes do play an important role—especially their sclera, or “whites.” Fear-filled or surprised eyes expose a larger area of sclera than do eyes reflecting “happy” or other expressions.

We reconcile the meaning of facial expressions, including fear, through a neural network that involves emotion-related connections and areas of the brain devoted to processing higher-level visual representations. This network, says Nelson, is

active even in infants. Nelson adds that although infants as young as five months do not show anything resembling fear when they see a fear-filled face, “there’s a threshold at which the central nervous system responds to fearful faces that seems to activate the brain’s fear circuit.” Nelson notes, however, that we don’t yet know how an infant’s brain recognizes facial expressions as fearful, since most infants have yet to experience—or understand—frightening situations.

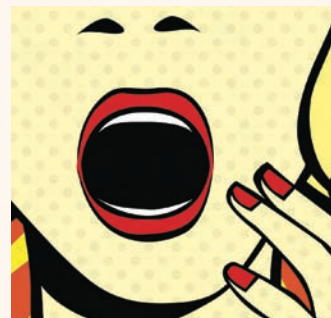
Fearful expressions cause us to react quickly, almost without seeming to think. At Vanderbilt University, researchers found that people not only react faster to fear-filled expressions than they do to either happy or neutral facial expressions but that they consistently react more slowly to happy faces than to those expressing other emotions. Many scientists think this response variation exists because evolution favored those individuals who responded quickly to dangerous situations, preserving and building the neural response to react almost instinctively to potential threats. Thus fearful expressions exist not merely to express fear, but also to promote our survival.

Fear Central

The core of the brain’s fear mechanism is the amygdala, an almond-shaped cluster of nerves located deep within the brain. The amygdala is the brain’s center for emotions and performs a primary role in the processing and memory of emotional reactions. In addition, the amygdala is connected to the orbitofrontal cortex, a region of the frontal lobe that is involved in such cognitive processes as decision-making and fear inhibition.

“Although the amygdala may say that something is fearful,” says Nelson, “it is the orbitofrontal cortex that puts it in the context of ‘Should I be afraid? Should I run away?’ The amygdala itself doesn’t interpret the fear.” Studies have shown that when the amygdala captures a fearful visual signal—something as simple as a broadening of the visible area of the sclera—it becomes hyperactive, bypassing the brain’s normal visual processing pathway to allow the body to respond even before the brain has fully translated all information about the potential danger. But if the brain realizes the stimulus is not threatening, a tempering process kicks into gear: The rostral anterior cingulate cortex, located in the frontal lobe, dampens activity in the amygdala and extinguishes the fear response.

This is the fourth in a series of articles on how internal and external forces affect the brain.



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The Balancing Act of Epilepsy

WATCHING SOMEONE, especially an infant or a young child, have an epileptic seizure can be a frightening experience. Physical spasms may cause them to jerk or thrash about involuntarily. The seizing person might lose unawareness of what's happening around him or her—or completely lose consciousness.

Epilepsy is a chronic neurological disorder that afflicts nearly three million people in this country. More than 325,000 children under the age of 14 have some form of epilepsy, according to the Epilepsy Foundation. The disorder is characterized by unprovoked seizures, which are signs of abnormal, excessive activity by the brain's nerve cells. During seizures, neurons fire electrical impulses at outsized speeds often as high as four times their normal rate, creating a sort of electrical storm in the brain. Although seizures can occur and not be associated with epilepsy, when their pattern becomes repetitive, they usually are considered a symptom of the disorder.

New cases are more likely to be diagnosed in children than in adults and adolescents, especially during the first year of life. Afterward, the rate gradually declines; among children age 10 and older, the rate stabilizes to that for adults. After age 55 or 60, however, the rate again begins to climb, as the incidences of stroke, brain tumor, or Alzheimer's disease, each of which can trigger epilepsy, increase.

"Young children's brains function on a balance between excitatory and inhibitory activity," says Frances Jensen, MD, an HMS professor of neurology and the director of epilepsy research at Children's Hospital Boston. "When there is too much excitatory activity, the balance tips, and seizures result."

This excitatory and inhibitory activity is regulated by neuron-produced chemicals called neurotransmitters. When neurotransmitters excite a neuron, for example, that nerve cell produces electrochemical signals that trigger activity in it and in other nerve cells in succession. By contrast, inhibitory neurotransmitters usually act to decrease the signaling activity of a nerve cell, dampening its ability to stimulate domino-like the activity of other cells.

Small Margins

Nerve cells in the brains of infants and young children function close to the tipping point between excitatory and inhibitory brain cell activity, says Jensen. This is not necessarily a bad thing: When we learn, new connections take hold in our brains,

and that process, an especially active one in young brains, requires neurons to turn on and off a great deal. "The immature brain has an imbalance of excitatory activity," she says. "That's why children learn faster."

An excess of excitatory activity, however, can cause the firings of some neurons to reach a critical level that upsets the brain's electrical balance. These high-firing cells in turn urge normally paced cells to increase their rate of fire. Many neuroscientists believe this recruitment occurs when there is an excess of excitation, a lack of inhibition, or both.

Seizures resulting from this excitatory imbalance can overactivate, interrupt, or destroy vital networks in the brain, each of which can profoundly affect cognitive function and learning. The developing brain often can compensate for these disruptions by creating new neuronal networks, a remodeling process called plasticity. Unfortunately, the potential for plasticity diminishes over time.

"We think seizures chemically change the molecules required for learning and memory and also alter the structure and function of the brain," says Jensen. "That's why many people with epilepsy have long-term cognitive, learning, and memory deficits."

A Faceted Disorder

There are several types of epilepsy—and of epileptic seizures—each with different causes, symptoms, and treatments. Types can be categorized as either cryptogenic, indicating that there is a likely cause but that this cause remains unidentified; or symptomatic, meaning there is a distinct and identifiable cause. Epilepsy and its accompanying seizures also may be described as generalized, involving the entire brain, or focal (partial), as when seizures emanate from a specific area.

"Anything that can affect this excitatory-inhibitory balance can be a cause of epilepsy," says Jensen. "We know that some epilepsy is genetic—that is, a gene or genes that regulate the activity of neurons may change, altering a neuron's ion charge and pushing that neuron into an excitation imbalance. Other forms of epilepsy can occur as a result of a damaging fever or a traumatic injury to the brain."

When describing epileptic seizures, physicians use one of six categorizations. Grand mal seizures, also known as generalized tonic-clonic, lead to unconsciousness, convulsions, and muscle rigidity,



while absence seizures can cause a brief loss of consciousness. Other categories focus on muscular involvement and movement: myoclonic, characterized by sporadic, isolated, jerking movements; clonic, identified with repetitive, jerking movements; tonic, characterized by muscle stiffness and rigidity; and atonic, associated with the loss of muscle tone, particularly in the arms and legs, which can lead to frequent falls.

Jensen says that although some forms of epilepsy are mild in symptom and seizure, nearly 50 percent of all patients develop some type of cognitive or psychological impairment. Some may manifest autism, depression, or attention deficit disorder. Research is ongoing to understand how seizures cause cognitive problems or which specific genetic defects lead to the emergence of seizures and cognitive dysfunction.

Epilepsy cannot be cured, but the seizures associated with it can be controlled with medication fine-tuned to address a patient's type of seizure. Some studies suggest that 50 percent of people with epilepsy gain complete control of their seizures for a significant period of time while on

medication and that another 20 percent significantly reduce the number of seizures they experience.

Unfortunately, some people have seizures despite medication. For these people, therapeutic surgery to remove seizure-producing areas of the brain is often considered. This surgical approach has been an accepted form of treatment for more than 50 years. The vast majority of such surgeries, says Jensen, are used to treat people with focal areas of epilepsy. Such surgery, she explains, is conducted with great care and precision so that only the smallest possible area of seizure-generating tissue is excised.

Rescue and Discover

In an effort to advance the treatment of epilepsy-associated seizures, Jensen is perfecting a method that uses brain tissue from patients who have undergone seizure-controlling surgery to test the usefulness of new medications. In her laboratory at Children's Hospital, Jensen examines this tissue for new therapeutic targets.

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Lessons During Evolution

When scientists speak of types of fear responses, they refer to two: innate and acquired. Innate fears are hardwired in our brains. A fear of snakes, for example, can be found in people who have never been exposed to these reptiles. Anthropologists say this response was likely conserved by evolution and passed down genetically from a time when snakes were a greater danger to humans. By contrast, acquired, or conditioned, fear is a learned response, gained when we learn to fear new threats, such as a wildfire, a snarling bear, or a man with a gun.

In conditioned fear, the amygdala forms an association with a seemingly neutral stimulus and attaches an emotion to it. When we are exposed to that stimulus, such as seeing a fearful expression on the face of someone we're talking with, the fear response sparks. The amygdala tags the association and triggers a strong physiological response: a frenetic heart rate, copious sweat production, and tensed skeletal muscles.

Memory and facial expressions are not linked early in life, says Nelson, but they are bound together over time. "If you and I were having a face-

to-face conversation and I looked afraid, you would likely look over your shoulder to see what was frightening me," he says. "This is based on experience: 'If he's afraid, then I should be afraid, too.'"

Memory does not need to be invoked for fear detection, Nelson adds. Memory becomes involved through associative learning.

At Children's Hospital, Nelson and his colleagues hope to soon begin studying a serotonin transporter gene, called 5-HTT, that may tell scientists more about the human fear response. The gene, he says, has two alleles, or variants, one long and one short.

"If a person has the short/short variant," Nelson says, "that person shows a great deal of brain activity and large metabolic changes in response to fearful facial expressions. Work by a former post-doctoral colleague of mine, in fact, shows that infants with the short/short allele have stronger responses to fear than do infants with the long/long allele."

In addition, Nelson is examining why fear commands such significant neural resources in our brains.

"There is something very compelling about a fearful face," he says, "but, mechanistically, we don't know yet what triggers that compulsion." ♥

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"Basically, we're taking drugs that in most cases have never before been used in humans and targeting them to certain receptors in cells of the brain tissue," she says. "We do this by implanting the tissue with electrodes and 'listening' to the activity of the brain cells so as to determine whether or not the receptor we are considering targeting is critical to the generation of the seizure. If it is, we apply the drug to the tissue to see if it makes the seizure go away."

Jensen says her team has preliminary evidence that some of the drugs may be effective against seizures. More tests are needed, however, before any substance can be considered ready for human use. Fortunately, some of these drugs have already been cleared as treatments for other disorders, a fact that may help pave the way for their eventual adoption as epilepsy therapy. ♥

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