THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• Emotion May Be More "Intelligent" Than We Thought

In following the trails that emotions blaze through the brain, researchers have long known the amygdala to be a prominent feature. This almond-shaped structure, which provides the emotional intensity that digs important events into the brain as memories, was first understood to play a role in unpleasant emotions such as fear. More recently, however, imaging studies in humans have found the amygdala to be involved in pleasant emotions as well.

In the February issue of *Nature Neuroscience*, Adam Anderson of Stanford University has drawn an important distinction between an emotion's intensity and its "valence"—whether the emotion is perceived as pleasant or unpleasant. Anderson and colleagues at Stanford, the University of California at Berkeley, and the University of Austria chose the realm of scent, which has strong connections to the brain's emotion centers but which allows intensity and valence to be easily separated. Sixteen human volunteers sniffed varying intensities of lemony citral acid and foul, rancid valeric acid while having

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Imaging Studies Bring ADHD into Sharper Focus

BY ANN MACDONALD

Attention deficit hyperactivity disorder (ADHD) is the most common neurobiological disorder diagnosed in children—and arguably the most controversial. Although medical consensus exists that ADHD is just as real as diabetes or heart disease, critics contend that the disorder is over-diagnosed and that too many children are being medicated, contributing to the creation of "Generation Rx."

"Some people seem to think we are putting chemical straightjackets on children" because their behavior isn't socially acceptable, says Martin Teicher, director of the Developmental Biopsychiatry Program at McLean Hospital.

Recent brain imaging studies, however, not only offer further evidence that the brains of children with ADHD differ from the brains of other children, Teicher says, but also are beginning to show how medications correct chemical and electrical irregularities in the brain associated with particular symptoms. Such studies should reassure people "that we're solving a problem, not just creating another one," he says.

Commercial imaging tests are being developed. But experts caution that it is too soon to use these tests to confirm a diagnosis or to evaluate treatment.

"No one should pay a penny right now on commercial imaging studies for diagnosis or treatment," says Judith Rapoport, chief of the Child Psychiatry Branch at the National Institutes of Mental Health. "The science is interesting, but I would predict that we're not going to have an objective test for ADHD for years."

Teicher agrees. The data from some studies are conflicting, he says, and not yet specific enough to be helpful in individual cases: "Avoid any test until it is extremely well established."

Zooming In on the Problem

According to criteria listed in the DSM-IV, the standard manual of diagnosis for psychiatric disorders, there are three subtypes of ADHD:

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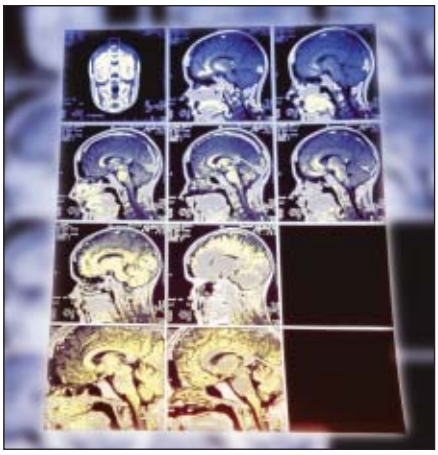

Magnetic resonance imaging (MRI), just one imaging tool researchers are using, provides a look at the anatomy of the brain and can help explain why abnormalities develop.

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the primarily inattentive type, the hyperactive/impulsive type, and a third type that combines inattention with hyperactivity. Diagnosis is usually made on the basis of behaviors observed by parents, schoolteachers, and the physician.

One reason for controversy is that nobody really knows how common ADHD is. The National Institutes of Health estimates that 3 to 5 percent of school-age children have the disorder. Various studies, however, yield figures of anywhere from 1 to 20 percent. Estimates of prevalence vary because diagnostic criteria have changed over the years and the disorder is diagnosed more often in some parts of the world than in others.

Complicating things still further, many children with ADHD have co-existing disorders with symptoms that muddy the diagnostic picture. About one in three children with ADHD has a conduct disorder (aggressive, destructive, or deceitful behavior), one in four has an anxiety disorder, one in five has a mood disorder, and as many as six in ten are diagnosed with a learning disability.

To determine the root cause of ADHD, and how it differs from other disorders, past studies have identified several areas of the brain that are under-active in people with ADHD. These include the prefrontal cortex, basal ganglia, and cerebellum. Others have shown that two neurotransmitters, dopamine and norepinephrine, are somehow involved.

The most recent imaging studies are helping researchers to fit some of these early findings together in a way that will better explain why brain abnormalities develop and how they contribute to a child's being unable to sit still and pay attention. The imaging techniques vary. Some, like magnetic resonance imaging (MRI), provide information about brain anatomy. Others, such as positron emission tomography (PET) and electroencephalography (EEG), provide insight into brain function.

Researchers at NIMH, for instance, are using MRI technology to measure brain size and growth in healthy children, as well as in those with ADHD and other disorders. The studies involve hundreds of children who have been followed for as long as 10 years.

Rapoport says the goal is to establish ranges of normal brain development, similar to the height-and-weight charts found in pediatricians' offices. "We are generating information about what is normal in brain development, the characteristic growth curves, and how they change over time," says Rapoport. "That will help us to determine how children with ADHD and other disorders compare."

Suggestive information already is emerging. In October 2002, the NIMH researchers reported in the *Journal of the American Medical Association* that children with ADHD had 3 to 4 percent smaller brains, on average, than other children. Because this study was the first to involve children with ADHD who were not yet on medication, the researchers concluded that the size difference was not a side effect of drug therapy (as some critics feared). They also found that over time, the overall pattern of brain growth in children with ADHD parallels that of other children, suggesting that whatever biological insult is to blame for the disorder occurs early in development.

"We are generating information about what is normal in brain development, the characteristic growth curves, and how they change over time."

Function and Treatment

Children with ADHD are generally treated with a combination of behavioral interventions and medication. Stimulants such as methylphenidate (Ritalin) are most often prescribed and help by improving alertness and focus. Until recently, however, it wasn't clear how stimulants accomplished this. It was also not clear why some people with ADHD respond to treatment with stimulants while others do not. Functional imaging studies have helped to provide some answers.

Nora Volkow and colleagues at the Brookhaven National Laboratory have conducted PET studies showing that methylphenidate increases levels of dopamine in the brain, which may help to activate neural circuits that are under-active in people with the disorder. In more recent research, Volkow's team has shown that inborn variations in dopamine cell activity—which occur in healthy people as well as in people with ADHD—may explain why some

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NEW TREATMENTS SHOW PROMISE

The Food and Drug Administration recently approved the first-ever non-stimulant medication for ADHD, which is also the first new drug approved for treatment of the disorder in 30 years. The drug, atomoxetine, marketed under the brand name Strattera, is easier to prescribe because it is exempt from regulations affecting stimulants such as Ritalin, which are considered controlled substances under the law. It may also provide a new option for people with ADHD who don't benefit from stimulants. While Ritalin affects dopamine levels, Strattera acts on the other neurotransmitter involved in ADHD: norepinephrine. This alleviates symptoms in some people, although it is not yet understood precisely how.

Another drug, modafinil, marketed under the name Provigil, is being investigated in clinical trials for use in treating ADHD. Provigil has already been FDA-approved for the treatment of narcolepsy, but is being used "off label" by shift workers and people trying to stave off jet lag. The drug's promoters say that it stimulates only the brain while sparing the rest of the nervous system—thereby avoiding the "jitters" and other side effects that stimulants can cause. But it is not yet clear exactly how the medication works.

people respond to methylphenidate but others do not.

In related research, Adam Clarke and colleagues at the Brain and Behavior Research Institute in Australia have found that stimulants increase electrical activity in the cerebral cortex of children with ADHD, restoring it to normal levels, but that the type of medication that works best depends on the type of abnormality the child has. Children with an under-active cerebral cortex responded best to methylphenidate; those who demonstrated a "maturational lag" in brain development responded best to another commonly prescribed stimulant, dextroamphetamine.

Future Directions

Teicher, who has conducted his own studies of brain anatomy in ADHD and the impact of medication on symptoms like hyperactivity and inattention, predicts that imaging studies will collectively help researchers to identify multiple brain circuits involved in the disorder. "It will turn out to be complicated," he predicts. "I think we're going to find out that ADHD is not really a disorder, but a syndrome, like congestive heart failure." In a syndrome, he explains, the same symptoms can be caused by any one of a number of defects. "The imaging technologies will provide us with a much more specific delineation of what these are," he says.

Clarke agrees. His team has already published a series of studies showing how EEG readings can be used to distinguish people with ADHD from other people, and even to differentiate one subtype of ADHD from another. Although the research is preliminary, Clarke believes that subtypes of ADHD will one day be defined by underlying circuit abnormalities rather than behavioral profiles.

In the meantime, Rapoport advises physicians and parents to continue to rely on observational evidence. Teachers in particular may be important because they can compare the behavior of a given child with that of others his or her age. Behaviors typical of a child with ADHD include failure to listen even when addressed directly, a tendency to make careless mistakes in schoolwork, inability to sit still, excessive chattiness, and a tendency to interrupt others while they are speaking or blurt out an answer before a question is finished. Although all children occasionally display one or more of these behaviors, children with ADHD consistently display them, often at the same time. The DSM-IV requires that six or more behaviors characteristic of inattention or hyperactivity-impulsivity be demonstrated to a degree that is markedly different from peers for at least six months.

"People tend to disregard behavior, but it can be very helpful," Rapoport says. The best way to determine whether a child has ADHD, she says, is to determine whether the behavior causing concern is sustained over a long period of time and is observed by several people who can compare it to the behavior of peers and thus put it in context.

Ann MacDonald writes about science and medicine from Wakefield, R.I.

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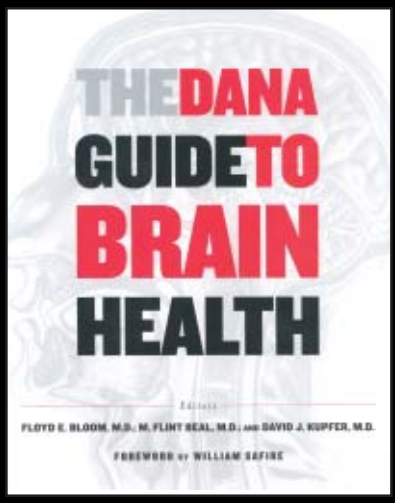

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Autism, Mating, and Maleness

BY MAIA SZALAVITZ

Though opposites can attract, most people settle down with partners much like themselves in terms of values, physical attractiveness, and intelligence. But could this tendency of like to seek like also account for recently observed increases in autism rates? Could the quality linked with the increase be a brain-based talent for mathematics, engineering and/or computer programming, with the Internet boom bringing together men and women with genes for such skills who had never previously had a chance to meet and mate?

Two controversial but complementary theories about autism, a devastating childhood brain disorder, suggest that the answer to both of these questions may be yes. One theory proposes that "assortative mating" (people's tendency to seek spouses similar to themselves) may partially account for a recent spike in autism rates.

The idea is suggested by a phenomenon seen in other genetic disorders, in which a gene associated with a given disease occurs so frequently in a population that it must have some beneficial effect; if the gene were always detrimental it presumably would have died out. In such conditions, one copy of the problem gene gives a person some advantage, but two copies (one from each parent) may be "too much of a good thing" and cause illness.

The classic example is sickle cell anemia. People with one copy of the sickle cell gene have a greater resistance to malaria, which provides an obvious survival advantage, particularly in tropical regions. Those with two copies, however, develop sickle cell anemia, which causes severe pain and shortens life expectancy due to greater risk of infection, stroke, and organ failure.

The second theory regards the nature of the possible advantage the gene (or most likely, genes) could offer. In the case of autism, such genes may confer excellence in a style of thinking that Simon Baron-Cohen, professor and co-director of the Autism Research Centre at Cambridge University, calls "systemizing." This is a talent at understanding, organizing, and manipulating complex, rule-governed areas of knowledge such as computer languages and mathematics, which tends to predominate in males.

Some children with autism are extraordinarily talented at mathematics and have outstanding memories. The condition reveals itself as a disorder in the way that such children avoid eye contact and physical affection, have extreme difficulty with language and with relationships (even with their parents), and are more drawn to objects than people. Autism is now believed to occur on a spectrum, with people on the mild end (who have a condition called Asperger's syndrome) simply being less social and more obsessed by rigidly ordered systems including collections, machines, railroads, and computers.

It is possible that as with sickle cell disease, one copy of a yet-to-be-identified autism gene enhances analytical ability, while two can impair social and language skills. But because the disease probably is multi-genetic, the story likely will be more complicated.

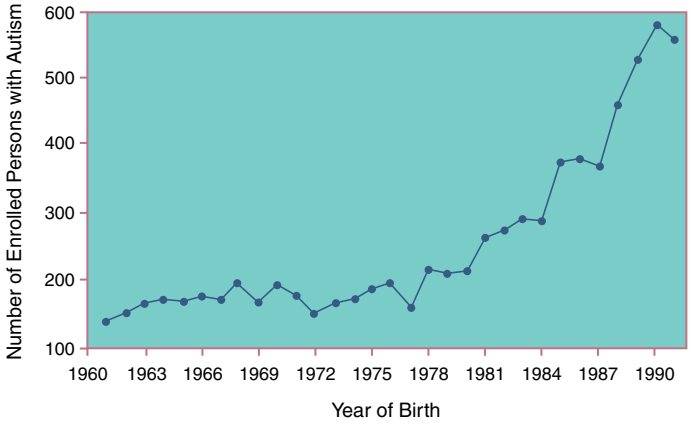
Autism Rates Skyrocket

Research suggests that autism rates have increased dramatically in the past decade. A study conducted for the state of California in late 2002, for example, found a 273 percent increase in autism diagnoses in California; similar increases have been seen in New Jersey and Georgia. Although some researchers (including Baron-Cohen) believe that greater awareness and better treatment account for the higher numbers, others think the increase is genuine.

Dr. Robert Byrd, principal investigator on the California study and associate professor of clinical pediatrics at the University of California-Davis, says, "Looking at the epidemiology of autism over the last 30 years, every study recently conducted shows rates greater than pre-1985." Byrd's study also analyzed whether changes in diagnostic criteria, misclassification of some autistic children in the past as mentally retarded, or people moving to the state to seek enhanced services could explain the rise. It found that they could not.

The accumulation of suspected "autism genes" has occurred too quickly to reflect a genuine increase in the prevalence of such genes in the overall population. But because autism is such a highly genetic disorder (90 percent of identical twins share the disorder, while with many other conditions considered to be strongly genetically influenced, only 50 percent of identical twins are both affected), researchers have looked for other ideas, such as assortative mating.

And assortative mating has been documented in several other psychiatric disorders. Studies have found that people with bipolar disorder often marry similarly moody people, and people with depression tend to find equally gloomy mates. Those with antisocial behavior and alcohol or other drug addictions often choose like-minded partners. Intriguingly, one study found that assortative mating



Autism cases per birth year at a center in California have steadily increased since 1981. Similar increases have been reported in New Jersey and Georgia.

may occur in Tourette's syndrome, a brain disorder in which people have 'tics,' or uncontrollable, repeated odd behaviors or speech patterns. Tourette's often occurs along with Asperger's and autism.

Baron-Cohen has found that parents of autistic children are twice as likely to be engineers as the general population and that on a test of autistic thinking, people with physics, computer sciences, and math degrees score far higher than others.

Reports that autism rates in Silicon Valley are significantly higher than those in the rest of California or the country are not borne out by the California study. Seattle-based Microsoft does provide an unusual package of benefits for children with autism, suggesting a high rate of need among employees, and higher rates of autism in the area with the highest density of computer professionals would support the assortative mating theory. But the fact that they do not immediately jump out in the California study doesn't rule it out, Byrd says.

Robert Moyzis, a geneticist and professor of biological chemistry at the University of California-Irvine, finds the assortative mating theory intriguing. "I don't think there's any proof yet, but one change in the world over the last few decades is that people are moving around more," he says. "Say you had a high-functioning individual who likes sitting at a computer but doesn't like talking to other people much. Thirty years ago, he might have married his high school sweetheart; he wouldn't marry someone of the same genetic makeup. But now people in the computer industry are coming together, and suddenly in the next cubicle is a girl just like him."

Assortative mating could increase the prevalence of a condition dramatically if it rapidly brings together people with less common, recessive genes who wouldn't previously have mated.

Hormones May Play Role

Baron-Cohen, author of "The Essential Difference: Men, Women, and the Extreme Male Brain" (Perseus, 2003), is looking at the specific ways in which such genes might affect the brain. He has found fascinating male/female differences that may shed light on autism. While he cautions that these gender differences only occur in aggregate—a particular female will often rate higher than a particular male on qualities where, in general, males excel—he thinks sex hormones may play a role in the disorder.

His theory starts from the premise, borne out by numerous studies, that women tend to excel in socializing, language skills, and empathy while men do better at manipulating systems of objects or ideas.

Early autism researcher Hans Asperger (of syndrome fame) first noted that autistic people seem to have an extreme form of "male" intelligence; "female" skills such as empathy and language use are impaired. In fact, the inability to empathize, use language, and socialize is essentially diagnostic for autism.

Baron-Cohen has been studying the relationship between levels of testosterone in the womb during pregnancy, which can be measured in the mother's saliva or by testing the placenta immediately after birth, and the behavior of the children of those pregnancies.

"We have found that the higher the level of prenatal testosterone, the less eye contact you make and the slower the development of vocabulary at 18 months," he says. "Our prediction is that prenatal testosterone levels should be directly related to systemizing skills, and that is currently being tested."

Other evidence favoring the connection is the fact that in high-functioning people with autism, the ratio of males to females is 10 to 1.

Baron-Cohen cautions that both theories are far from being proved. While like-minded people undoubtedly always will seek each other, further research is likely to reveal promising ways to limit autism risk should proof of these theories emerge.

Maia Szalavitz is a freelance science writer from New York, N.Y.

A Window into the Secret Life of Neurons

BY RABIYA S. TUMA

During the waning days of 2002, two research groups announced that they had done what neurobiologists have dreamed of for more than a century: They were able to *watch* individual neurons change in the brains of live animals over extended periods of time.

Working independently, Karel Svoboda and colleagues at Cold Spring Harbor Laboratory, and a team led by Wenbiao Gan at New York University, imaged the tiny living protrusions called dendritic spines. These spines receive signals from neighboring neurons and are likely to be key players in learning and memory. Larry Katz, a Howard Hughes Medical Institute researcher at Duke University in Durham, N.C., calls the results exciting. "We've had the longstanding belief that things like learning and memory involve structural changes in the dendrites of nerve cells," he says. "But that has never been directly testable because it's not been possible to see the neurons when such things take place—until now."

Previously, researchers pieced together their best estimate of what happens in an animal's brain based largely on two indirect methods: to take electrophysiological measurements of the electrical currents in the neurons of living animals and to look at the neurons in post-mortem brain slices. But each method left unanswered questions.

With the new approach, researchers can actually watch the behavior of neurons in the cortex of the brain of a living mouse as the changes happen. "For the first time, the technique provides a unique window to look at tiny connections over a long period of time," Gan says.

Imaging Overcomes Obstacle

The breakthrough results from a combination of methods. First, both

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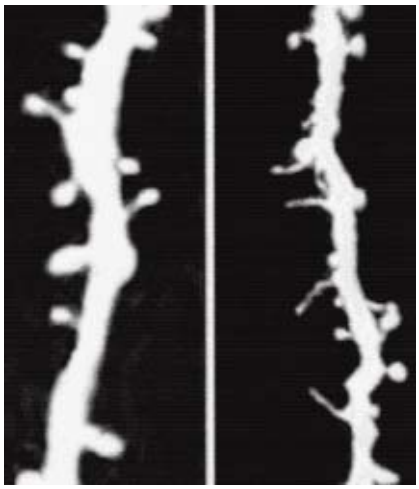
research groups used "transgenic" mice that were genetically engineered to produce, in a few scattered neurons, a fluorescent green protein that glows when exposed to light. Then they used a relatively new technique called two-photon microscopy to surmount a longstanding obstacle: Only infrared light can penetrate tissue far enough to illuminate brain structures such as the cortex, but it only has half the energy needed to "excite" the fluorescent neurons into visibility. With two-photon microscopy, the neurons are bombarded with infrared light; when one neuron gets hit with two photons within a very short time, the energy combines to excite the fluorescent neurons. Using this approach, both teams were able to see, over periods as long as one month, how the neurons changed shape, what connections they made or broke, and how these features changed in response to new physical stimuli.

Both groups focused on the tiny protrusions called dendritic spines—sites of connection where structural changes are likely to occur. While both groups saw spines change, the details differed. Svoboda's group found a large amount of spine formation and retraction even over short periods, with as many as 50 percent of the spines forming or retracting over just a few days. In contrast, Gan found that more than 70 percent of the spines were stable over a month.

The possible reasons for the different results are myriad. For example, Svoboda's group looked at essentially teenage mice, whereas Gan's team looked at fully adult mice. In the younger mice, the neurons could still be forming their adult connections, which might explain the higher rate of spine formation and retraction that Svoboda detected. Second, the two groups were studying different regions of the cortex.

The differences, though, are discounted by many researchers who believe that the ability to watch cortical neurons over time is paramount. The new technique will make brain function—and dysfunction—transparent. Scientists will be able to watch neural circuits form during development. They



These visual cortex images show dendritic spines in a 3-week-old animal, right, and their absence in a 4-month-old animal.

will also be able to witness the degeneration of neurons in mouse models of disease. For example, by crossing the transgenic mice with animals carrying mutations involved in Alzheimer's disease, the scientists will be able to follow the pathology of the disease from its earliest stages, seeing when and how the neurons are affected. But perhaps the most exciting of all is that they will be able to test—directly—if, when, and where structural changes occur in response to learning and memory formation.

Svoboda's team has already examined how the neural circuits in the barrel cortex respond when the animal is exposed to a new environment after its whiskers are clipped, a technique the researchers liken to covering one eye with an eye patch. The result is increased turnover in the points of connection called synapses, as if the connections were being rearranged to compensate for a new input system.

Katz says that with these new tools in place, researchers no longer have to try to understand the rules of the game by piecing together unconnected snippets of data and inferring what happened in between. Now they will be able to watch as the brain lays down the pattern during learning and memory formation or retrieval—and finally, they will learn just what those rules are.

Rabiya S. Tuma is a science and medical writer in New York, N.Y.

Cholesterol May Play Role in Alzheimer's

BY SANDRA J. ACKERMAN

Cholesterol is already notorious for its contribution to heart disease, but now scientists have uncovered evidence to indicate it plays a major role in the development of Alzheimer's disease as well. In the January 2003 *Archives of Neurology*, a research team based in Switzerland identifies a new "susceptibility gene" for late-onset Alzheimer's disease, a common form of the ailment that occurs primarily in people over age 65. The new gene, *CYP46*, has an important job: maintaining a balanced level of cholesterol in the brain.

It appears that cholesterol endangers the health of the brain by encouraging the production of beta-amyloid peptides, which bring on the formation of the tangles of protein that characterize Alzheimer's disease. Normally, *CYP46* averts this danger by modifying the cholesterol molecule in a way that allows it to slip out through the blood-brain barrier, the dense mesh of blood vessels that prevents large and potentially harmful molecules from entering the brain. However, studies led by psychiatrist Andreas Papassotiropoulos, of the University of Zurich, have determined that people who carry an alternate version of *CYP46* known as the *TT* genotype have significantly higher brain levels of beta-amyloid than those with any other genotype. The finding suggests the *TT* genotype of *CYP46* produces less than the usual amount of cholesterol-modifying protein.

"Less *CYP46* protein presumably leads to more cholesterol," explains Benjamin Wolozin, of the department of pharmacology at Loyola University (Chicago) Medical Center.

In a separate set of studies focusing on genetic factors, Papassotiropoulos and his colleagues have found that the *CYP46*TT* genotype is associated with an increased risk—approximately double the normal level—of developing late-onset sporadic Alzheimer's disease

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the blood oxygen levels in their brains monitored by functional magnetic resonance imaging (fMRI).

The researchers did see strong amygdala activation when the subjects smelled intense odors of both kinds. However, the degree of pleasantness or unpleasantness corresponded with activity in another brain area, the orbitofrontal cortex. This region serves the brain's "higher," cognitive functions, but according to the researchers the fact that it plays a role in emotion makes sense. "If we take the psychological view that human emotion is a complex reaction to a situation, not just a response to a stimulus, it's likely that the more integrative and evolved functions of the cortex come into play," says Anderson.

.••• **Gene Plays Key Role in Serotonin Production and Behavior.** The neurotransmitter serotonin is best known for its leading role in mood. Low levels of serotonin have been implicated in anxiety, depression, and aggression. Recently, researchers at Case Western Reserve University, Cleveland, and Baylor College of medicine, Houston, provided an important new piece of the genetic puzzle.

Previously, the authors had identified a transcription factor (a protein that directs gene expression) they thought to be involved in the development of serotonin-producing neurons. In a study published in the January 23 issue of *Neuron*, the team developed a strain of "knockout" mice that lacked the gene, called *Pet-1*. In these mice, the serotonin-producing neurons failed to develop properly, and there were lower-than-normal levels of the neurotransmitter in key areas of the brain. The animals were more aggressive than normal mice, and also proved to be more "anxious" than normal mice.

Human behavior can't be traced to a single gene, says lead author Evan Deneris. "But it's possible that particular variants of this gene result in a disturbance in the serotonin system, which may play a role in these behaviors," he says.

••• **Common B Vitamin Prevents Diabetic Nerve Damage.** Although diabetes is not primarily a disease of the nervous system, its most severe complications include blindness, limb amputation, and stroke—all of which result from blood vessel damage that cuts off the oxygen supply to key nerves. Using a widely available derivative of Vitamin B1 (thiamine), a team of researchers has found a way to block three of the biochemical pathways through which this vascular damage takes place. The treatment also prevented a form of diabetic blindness in rats, Michael Brownlee of the Albert Einstein College of Medicine, Bronx, NY, and colleagues at three universities in Germany, reported in the March issue of *Nature Medicine*.

The pathways of vascular damage are set in motion when metabolites, or byproducts, of blood sugar (glucose) are present at high levels, as is the case in diabetes. The researchers knew that an enzyme called transketolase converts these metabolites into less damaging compounds—and that transketolase works in conjunction with thiamine.

Working both with cultured blood vessel cells and with rats that had an experimental form of diabetes, the researchers showed that the thiamine derivative, benfotiamine, blocked the biochemical pathways in question. It did so by activating transketolase, thus rendering harmless the excess glucose.

"Treatment of diabetic patients with benfotiamine or other … thiamine derivatives might prevent or delay the development of diabetic complications," the researchers write.

••• **New Insight into Drug-resistant Epilepsy.** About 20 percent of epilepsy patients have intractable, or drug-resistant, seizures; for these patients, surgery is the only option. Researchers seeking better ways to treat intractable epilepsy are hampered by a lack of information about how and when seizures become drug resistant. But a study published in the January 28 issue of *Neurology* provides some intriguing, if early, clues.

In a multicenter study of approximately 300 patients with a form of the disease known as temporal lobe epilepsy, a team of researchers found that an average of nine years elapsed between

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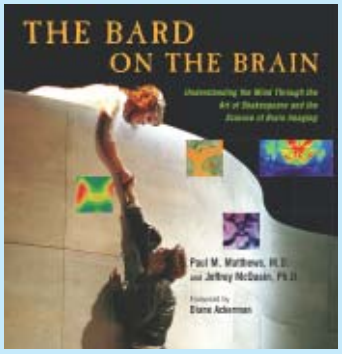
New From THE DANA PRESS

EXPLORE THE GENIUS OF SHAKESPEARE, DISCOVER THE WONDERS OF THE BRAIN



Distinguished neuroscientist Paul Matthews and Jeffrey McQuain, author and Shakespeare scholar, have woven together two timelessly fascinating topics—the mysteries of the brain and the genius of Shakespeare.

"***Paul Matthews and Jeffrey McQuain have given us new insight into the works of Shakespeare and the working of the human brain. I am honored to be included in this wonderful book.***"
–Stacy Keach, actor

"Here, at last, is a compelling and beautifully illustrated book that unites the study of the brain to that of Shakespeare in a thrilling read."
–Semir Zeki, Professor at University College London and Institute of Neuroesthetics and author of *Inner Vision— An Exploration of Art and the Brain*

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("sporadic" here meaning that it affects relatively few individuals within a family). The authors caution, though, that because the number of people in their studies was fairly small, ranging from 76 to 248, the findings must be replicated by other researchers.

What is the relation of *CYP46*TT* to the better-known gene of risk for Alzheimer's disease, *APOE4*? In a study comparing and combining the effects of the two genes, the researchers observed what they call "genetic synergism." Whereas *CYP46*TT* approximately doubles the baseline risk of Alzheimer's disease, and *APOE4* more than quadruples it, the presence of both these genes together multiplies the risk almost tenfold.

"How the body handles cholesterol is clearly a major challenge for the body as we age," says Wolozin. "There is increasing interest in understanding how the cholesterol in the central nervous system might affect disease." With late-onset Alzheimer's disease now in the spotlight as the most common degenerative disease of the brain, the new evidence about *CYP46* may help scientists to fill in a hitherto-unsuspected piece of the Alzheimer's puzzle.

Sandra J. Ackerman is a science writer based in Durham, N.C.

CREDITS: *p. 1: © IFA/ eStock Photography (PQ price control!)/ PictureQuest; pg. 4: From* Report to the Legislature on the Principal Findings from The Epidemiology of Autism in California: A Comprehensive Pilot Study, *October 17, 2002. Sacramento CA: MIND Institute at University of California at Davis: (Originally appeared in* Changes in the Population with Autism and Pervasive Developmental Disorders in California's Developmental Service System: 1987-1998). *Redrawn by Leigh Coriale Illustration and Design by permission; Page 6: image courtesy of Wenbiao Gan.*

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the patient's first seizure and the time that the seizures became intractable. (Intractability was defined as failure to respond to two separate medications at maximum dosages.) In patients who had their first seizure before age five, the condition did not become intractable for an average of 15 years. When the age of onset was 30 or 40, however, seizures became intractable in only three years.

If additional research confirms these results, the work may establish baselines important in studying drug-resistant epilepsy. "If it's true that an early benign course does not ensure a good long-term outcome, then this is sobering news," says study author Anne Berg of Northern Illinois University. "But it does give us a chance to identify those patients whose condition may become intractable. Then we could begin to study the mechanisms involved, and ultimately prevent epilepsy from becoming intractable."

"News" is written by Elizabeth Norton Lasley, a science writer in Woodbury, Conn.

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