THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• **Easing the impact of mid-stage Alzheimer's disease.** For people with moderate to severe Alzheimer's disease and for the people who care for them, help may be on the way at last. A research group led by Barry Reisberg, of the New York University School of Medicine, reported at the April meeting of the American Academy of Neurology that a new drug called memantine significantly slows the progression of the disease in its middle and advanced stages.

In mid-course and later, Alzheimer's disease brings new distress for both patients and caregivers as the continual mental decline begins to complicate even the simplest tasks. The drugs currently available to help with the early symptoms of Alzheimer's disease, such as minor lapses of memory, seem to have little effect once the disease becomes moderate to severe. Memantine, however, is "a completely different chemical way of getting at the disease," says Reisberg.

Memantine, developed by Merz Pharmaceuticals in Frankfurt, Germany, works by blocking the brain's receptor sites for an excitatory neurotransmitter, thereby protecting it from overstimulation. Many scientists believe such

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Mental Illness and Addiction Genes:

Answers Remain Elusive

BY BRENDA PATOINE

Fifty years after Watson and Crick discovered the structure of DNA, and three years after the draft sequence of human DNA was published, "genomics" (the study of genes and their functions) unquestionably has begun to transform medicine. But what has genomics taught us about mental disorders and addictions, which affect one in five Americans, and for which current treatments are for the most part inadequate?

As with many of the most common diseases that affect humans, unraveling the genetics of mental illnesses has turned out to be an incredibly complex task. Though conditions such as bipolar disorder, schizophrenia, autism, depression, anxiety, eating disorders, and substance abuse certainly have a genetic component—studies that compare identical with fraternal twins suggest a very significant role for inherited factors—these illnesses cannot be traced to a single gene. Rather, they appear to develop from a complex interplay of inherited and non-genetic factors, both environmental and "chance." Illnesses' "multigenic" nature is one reason that, despite years of concerted effort and undeniable recent progress in some areas, scientists have yet to precisely identify any gene that can be unequivocally linked to the major mental illnesses.

"In the aggregate, genes have an enormous amount to say about one's risk for mental illness," says Steven E. Hyman, former director of the National Institute for Mental Health and currently the provost at Harvard University. "The problem is that each gene may contribute only a small increment to one's total risk. That makes the hunt for these genes extremely difficult."

That's not to say progress hasn't been made. So-called "linkage" studies, which compare the genomes of people affected by mental illness with both unaffected and affected family members, have narrowed the search to likely target regions on chromosomes

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Genes play a significant role in mental illness, but that role is complex and has been extremely difficult to discern.

(MENTAL ILLNESS, continued from page 1)

that may harbor the genes involved in individual disorders. Still, none of the genes that will ultimately be found are expected to be "causative," meaning all those who inherit the gene will eventually develop the disease. (The genes for Huntington's disease and cystic fibrosis, for example, are causative genes.)

Instead, genes for mental illnesses and substance abuse, as with other common disorders such as diabetes, coronary artery disease and prostate cancer, will confer risk. As such, they are termed "susceptibility" genes, or "vulnerability" genes. An example of a susceptibility gene is APOe4, the only gene so far associated with the common, late-onset form of Alzheimer's. Carrying the APOe4 gene increases one's risk for Alzheimer's, but not everyone who carries it develops the disease. Moreover, not everyone who has Alzheimer's carries APOe4, which suggests that other factors—genetic and environmental—play a role.

Like Alzheimer's and others, most mental diseases are the result of "multiple genetic pathways," says Hyman. "Just as there are many ways to become a high-risk person for, say, heart disease, there are many ways to become high-risk for major depression, as one example," he says. "That fact decreases the influence of any individual gene, further complicating the search."

In practical terms, this means that genetic studies must be conducted on huge numbers of families with an affected relative in order to focus in on a short list of genes from among the 30,000 or so in the human genome.

Underestimating the Enemy

Wade Berrettini, a genetics specialist at the University of Pennsylvania, has been searching for the gene for bipolar disorder since the early 1980s. Inspired by a paper by genetics pioneer James Gusella describing the method Gusella and colleagues used to find the gene for Huntington's disease, Berrettini applied the same method to his hunt for bipolar genes. Two decades later, he's still searching.

"We seriously underestimated our foe," says Berrettini. The genetic roots of bipolar disorder have turned out to be far more complex and elusive than those of Huntington's, which is a classic autosomal dominant disease (i.e., if either parent carries the gene and passes it along to an offspring, the offspring will develop the disease). Berrettini has just completed a four-year collaboration with nine other medical centers in which DNA samples were collected from 700 families with at least one relative who has bipolar disorder. He predicts that at least 1,000 families—a minimum of 2,000 genomes—will be needed to get the answers he seeks.

The effort has already resulted in several "hits": Berrettini says the teams have identified "at least 10 [chromosomal] sites around the genome where there is a high probability that susceptibility genes for bipolar disorder reside." Each of these sites consists of roughly 10 million to 20 million base pairs, the individual linked units that are the fundamental building blocks of DNA.

To pinpoint the genes within those target regions, researchers (armed with powerful computers) must sift through more than 100 million to 200 million base pairs in order to find the particular sequence that is repeated in affected people. As if that's not difficult enough, it's likely that each gene has several different variants—or alleles—that confer varying degrees of risk.

"The haystack is finite .... The problem is, it's also a small needle, and the needle looks a lot like the straw that's all around it."

Finding the 'Needle'

If this sounds like the proverbial "needle-in-a-haystack" search, it is. But, says George Uhl of the National Institute of Drug Abuse (NIDA), "The haystack is finite—30,000 or so genes. The problem is, it's also a small needle, and the needle looks a lot like the straw that's all around it."

These high hurdles are not unique to mental illness or addiction gene searches. The experts point out that gene hunts for heart disease, diabetes, and a host of other common conditions include the same dilemmas. But, as Berrettini says, "It's different because it's mental illness, and we know so much less about the brain than we do about heart disease, for example."

Collecting enough DNA samples is also a challenge that pervades genetics research. Bipolar disorder is one of the most common mental conditions, affecting about 1 percent of the population. Anorexia nervosa, which Berrettini also studies, affects about one-tenth of 1 percent of the population, making it even more critical to establish networks of researchers and

BRAINWORK

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Editor
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Design
FTM Design Studio

A PUBLICATION OF THE DANA PRESS

Jane Nevins, Editor in Chief
Walter Donway, Director

Editorial office:
The Dana Center
900 15th Street, NW
Washington, D.C. 20005
E-mail: danainfo@dana.org

THE DANA FOUNDATION
745 Fifth Avenue Suite 900
New York, New York 10151

For free subscription or change of address:
rtalley@dana.org, or fax to 202-408-5599

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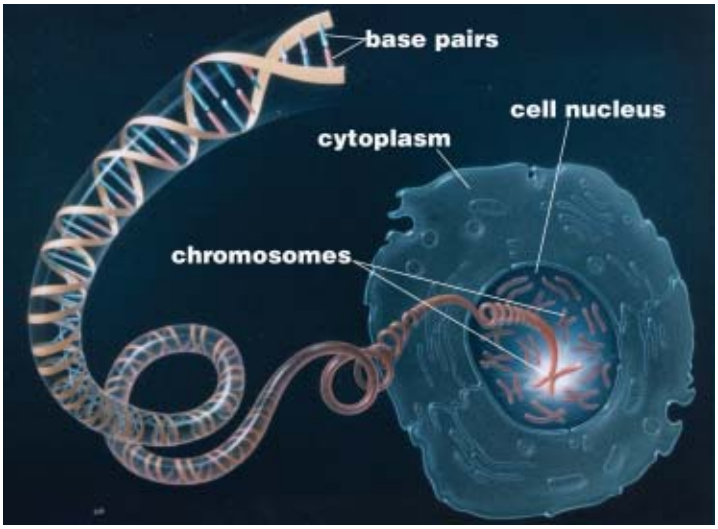
"to build bridges with patient groups" to locate enough affected families and achieve the statistical power needed to make meaningful progress. In the case of autism, a patient advocacy group called Cure Autism Now has taken the lead in identifying families and collecting DNA samples; this initiative is viewed as a model strategy for speeding gene searches.

'Overlap' in Addiction Genes

As with the major mental illnesses, concrete evidence is lacking for a single gene that has a major effect on one's vulnerability to substance abuse, says NIDA's Uhl. Yet, while the search for addiction genes is relatively young compared to the search for bipolar genes, there has been a "remarkable convergence" of data from independent groups that point to more than a dozen chromosomal regions that may harbor susceptibility genes, he says.

Recently, various groups of NIDA-funded researchers have identified possible gene loci for alcoholism, nicotine addiction, and "polysubstance abuse," that is, vulnerability to various drugs of abuse. In addition, researchers studying families and unrelated individuals have identified several chromosomal regions that harbor "relatively common" gene variants that each may contribute to addiction vulnerability, Uhl says. This apparent overlap in the genomic regions of interest suggests a common genetic link that may manifest differently depending on other inherited traits or environmental factors.



The twisting double-helix structure of DNA is shown in this representation of a cell. DNA is packaged in chromosomes within the cell nucleus; the information it contains interacts with the environment to produce all human traits.

The impact that environmental factors have on the development of mental illness and addiction confounds even the most thorough genetic studies. In most cases, scientists simply don't understand how environmental factors that increase or decrease one's risk interact with inherited tendencies.

The Payoffs

For all the unknowns, what is clear is that much can be gained from identifying these genes. First and foremost, says Hyman, finding disease genes enables a better understanding of the molecular events that cause the disorder.

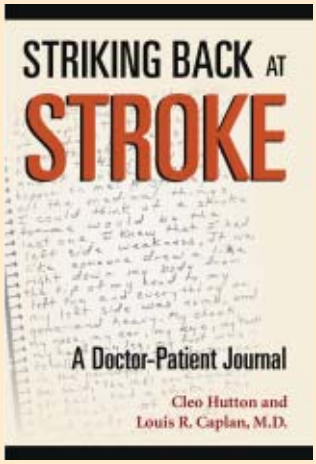
Gene identification can also drive therapeutic advances, both by pointing to potential new targets for interrupting the processes that lead to disease and by using the gene to create animal models. Even though such models would be "imperfect" because it's impossible to precisely model psychiatric illnesses in animals, Hyman says, "Even partial animal models are important for testing and developing drugs, and we are sorely in need of new medicines for mental illnesses."

A better understanding of the genetic underpinnings of mental illnesses also should allow scientists to unravel the timing of gene expression, which Hyman says might give clues to environmental factors that come into play at various points in development to trigger certain genes to turn "on" or "off." This in turn could lead to intervention strategies that could potentially interrupt these triggers.

Without doubt, experts in this area say, genome-sequencing efforts have made a significant impact on the search for mental illness genes. Despite the imperfections of the draft sequence, it has provided a rough road map that researchers can refer to once they have identified regions of interest through linkage studies. Berrettini likens the situation to early explorers who were trying to discover a new land without a map to show its location. Like them, he says, "We need a good map of the world."

Brenda Patoine is a medical and science writer based in LaGrangeville, N.Y.

New From THE DANA PRESS



STRIKING BACK AT STROKE
A Doctor-Patient Journal

"I highly recommend this book to stroke patients and their families as well as to health professionals working with stroke patients. For patients and family members, it will take you by the hand to help you cope with a stroke. For the health professional, it will remind you of the day to day trials and tribulations and ultimately successes of the patients you care for and inspire you in your clinical care and research endeavors."

Jordan Grafman, Ph.D.
Chief, Cognitive Neuroscience Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health, Bethesda, Maryland

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Transcranial Magnetic Stimulation:

Non-Invasive Method Can Help Diagnose, Treat Neurological Disorders

BY THOMAS S. MAY

When Wilder Penfield, the famous Canadian neurologist, first identified parts of the human cortex as being responsible for various sensory and motor functions about half a century ago, he did it by electrically stimulating the surface of the brain. Today, scientists can stimulate a small area of the brain and investigate its function without having to open up the skull. The technology that makes this possible is called transcranial magnetic stimulation, or TMS.

TMS is a safe, painless, non-invasive technique that is based on the principle that a changing magnetic field induces an electrical current in any material that conducts electricity—including human brain tissue. Currently, transcranial magnetic stimulation is used primarily for studying the brain and localizing various brain functions. Though its use is not widespread now, some experts say TMS is poised to become an important therapeutic tool that will help doctors diagnose and treat a number of neurological and psychiatric disorders in the future.

TMS vs. MRI

While both TMS and functional magnetic resonance imaging (fMRI) use powerful magnetic fields to determine which parts of the brain are associated with a given function, the similarities between TMS and MRI end there. "They are clearly different methods," says Mark Hallett, chief of the Medical Neurology Branch at the National Institutes of Health (NIH). One important difference is that MRI uses a static magnetic field, whereas in TMS, the magnetic field goes from zero to maximum in a few microseconds, and then it goes back to zero very rapidly, Hallett explains.

The type of information one gets from these two methods is also different, he adds. "Functional magnetic resonance imaging is mainly used to show what parts of the brain are active during a particular task and has the ability to look at the whole brain. Magnetic stimulation, on the other hand, can only deal with the cortex, and the region is not quite as focused as it is with fMRI." Hallett notes, however, that by blocking part of the brain temporarily, TMS can reveal not only if that part is active during a task, but also whether it is necessary for that task. "Moreover, magnetic stimulation can also tell you when that part is required in a given task," says Hallett, "whereas fMRI is not very good in the timing of events."

Diagnosing Dysfunction

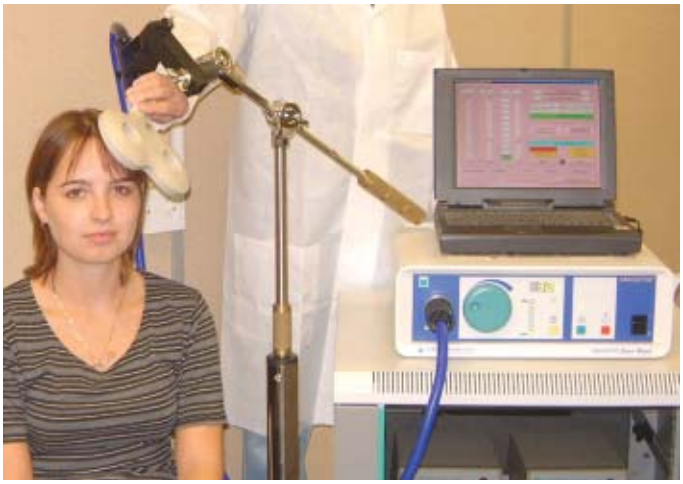
Since magnetic stimulation can provide investigators with important timing information relating to various neurological events, it can also be used to diagnose certain neurological disorders. Evaluating the conduction of the motor tract non-invasively is one of the most important applications of TMS, according to Yasuo Terao of the Department of Neurology, University of Tokyo. When you apply magnetic stimulation transcranially (through the skull) over the motor cortex (an area of the cerebral cortex specialized for movement control), you may get a twitch in a hand or leg muscle, for example, depending on where you place the magnetic coil over the scalp, Terao says. The electrical impulses evoked by stimulation can also be recorded, and one can calculate the conduction time—the time it takes for the stimulus to travel along the motor tract, he adds.

Conduction time is an important measure, Terao notes, because abnormal conduction times may indicate neurological dysfunction. "In cases where there is a lesion somewhere in the motor tract, the conduction time in the corresponding part is prolonged," he explains. "For example, in patients with cerebral infarction (tissue death caused by interference with circulation), you get a longer-than-normal conduction time between the cerebral cortex and the brainstem. In patients with cervical spondylosis (a degenerative spinal disease), you get abnormally long conduction time between the brainstem and the spinal root."

Exciting Possibilities

TMS can also be used to measure—and modify—the excitability of neurons, says Alvaro Pascual-Leone, director of research at the Behavioral Neurology Unit of Beth Israel Deaconess Medical Center in Boston. By applying a train of magnetic pulses to an area of the cortex, one can modulate cortical excitability in that area, Pascual-Leone says. Such repetitive transcranial magnetic stimulation (rTMS) can cause either increased or decreased excitability, depending on the frequency of the stimulation, he explains.

These effects are not limited to the targeted area, but are spread along specific connections within the brain, according to Pascual-Leone. For example, when he and his colleagues applied



Transcranial magnetic stimulation (TMS), which involves stimulators such as the one shown above, is a non-invasive way to study brain function. TMS may soon become an important therapeutic tool.

high-frequency (5 pulses per second) rTMS to an area of the cortex of patients with Parkinson's disease, increased activity occurred not only in the cortex, but also in subcortical areas, resulting in increased dopamine production, along with some mild therapeutic effects, such as improved hand function. However, these results were not very robust, Pascual-Leone cautions. "While some patients clearly benefited, others appeared to have no benefit at all."

Although rTMS has been applied successfully to treat some other disorders, such as depression, Pascual-Leone believes that, in the future, magnetic stimulation will mainly be used not as a stand-alone treatment for various diseases but as an "adjunct," in combination with other treatments. "There are two fundamental ways in which I see this playing out. One is that TMS could be used to increase the effectiveness of other treatments or interventions," he says. For example, stroke patients who have some brain damage in one hemisphere might be given magnetic stimulation to suppress activity in the healthy hemisphere, Pascual-Leone suggests. This way, these patients would have to exercise the damaged hemisphere and would therefore derive greater benefit from rehabilitation, he contends.

TMS also could be employed to provide "proof of principle," to show that a certain intervention can have a positive impact on a patient's well being, Pascual-Leone says. For example, magnetic stimulation could be given to patients with various pain syndromes in order to demonstrate that, by targeting a certain part of the sensory-motor cortex, one can suppress the pain experienced by such patients. "Even if the analgesic effect of TMS lasted only a few hours or days," Pascual-Leone says, "it would provide support for an argument to implant a small strip of electrodes and a stimulus generator, which could result in longer-lasting relief."

Thomas S. May is a science and medical writer based in Toronto, Canada.

Blood Sugar May Affect Memory

BY ANN MACDONALD

Bad memory? Your brain may be running on empty. A new study adds to a growing body of evidence that memory suffers in people with impaired glucose tolerance—a condition in which glucose in the bloodstream cannot be utilized efficiently by tissues and cells that need energy.

Impaired glucose tolerance, also known as insulin resistance or pre-diabetes, most often develops because of some combination of genetics, lack of exercise, and obesity. The American Diabetes Association estimates that 16 million people in the United States have impaired glucose tolerance, which increases the risk of type 2 diabetes and heart disease. This new study suggests that the brain is also at risk.

In the February 18 issue of the *Proceedings of the National Academy of Sciences*, researchers led by Antonio Convit, a neuroscientist at the New York University School of Medicine, found that people with poor peripheral blood glucose regulation also performed poorly on a memory test. Both immediate and delayed recall were affected.

This finding confirms earlier research in both animals and people. A surprise, however, was that the volume of the hippocampus, a key area of the brain involved in learning and memory, was significantly smaller in people with impaired glucose tolerance than in others. Those people with the most impaired glucose tolerance were most likely to have the worst memory performance and the smallest hippocampi.

"This is one study, and it needs validation, but it is consistent with other research about problems caused by blood glucose that is not in the normal range," says Fran Kaufman, M.D., president of the American Diabetes Association. Noting that the problem can be prevented, she adds, "We view this as another call to action. Maybe you don't care about diabetes, or your weight, but you might care that you will lose cognitive function later on."

The Blood Sugar Theory

"The reason I started studying this was because for every person with Alzheimer's disease, there are eight with memory problems that affect quality of life," Convit says. His team estimates that one in four Americans older than 65 has significant memory problems that are not yet bad enough to be considered dementia.

No one is sure why memory suffers as people age. But studies in animals and people with diabetes suggest that impaired blood sugar regulation may be a factor. Diabetics, for instance, tend to have difficulty recalling new information. Convit wondered whether this would also be true of people whose glucose regulation is impaired but has not yet progressed to diabetes.

The study involved 13 men and 17 women, ranging in age from 53 to 89, who were not diabetic and were not suffering from dementia. The scientists measured individuals' glucose tolerance in three different ways and used MRI images to determine overall brain size and the volume of various subcomponents such as the hippocampus.

Participants were asked to recall the contents of a paragraph immediately after reading it and 10 minutes later. Researchers then compared how well the participants regulated glucose with how well they performed on the memory tests. They found that performance on the test was inversely correlated with blood glucose levels during a glucose tolerance test: The higher a person's blood sugar (and thus the worse his glucose regulation), the worse the performance on the test. Individuals with high blood sugar also had significantly smaller hippocampi than others, although overall brain volume and adjacent brain structures were not affected.

The Sugar-hungry Brain

The body's ability to metabolize blood sugar is particularly important for cognitive functioning, because glucose supplies 99 percent of the energy the brain requires. When a person

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thinks or remembers, activating specific areas of the brain, the demand for glucose increases in those areas—just as an automobile consumes more gas when it accelerates.

The hippocampus is a real glucose guzzler. Studies have shown that when animals draw on memory to navigate a maze, glucose demand increases dramatically in the hippocampus, leading to a significant drop in glucose levels in that part of the brain. Older animals experience the steepest drops and do not navigate the maze as well.

Other research suggests that diabetic animals lack the mechanism to transport additional glucose to the brain. Convit thinks the same problem may affect people with impaired glucose tolerance. When they try to recall new information, activating the hippocampus and draining its glucose supply, they cannot "refuel" to complete the task. It's as if the hippocampus tries to accelerate and then runs out of gas. Over time, Convit theorizes, the glucose-starved hippocampus—a part of the brain particularly prone to damage—may atrophy.

Next steps

Convit cautions that the findings are preliminary and need to be confirmed by a larger ongoing study that is now under way. Two other potential culprits for poor memory are stress hormones, such as cortisol, and oxidative damage. Both factors tend to increase with age and may also damage the hippocampus.

If further research confirms that impaired glucose tolerance does indeed worsen memory, Convit hopes that it will one day be possible to prevent the problem. "We know that the brain is plastic and constantly regenerating itself," he says. "It would be interesting to see if we could improve memory by improving glucose tolerance."

That could involve a change in lifestyle, says Kaufman: "It's a matter of exercising, eating right, and not becoming obese."

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

Sniffing Out Brain Coding for Pheromones

BY MAIA SZALAVITZ

A blind mouse may be more likely to become the cat's dinner—but he'd probably be more successful with Minnie than a mouse that couldn't sense pheromones, the scent signals which help many animals decide whether to mate with or attack members of their own species.

Lawrence Katz, professor of neurobiology at Duke University, and his colleagues recently published a paper in *Science* showing how pheromonal signals are encoded in the brain when one mouse meets another. Neuroscientists still debate whether humans utilize pheromones, but no matter how that dispute is ultimately resolved, this research could lead to greater understanding of how the brain receives, understands, and changes its behavior in response to sensory experience.

Katz recorded the activity of single neurons in the accessory olfactory bulb, the brain area that receives input from the vomeronasal organ (VNO), which senses pheromones. He found that certain neurons fire only in response to certain types of animals. One might fire in a male only when he detected a female of a different strain of mouse, for example.

The cells respond so precisely to individual features that Katz was reminded of cells in the human cortex that are specialized to detect faces. These cells help people recognize each other, and some fire only when a familiar face is seen. Like people, "Mice can recognize other individuals," he says. "These cells allow them to detect unique features of the other animal's pheromonal repertoire."

Research shows that pheromones are critical for mice in determining the sex of another mouse. Catherine Dulac, professor of molecular and cell biology at Harvard, knocked out a gene that encodes an essential signaling molecule and created a mouse that could not detect pheromones. All of its other senses remained intact. "The animal is able to see, hear and smell the differences between males and females," she says, "but it cannot make sense of them to discriminate gender."

When placed in a cage with a female, the knockout male will mate as usual, which puzzled the researchers at first, because they thought lack of pheromones would disrupt sexual behavior. But when met by another male—a situation in which male mice usually fight—the knockouts still try to mate. "Mating is the default behavior," says Dulac. "The default path is love, not war."

Katz's finding that cells in the VNO respond specifically to the strain of another mouse is also important. Different strains of mice are genetically different from each other, and detecting genetic differences could potentially allow mice to avoid mating with close relatives. Though mice will mate with their parents or siblings if there are no other members of the opposite sex available, they avoid doing so if given any choice.

Neurons in the VNO are activated only when the mice are in close contact—sniffing each other's faces or anogenital areas. The VNO is an entirely separate organ from the nose, even though it is located in the same region. A normal smell—like that of a predator or of food—can be sniffed rapidly from the air at a distance, allowing quick shifts in behavior. But VNO stimuli require close contact to activate the appropriate receptors.

"It doesn't do much good to know there's a predator when you are already in physical contact with it," says Katz, smiling. "The [pheromonal] system is used in very specific social behavior."

In humans, the vomeronasal organ appears to be vestigial, with few if any nerve connections to the brain. According to Katz, all but three of the 300 mouse genes discovered for pheromone receptors are pseudo-genes in humans, which means that they exist but are not transcribed into proteins and utilized.

However, researchers are particularly interested in studying the pheromonal system in animals because it is simpler than ordinary smelling and tasting. Once scientists understand how this

less complicated sensory system works, they should have greater insight into how to decode the others.

Both Katz and Dulac believe that human behavior can be affected by smells, but these are probably sensed via the nose rather than the VNO. "I have an open mind," says Katz. "But I don't believe you can spritz on some perfume and drive women wild. It doesn't work that way with mice, either. And a lot of pheromones are involved with aggression—you are just as likely to have a guy in a bar slug you in the face as you are to attract more women."

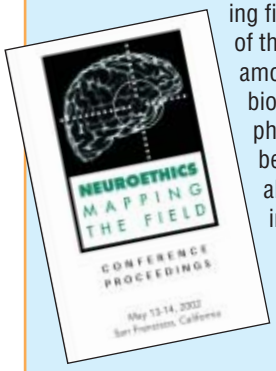
Katz does think that one human phenomenon may relate to earlier pheromone-sensing behavior, however. "I think that kissing could be a behavioral remnant of what mammals do for pheromonal communication," he says. "There are unusual secretions from facial areas like the ears and around the lips—areas that people have a special interest in. Lots of animals nuzzle each other; it would not be surprising if that got co-opted into the olfactory part of our courtship behavior."

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

NEUROETHICS

Brain-related scientific findings open doors, but they also raise questions. "Neuroethics" is the study of the moral and ethical questions involved in applying these findings, and how medicine, government, business, law, and society will respond.

In May 2002, a cross-disciplinary group of more than 150 scholars and experts met to discuss what the future holds for this emerging field. The transcripts of these discussions among neuroscientists, bioethicists, philosophers, and more have been edited for readability and organized into this free proceedings book, providing insights to readers.



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News
FROM THE FRONTIER

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overstimulation damages brain cells and may help to trigger neurodegenerative diseases such as Alzheimer's.

At the beginning and the end of a 28-week study of 252 Alzheimer patients, age 50 to 80, with moderate to severe disease, the patients were evaluated on several well-known scales of normal daily functioning and cognitive abilities, among other things. The patients receiving memantine showed about half as much decline as those who had received a placebo. The memantine patients also required less help and attention from their caregivers—on average, about 90 minutes less per day.

Currently under review by the FDA, the new drug shows promise of offering millions of people a reprieve from the unrelenting decline that characterizes Alzheimer's disease—a prospect Reisberg calls "a researcher's dream."

••• **Brain cells that thrive on uncertainty.** In many aspects of our lives—employment, health, prospects for retirement—uncertainty is a bane. Yet, in other realms, we like to play with unpredictable outcomes, whether by scrambling for a seat in a game of musical chairs or calling a bluff in poker. How does the human brain come to associate uncertainty with pleasure—and why?

Scientists in England and Switzerland, led by anatomist Christopher Fiorillo of the University of Cambridge, have come up with a surprising answer to this puzzle. Using monkeys as a model for humans, the scientists were able to show that dopamine neurons, already known for their role in the "reward" circuits of the brain, are activated as well by the *possibility* of a reward. These neurons increase their activity in proportion to the size of an anticipated reward, and they become most active as uncertainty about the reward reaches its peak. Fiorillo and his co-authors suggest, therefore, that the involvement of dopamine is what gives a pleasurable edge to dealing with uncertainty. The greater the uncertainty or the higher the stakes, the stronger the dopamine signal.

Such an arrangement can go awry, of course, if the dopamine lure of high-stakes uncertainty overwhelms other, more rational considerations, as in the case of compulsive gambling. But the English and Swiss scientists speculate that on the whole this brain circuit is beneficial, helping to motivate and reinforce a basic drive toward learning—that is, the willingness to tackle uncertainty in pursuit of a reward of information.

••• **In Parkinson's disease, risk factors vary by sex.** A long-standing mystery in Parkinson's disease is why the risk of developing the disease is twice as high for men as for women, at any age. A study published online in March in the journal *Movement Disorders* may offer the beginning of an answer. The study, headed by Demetrius Maraganore, of the Mayo Clinic in Rochester, Minnesota, examined the relative importance of three genes known to be associated with Parkinson's disease: *alpha-synuclein*, *UCHL1*, and *parkin*. The scientists sought to determine whether common variants of these genes contribute to the risk of the disease in the population at large.

Maraganore and his colleagues collected medical information from 298 people with diagnosed Parkinson's disease and 185 healthy "control" subjects. The scientists found that when common variants of *alpha-synuclein* and *UCHL1* interact, the risk of Parkinson's disease rises significantly—but only in women. (Variants of *parkin* do not contribute to the risk.) In men, risk factors posed by the environment, such as pesticides, industrial chemicals, and even work-related head injuries, play a greater role.

Maraganore traces the difference in primary risk factors between women and men to differing levels of exposure. "Traditionally, men have been out in the workforce becoming exposed to envi-

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ronmental risk factors," he says. By contrast, women may have had less exposure to these factors; hence, for women, genetic factors account for more of the risk. "For a woman to get Parkinson's disease, she has to inherit certain gene variants," Maraganore explains. Since men are more likely to undergo exposure to environmental risk factors than women are to inherit exactly the right combination of genes, Parkinson's disease is more common in men.

•••**An unfelt filter.** Like a well-built radio, the brain has a filter that sorts out meaningful signals from random noise—the "noise" in this case being sporadic, low-level bursts of electrical activity that occur on their own in the thalamus, the main relay station for the signals from our five senses. When the filter is not working properly, one of the results may be abnormal sensations with no apparent cause.

Up to now, the nature of this noise filter has been unclear. But in the March 21 issue of *Science,* a team of researchers led by neurologist Felix Blankenburg of the Berlin NeuroImaging Center reports evidence on where the filter resides in the brain and how it works.

The scientists used functional magnetic resonance imaging (fMRI) to monitor the brain activity of research volunteers while applying minute levels of electrical stimulation to their fingers. This "subliminal" stimulation fell well below the threshold of perception, and the usual patterns of brain activity that go along with normal somatosensory perception did not occur. What the scientists observed instead was a *decrease* in signaling in the brain region corresponding to the stimulated hand. When the scientists then applied stronger stimuli, at near-threshold levels, along with the subliminal stimulation, the response to the stronger signals was dampened as well.

Blankenburg and his colleagues suggest that the lowest-level stimulation given in their experiment, even though it was never felt, nonetheless activated a certain type of neuron in the cerebral cortex that is responsible for inhibiting signals rather than transmitting them. These so-called inhibitory interneurons, the authors say, could screen out sporadic electrical spikes that occur spontaneously in the thalamus, thereby freeing the cerebral cortex to focus on the billions of neuronal signals per second that actually do mean something.

"News" is written by Sandra J. Ackerman, a science writer based in Durham, N.C.

Correction

Researchers have found that compound A-317491 acts as an antagonist for both $P2X_3$ and $P2X_{2/3}$, two ion channels that appear to play a role in the sensation of pain, thus reducing pain sensation. In the January-February 2003 *BrainWork*, we misstated the action of the compound. We regret the error.

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THE DANA FOUNDATION
745 Fifth Avenue Suite 900
New York, New York 10151

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