THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

The following items were among the other significant research featured at the Society for Neuroscience Annual Meeting.

••• **Why Only Some Become Addicted.** Although it may seem obvious that not everyone who drinks becomes an alcoholic, the reason for that difference is anything but obvious. Now, as scientists become more familiar with the biochemistry of both healthy and addicted brains, they are beginning to tease out some of the differences between people who become addicted and those who do not.

At the opening public lecture, Nora Volkow, M.D., Director of the National Institute on Drug Abuse, described her recent work on the biochemical differences between individuals' brains that may lead one person down the path of addiction while allowing another to sidestep the trouble.

"Drugs themselves are not sufficient to cause addiction," Volkow says. A person's environment and genes also influence the likelihood a person will become addicted. With that view in mind, her team has been looking for

(Continued on page 10)

Inside:

Sleeping Brain Stays Busy — Page 3
Neuroethics — Page 5
Love and Trust — Page 6
Huda Akil Interview — Page 7

SOCIETY FOR NEUROSCIENCE ANNUAL MEETING

Editor's note: *BRAINWORK* devotes this issue to reports from the 33rd annual meeting of the Society for Neuroscience, held Nov. 8-12 in New Orleans. Covering the program were Rabiya S. Tuma, a science and medical writer in New York, N.Y.; Sandra J. Ackerman, a science writer based in Durham, N.C.; and Dan Gordon, editor at the Dana Press. Sessions focused on important challenges that lie ahead for neuroscience, including neuroethics, covered on page 5, and understanding the interaction between genes and environment in brain-related disorders. As Society for Neuroscience President Huda Akil says in an interview on page 7, "Understanding this complex interplay … is really a big challenge." These topics piqued the interest of the nearly 29,000 attendees.

Have No Fear:

We May Be Able to Unlearn Responses

BY RABIYA S. TUMA

In 1904 Ivan Pavlov won the Nobel Prize in medicine for his work on conditioned learning. Now, nearly 100 years later, researchers are learning how the brain can unlearn such conditioned responses, a process called "extinction."

The goal of the work is twofold: to decipher the basic brain circuitry involved in the extinction of conditioned responses and to improve treatments for disorders involving them. Already, the researchers are finding new ways to help people overcome unnecessary anxieties and phobias, and perhaps mitigate the effects of post-traumatic stress disorder.

In the classic example of conditioned learning, Pavlov paired the appearance of food, which will normally make a dog salivate, with the simultaneous ringing of a bell. After several trials, the dog began to salivate in response to the bell alone. The response of salivation had become conditioned by the stimulus of the bell.

While conditioned learning may appear as little more than a curiosity when presented in terms of dogs and salivation, it is an important aspect of how humans learn, and much research

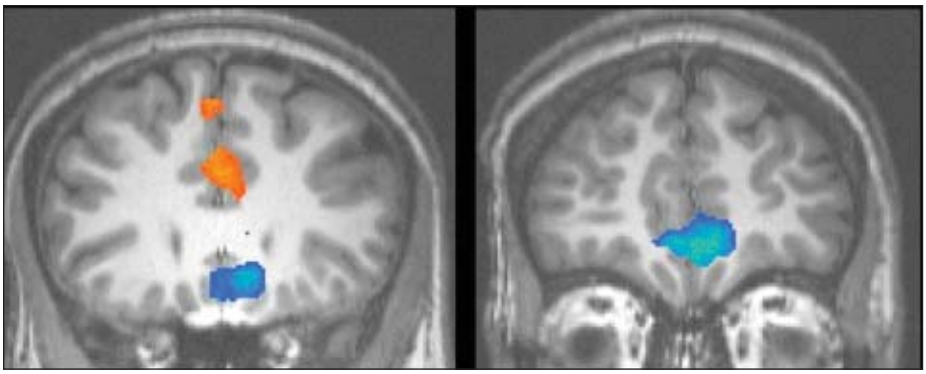
(Continued on page 2)

Russian physiologist Ivan Pavlov is best known for his studies of conditioned reflexes. Now scientists are examining the "extinction," or unlearning, of such responses.

(NO FEAR, continued from page 1)

has gone into understanding the brain mechanisms that underlie it.

More recently, however, scientists have begun to study the mechanisms behind inhibition of this response, that is, how people can unlearn previously conditioned responses. Interestingly, they have found that extinction of the conditioned response does not actually undo the original process but rather involves overlaying a new neural circuit on top of the old one.



These Functional Magnetic Resonance Imaging (fMRI) scans indicate pathways involved in the extinction of fear. Decreased activity in the medial prefrontal cortex is shown in blue; active regions (orange) are the medial frontal gyrus and the rostral anterior cingulate.

Speeding Extinction Learning

Currently the best way to help people overcome their fears or maladaptive behaviors is through behavioral psychotherapy, says Mark Barad of the University of California at Los Angeles. "The problem with behavioral psychotherapy, like all psychotherapy, is that it is difficult, takes a long time, involves a lot of practice on the part of the patient, and still sometimes fails," Barad says. "And even those people who get better often get worse again. Understanding the mechanisms of extinction should help us understand how to make psychotherapy more effective."

Already scientists have found that the amygdala, which is critical for feeling fear, is also necessary for extinction of conditioned responses. Furthermore, they know that the NMDA receptors, which bind the neurotransmitter NMDA in the synapses and pass a signal from one neuron to another in the amygdala, are required for extinction as well.

Given these observations, Michael Davis of Emory University in Atlanta hypothesized that by accentuating the NMDA receptor response he could speed the rate of extinction learning in animals, and perhaps in people. And, in fact, that has been the case.

If his team turns on a light at the same time they deliver a small electric shock to a mouse's foot, the mouse learns to fear the light. If the mouse is then exposed to 60 rounds of light with no shock, the mouse unlearns the fear. When Davis repeats the experiment but now gives the mouse a drug, D-cycloserine (DCS), that enhances the function of the NMDA receptor, 30 cycles of the light are sufficient to retrain the animal.

Furthermore, DCS appears to help stabilize the retraining pathway. Researchers and psychologists know that extinction learning is fragile, which is why people frequently revert to their phobias or anxieties even after successful psychotherapy. However, animals that receive DCS prior to retraining are less likely to revert to fearing the light than animals that were retrained in the absence of DCS, says Davis.

Human Indicators

The real question is not whether animals can be retrained but whether DCS can speed relearning in humans. To test this possibility, Davis designed the following study. Thirty patients who have an extreme fear of heights were randomly divided into two groups. One group received DCS, which has previously been used to treat people with tuberculosis and is known to be safe, and the other group received a placebo. Neither the patients nor the researchers knew which patient received the drug and which received the placebo. The patients were then put into a virtual reality setting that made them feel as if they were riding in a glass elevator in a hotel atrium. Initially all of the patients had similar responses, with anxiety climbing as the elevator climbed. Although the drug had no effect in the first session, after eight retraining sessions, the patients who had taken DCS had approximately two to three times greater reduction in their fear response than those that had the placebo, though all patients improved significantly during the retraining.

And the retraining seemed more

BRAINWORK

The Neuroscience Newsletter

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durable in the DCS patients: At the three month follow-up appointment, it was clear that the patients who had been given the drug had a substantially better response to the therapy than those who had the placebo. "The patients given DCS had two times as many real-life encounters, going over bridges or up elevators, as did the placebo group," says Davis. The fact that they are exposing themselves to things they previously feared, he says, is crucial proof that the extinction therapy works—and that enhancing the NMDA receptor activity with DCS significantly strengthens the response.

Davis has now applied for a patent on the idea of combining NMDA receptor agonists, such as DCS, with psychotherapy.

Other Brain Areas Have Role

Though Davis' work and that of others illustrate clearly that the amygdala is involved in extinction, scientists know it is not the only brain region involved. Animals with lesions in the medial prefrontal cortex, which is connected via neural circuits to the amygdala, have trouble with extinction learning, though they have no problems with conditioned learning, says Gregory Quirk of the Ponce School of Medicine in Puerto Rico.

When these animals go through extinction training, they experience the same decrease in sensitivity to the conditioning stimulus on the training day as healthy controls do, but the next day it is as if they never had any retraining at all. In other words, they experience the activity of extinction normally, but the memory of it is not consolidated in their neural pathways.

To more specifically identify the neural pathways in the prefrontal cortex that are required for consolidation of extinction, Quirk's team has been working with rats. They have found that a particular group of neurons in the medial prefrontal cortex called intralimbic neurons become activated during extinction training. Therefore, Quirk hypothesized that if they electrically

(Continued on page 12)

The Remarkably Busy Sleeping Brain

BY SANDRA J. ACKERMAN

Little-known fact: The most widely used pharmaceutical compounds in the world are the sleep inhibitors coffee and tea. A host of new scientific studies suggest it is a regrettable fact, as well, because the hours we spend asleep actually have great educational value.

The work of cognitive neuroscientist Robert Stickgold, of Harvard Medical School, demonstrates the importance of sleep—not just rest, but real slumber—for learning and the consolidation of memory. Research volunteers were trained in a task of visual learning and then tested to establish their baseline performance. When retested at three, six, nine, or twelve hours after training, they showed no improvement over the baseline, whereas they performed significantly better if tested after a night of sleep. However, if deprived of sleep that night, the subjects lost all the benefit of training and performed as if they had never encountered the task before.

In another study from Stickgold and his colleague Sara Mednick, subjects who were trained on a task of discriminating various visual textures in the morning and then were tested repeatedly throughout the day performed more poorly with each test. The addition of 60- or 90-minute naps during the day allowed the subjects to bring their performance back up to the baseline level, and, when the naps were long enough to include REM sleep, resulted in actual improvement—as much as after a good night's sleep.

Two distinct stages of sleep appear to play different roles in learning and the consolidation of memory: SWS, or slow-wave sleep, and REM, or rapid eye movement sleep. The fact that short naps allow for SWS but not for REM sleep suggests it is SWS that contributes to the stabilization of memory, but it takes REM sleep as well as SWS to convert temporary memories into enhanced, long-term learning. It's no wonder that, in Stickgold's words, "The cutting edge of memory research is now bound up with research on sleep."

(Continued on page 4)

Electroencephalograph (EEG) electrodes attached to the head of a sleeping volunteer monitor changes in the brain's electrical activity. Research shows that two stages of sleep play important roles in learning and memory.

(SLEEPING BRAIN, continued from page 3)

Effects of Sleep Disruption

This combined perspective promises to shed new light not only on sleep and memory in the healthy brain but also on certain brain ailments that may interfere with normal sleep. For example, Dara Manoach, a neuropsychologist at Massachusetts General Hospital, has found that people with schizophrenia can show normal learning of a motor skills test during the day, but, unlike their healthy counterparts, fail to show any improvement after a night of sleep. The disruptions of sleep that often accompany psychiatric disorders, and addiction as well, may one day help to explain the cognitive deficits observed in these conditions.

In studies focusing on chronic sleep restriction (with sleep limited to four hours per night for nine nights) rather than a complete lack of sleep, behavioral neurologist Daniel Press of Beth Israel Deaconess Medical Center in Boston trained his research volunteers on an item-recognition test. He found that under such conditions of sleep restriction, similar to those experienced by medical residents who are "on call," the brain handles a short list of items fairly well but responds more slowly as the list grows longer. In addition, sleep-restricted subjects show no improvement in their memory performance when retested over the course of five days, whereas those allowed to sleep normally perform better each day. The discrepancy is not overwhelming, but it is significant, "like the difference in performance between a 1.4 gHz computer and a 2 gHz computer," says Press.

Another series of experiments with sleep restriction, using rats instead of human subjects, comes from a research team headed by Craig Heller and Robert Sapolsky at Stanford University. The rats were trained in two tasks, using a water maze that contained a single platform. In the spatial learning task, the platform stayed in one location but was hidden from view, so that the rats could find it only by creating a mental map of the maze and remembering it over many days as they were tested and retested. By contrast, in the cue task, the platform was plainly visible and also was marked with a lemon odor, but had a different location in each round of testing. Rats that were allowed only half their usual amount of sleep did poorly on the spatial task, to no one's surprise. What was surprising, though, was that the same rats *improved* in their performance of the cue task. Ilana Hairston, a graduate student on the Stanford research team, explains the meaning of this dual result: Rats are predisposed to create and use mental maps and will do so whenever possible; however, if limited sleep interferes with this cognitive ability, they rely on the direct use of their senses, locating the platform by sight and smell.

Important During Development

Just as sleep supports learning and memory in the adult brain, it plays a crucial role in the still-developing brain. At the Riken Brain Science Institute, in Japan, Takao Hensch studies sleeping-brain activity in the visual cortex of mice during the so-called critical period of development. This is a time when sensory experience powerfully influences the development of the neuronal circuits. During the critical period, the REM stage of sleep gradually gives way to the slow-wave stage. If the animal is deprived of sight (by being raised in a dark room, for example) during the critical period, its visual cortex shows a great decrease in activity during slow-wave sleep, along with a slight increase of activity in the somatosensory cortex. (The latter is to be expected as the animal begins to depend on senses other than sight to explore the world.) But if the the animals are then moved to normal cages that are exposed to daylight, the visual system returns to its critical period. This new development is evident in the mouse's visual cortex during sleep, as slow-wave activity recovers its normal dominance.

With its active role in tasks that range from creating mental maps to wiring up the developing brain, scientists have just begun to keep track of all the items on the agenda of the sleeping brain. As Daniel Press observes, "It's interesting that in our society we're always trying to sleep less, whereas all the science indicates sleep is so important for memory that we should all be sleeping as much as we need." Sleep on it—you may learn something.

SLEEP THAT KNITS UP THE RAVELL'D SLEEVE OF THREE PROTEINS

Since it has a great many tasks to accomplish while we are sleeping, the brain has developed a way to make sure we sleep enough on a regular basis to let it get everything done. If we stay up too late or wake too early and fail to meet our quota, the brain unleashes a powerful mechanism known as "sleep rebound," which torments us with sleepiness throughout the next day and usually causes us to sleep longer the next night. How does sleep rebound work? Yoshihiro Urade, head of the department of molecular behavioral biology at Osaka Bioscience Institute, used three kinds of knockout mice to find out.

Three proteins are known to fill important roles in the brain's signaling pathway for the onset of sleep: prostaglandin D2 synthase, prostaglandin D2 receptor, and adenosine A2A receptor. Urade observed that mice lacking the genes for these proteins were physically incapable of making up for lost sleep; although they tried to sleep longer than normal after a period of sleep deprivation, they could not do so. Thus it appears that these three proteins act together to ensure we pay our sleep debts in full, and promptly.

"We believe our data are the first to demonstrate how sleep rebound is regulated in the brain," says Urade. This finding has two opposite clinical implications. If a drug can be developed to increase the activity of the prostaglandin D2 receptor or the adenosine A2A receptor, the result might be a new kind of sleeping pill with a very specific target and relatively few side effects. By contrast, a drug that inhibited the activity of those receptors could be used to ward off sleep—although it might never taste as good as cola, tea, or coffee. **—S.J.A.**

Challenging Questions:

Science editor discusses neuroethics

BY DAN GORDON

Are there ethical questions that ought to be raised about the ends of research? Are there ethical problems with enhancement versus treatment? And can we discover things about our nature, such as whether we have free will?

These are three questions Dr. Donald Kennedy, editor in chief of *Science* magazine, identified as central to the field of neuroethics during his Dana Alliance Lecture on Neuroethics, titled "Neuroethics: An Uncertain Future."

Regulation of experimental processes is not a problem, Kennedy said in response to his first question. The gray area lies in research that might be put to bad use, but also could do a lot of good.

As a university president, Kennedy said, he frequently rejected arguments that certain projects should be banned because they might be used for harmful purposes even though they also could provide benefits. Vetoing such research, he said, would be akin to prior restraint of free speech.

Treatment versus enhancement raises another set of concerns, he said, as new ways of knowing the brain introduce new challenges and problems.

"The technological speed of advance … is truly remarkable," he said. Researchers understand the biochemistry of neural signaling much better, creating opportunity for improvements in drugs for mood disorders and intervention in learning and memory.

For Kennedy, enhancement from a neuroscience perspective has social implications but is not a question of human nature.

"If by taking the right drug some persons can improve their position, questions should arise about whether the playing field is level—especially if the treatment is expensive and not available to some competitors," Kennedy said. But, he added, "I find a kind of naïve nativism in the view that there's a natural state that we are somehow messing with."

Enhancement is not a futuristic ethical issue, either, Kennedy said. Drugs are helping patients who have Attention Deficit Hyperactivity Disorder, but people who have not been diagnosed with ADHD are using it for enhancement, and concerns are stirring about prescribing drugs for the latter group. Similar questions arise in the areas of learning and memory function.

Kennedy also had a different twist on enhancement: the idea that there may be thoughtful objections to certain treatments, such as cochlear implants for deaf children.

"In a number of cases, deaf parents have said that they do not wish their deaf child to receive an enhancement of that kind," he said. "They have their reasons. The family has built an effective communication network based on shared capacities and limitations, and may have already invested heavily in building that network.

"On the other hand, one might argue that families don't, after all, stay together forever, and that the child needs to be equipped to deal effectively with hearing adults."

Kennedy, who did not propose a solution, said he mentioned the example to highlight the complexity of such neuroethical questions.

Privacy

In timely fashion, a piece in the Oct. 26 *New York Times Magazine* drew attention to the use of brain imaging for economic purposes. Kennedy discussed two applications: responses to advertisements in different media and an exercise in which subjects' neural responses are measured when they make economic choices.

Kennedy said he does not believe these applications introduce major ethical questions, but he is concerned that similar practices could take root in politics: "How will we feel when the next candidate for governor—of California, say—has been selected through the use of consumer-preference videos?"

Using a hypothetical case as an example, Kennedy also discussed the boundaries of functional magnetic resonance imaging (fMRI) and how it might one day be used to classify people for behavioral risk.

He is concerned, he said, with "knowledge we should do without."

"Through some future fMRI technology, it just might be possible to derive for an individual—just to take a few examples—a predictive moral choice profile, an executive skill assessment, and an estimate of the capacity to repress or retrieve old memories," Kennedy said. "Perhaps worse, it might generate a capacity to peer into intentions, or value systems, or behavioral predilections of various kinds."

Thus, Kennedy said, privacy becomes a central issue in neuroethics.

"I don't want a record of how my brain works trailing after me," he said.

Free Will

Kennedy closed his lecture with a discussion of the impact of increasing knowledge on our sense of ourselves.

"The more we know, does the will seem less free?" he asked.

Kennedy left the philosophical argument to others, saying only that our brains are complex enough that he does not see a threat to free will or our individual decisions. But he raised one final question: What will happen if we come to see more similarities between the brains of humans and animals than we see differences?

Kennedy is not concerned.

"I find great inspiration in the unity of nature," Kennedy said. "Anything that draws our species into a closer relationship with the rest of life strikes me as a gain in wisdom."

Several members of the audience approached Kennedy after his speech with additional neuroethical questions. Kennedy tackled some of them, then acknowledged that they were truly difficult.

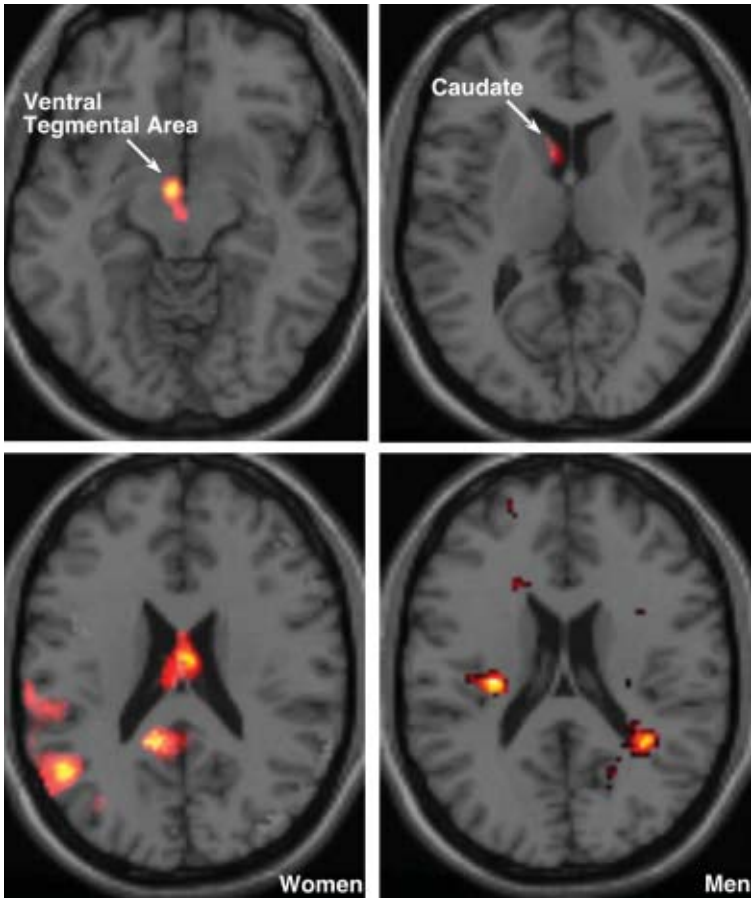
The important thing is to develop a personal sense of what is acceptable and what is not, Kennedy said.

Brain Maps of Love and Trust

Countless songs and stories have celebrated love as one of the greatest of all human emotions, residing in the heart. Now it appears that not only is love not located in the heart, it may not even be an emotion. And as for having a "gut feeling" about whether to trust someone or not, such signals tend to come from inside our skull rather than our intestines. With the help of techniques ranging from functional magnetic resonance imaging (fMRI) to a simple blood test, scientists are beginning to identify the specific brain sites and signals that work together to give rise to some of our most powerful feelings.

Helen Fisher, research professor in anthropology at Rutgers University, and colleagues Arthur Aron of SUNY-Stony Brook and Lucy Brown of the Albert Einstein College of Medicine use fMRI to trace one particular network of signaling pathways in the brain, what Fisher calls "the brain circuitry of romantic love." To find the neurological basis for this peak human experience, the scientists asked 17 young men and women who had just fallen "madly in love" to look at photographs of their beloved, alternating these glimpses with a distracting mental task such as counting backwards from 8,431 in increments of seven. According to the fMRI scans, when the subjects looked at the photos, their brain activity increased in the right caudate nucleus and the right ventral tegmental area, sites that are known to play a role in the neuronal signaling pathways for motivation and reward. The main neurotransmitter of the "reward" system is dopamine, for which these sites contain abundant receptors.

According to Fisher, the feelings that often accompany falling in love—heightened energy, exhilaration, an intense craving to be with the loved one—are those of a down-to-earth drive rather than a lofty emotion. She explains, "I believe romantic love is a developed form of one of three primary brain networks [the other two are emotional attachment and the sex drive] that evolved to direct mammalian reproduction." (The fMRI scans reveal, however, that even a primary network is subject to distraction now and then: One brain region that changes its activity when subjects look at their beloved's photographs is also known to respond specifically to the eating of chocolate.)



Functional magnetic resonance imaging (fMRI) scans localized some of the common brain effects in 17 people who had just fallen "madly in love" as they gazed at a photograph of their beloved.

If love is a drive as basic as the instinct for survival, what happens in the brain when that drive is thwarted? To address that question, Fisher and her colleagues are now scanning the brains of men and women who have been rejected in love, either recently or some time ago. Although the researchers have not yet collected enough data for a thorough analysis, Fisher anticipates that the two different stages of rejected love, protest followed by resignation, may produce two distinct patterns of brain activity.

Fortunately, love is not the only thread holding together the fabric of society. An equally important strand is trust, which underlies almost every interaction among people—even something as basic as strolling down the sidewalk with the assumption that the cars passing nearby will not jump the curb and begin mowing down pedestrians. At Claremont Graduate University in California, trust is the subject of a fascinating experiment by Paul Zak and his colleagues. Approaching the topic from an unusual perspective—Zak is a professor of economics—the scientists have designed a way to measure levels of trust, as well as its effect on the person being trusted, while observing exchanges of money among randomly paired volunteers.

The subjects never meet one another, and each pair can communicate only by computer. At the beginning of the experiment, each subject is paid a flat fee for his participation. Half the subjects are then told they can choose to send all, some, or none of that fee to their nameless and faceless partner. Whatever amount they send will be

tripled, and the unknown partner can then choose to return the favor by sending back all, some, or none of the larger fee. The money sent by partner A serves as a direct measure of her willingness to trust partner B, whereas the money sent back by B is a measure of his willingness to fulfill that trust.

Interestingly, participants in this experiment were unable to articulate why they behaved the way they did, Zak observes. "Nonetheless their brains guided them to behave in 'socially desirable' ways," to trust and to be trustworthy. If we often act on these tendencies without knowing why, that suggests they may be instinctual—perhaps even crucial to survival, in a species as highly social and interdependent as our own. In animal studies, a hormone called oxytocin has been found important for social recognition and for bonding, both between mothers and offspring and between pairs of adults cooperating to raise their young. Similar studies have not yet been performed in humans, so the Claremont scientists carried out blood tests of their subjects to measure their levels of oxytocin. They found that the hormone increased in B partners who perceived they were being trusted by their A partner; in turn, as oxytocin levels rose, the B partners became more and more trustworthy.

Zak and his colleagues are now studying brain-activity patterns in normal subjects as they perceive they are being trusted, and physiological responses to signals of trust in people with brain damage, in order to identify the neuronal circuitry that underlies trust and trustworthiness. The picture that emerges will doubtless be both complex and surprising: what to make, for example, of the recent finding that men and women who go in for massages tend to be more trusting?

—S.J.A.

'This Is a Great Time for Neuroscience'

Huda Akil, Ph.D., professor of neuroscience and psychiatry at the University of Michigan, just completed her tenure as President of the Society for Neuroscience. She spoke with Rabiya Tuma about the field of neurobiology, the role science and scientists have to play, and why the Society itself is so important.

Huda Akil

In recent years, disease genes have been identified for a variety of disorders, but neurobiology seems to be lagging behind a little bit in that success. Can you explain why that is and how to get around it?

The challenge in medicine broadly, and in brain-related disorders in particular, has been so-called complex disorders where a single gene is not at fault but a combination of genes and an interaction of gene and environment cause the disorder.

The concept then is that no individual gene you inherit is aberrant or mutated but they are each part of a normal variation in the population, so-called allelic variants. Genes come in say three or four "flavors" in the population and you inherit one particular flavor. Any one of these variants may not have a big impact alone, but combinations of these flavors make you more or less vulnerable to a particular illness. If then, you have a vulnerability and certain environmental events or developmental events take place in your life, that interaction between genetic predisposition and environmental insult can trigger the illness. That is one concept.

The other is that two twins that are identical genetically and have inherited the exact same set of genes can have very different life outcomes. One may be lucky and go through life and, say, never get severely depressed. The other may be unlucky and once he or she has a major stressor in their life they might get depressed. Then once a disease affects the brain, the brain itself changes, so you might get in a cycle where you are more and more vulnerable. So it is really a true gene-environment interaction.

Because the brain has this capacity to remodel, sometimes it remodels in a positive way and actually helps you fight the problem, but sometimes in its effort to cope, it can actually wind up making you more vulnerable.

So understanding this complex interplay between a whole range of genes that make you vulnerable and environmental impact on brain structure and function is really a big challenge. That is why it is so hard to put it all together.

Is the brain unusual in its plasticity or its ability to respond to the environment?

All tissue is capable of changing as a result of the environment. What you eat may change your [gastrointestinal] tract for example, or how much you exercise will change your heart. But I think the brain may be particularly programmed to cope and change.

First of all, it is incredibly complex in that even though it is one organ and one tissue, there are billions of cells and trillions of synapses, and each brain region has its own pattern of gene expression. While it has a great deal of richness, it also has specific mechanisms that respond to usage and demand. It is a machine that learns and part of its function is to cope with the environment and be very flexible.

(Continued on page 8)

(HUDA AKIL, continued from page 7)

Does this complexity and interplay account for the perhaps slower progress in neurobiology compared to other areas of medicine?

We have made a huge amount of progress.

If you are looking for a simple gene that causes schizophrenia, mania or depression, or Alzheimer's, we haven't progressed, but that is because there is no single gene.

But if you ask, compared even to just 10 years ago, if our understanding of gene expression, gene regulation, and its impact on the brain has increased, I would say hugely. A lot of work has been completed at fundamental levels, including molecular, cellular circuitry, and behavioral levels. We also have come to learn of other ways of evaluating and bridging the [impact] more subtle vulnerabilities have on actual brain function.

There are actually signatures of these disorders on the brain that we are beginning to identify and recognize, and I am very certain that this is going to be a path towards coming up with new treatments. There may be multiple ways to become depressed or schizophrenic or have a brain-related disorder, because different combinations of genes may exist in one family versus another and different environmental events might happen, but eventually the brain has a signature that says this is a depressed brain or this is a schizophrenic brain or this is an Alzheimer's brain. That signature holds in it very key information about how to break the cycle and how to reverse it. So we have made huge progress.

Even if we don't understand the very original cause of a disorder or only understand it partially, by studying what we do understand—the activities of the gene, the protein, the structural alterations—we can still come up with treatments. Indeed, the way we now treat patients with brain-related disorders, be they neurological or psychiatric, is very different and much more sophisticated than it was 10 years ago.

You just completed your tenure as president for the Society for Neuroscience. Why is such a society so important for scientists?

Neuroscience is a very interdisciplinary field. You can come at it from many different directions. You can study the genes that are involved in forming the brain, the patterns of activity that are necessary to organize it during development, how it is anatomically organized, how behavior affects it, how the environment affects it. There are also many different approaches from very simple organisms to very complex organisms and many different disciplines that come into the study of the brain at multiple different levels of discourse from very integrative to very reductionist.

It is very important as neuroscientists to hear from each other and also to understand progress in one system and take the lessons learned there to another system. For example, if something is figured out in the visual system, how much of that is or is not related to the auditory or olfactory systems?

Do you think scientists communicate enough with the general public or is there more communication that needs to happen?

I do feel very strongly that we need, as scientists, to interact with the public. We need to explain why it is so exciting to be a scientist—and how smart young people can become engaged in research. And we need to explain why it is important to continue to support research even in hard times because it takes time to solve complex problems.

I also think being educated about your brain and how it works and how it affects how you think and feel and function and interact with others is very helpful, especially to young people. Giving them a biological perspective on it is empowering and comforting. It is a nonjudgmental way of helping people understand more about themselves.

I actually feel that humanity seeks to understand its own behavior and its inner feelings and workings and has done so throughout history. That is the basis of literature and of expression in art—and there is a place for it in science as well. So the more we can make it available and share it and use it to help people understand themselves and each other the better. I really feel that is part of our mission as neuroscientists.

"Giving (young people) a biological perspective on (the brain) is empowering and comforting. It is a nonjudgmental way of helping people understand more about themselves."

Is there anything else you would like to add?

This is a great time for neuroscience. The human genome project has a huge impact on neuroscience because the brain expresses the majority of the genes in the genome. We have many new tools that are very exciting and we are ready to bring all of it together so that we can understand brain function and brain disorders. It is really only now that we have what we need to go forward. Obviously we need significant funding and man and woman power, but we have the intellectual resources that are important to make significant and dramatic progress, and I hope we will have the opportunity to keep going. The research funding situation is something that obviously concerns me at this point. I really hope it will let us do what we can do.

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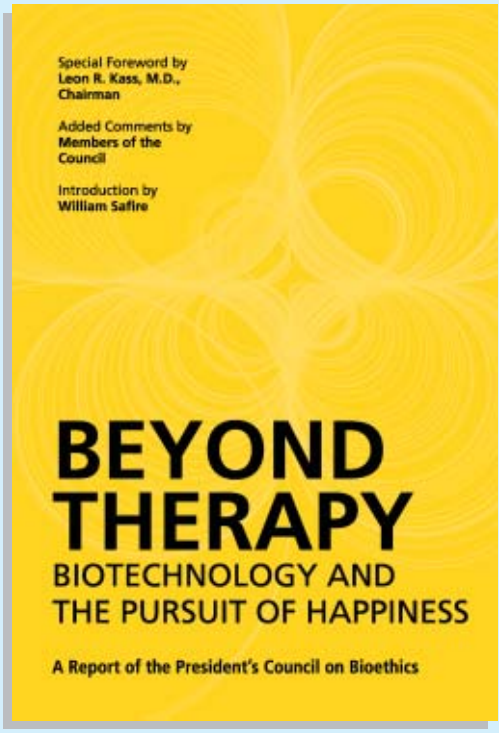

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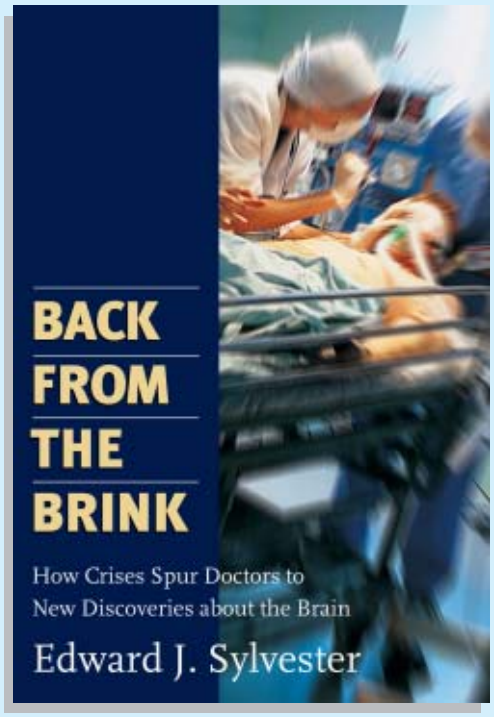

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News FROM THE FRONTIER

(Continued from page 1)

a biochemical factor that could predispose someone to addiction, something that would be affected by a wide variety of addictive drugs, not just one or two.

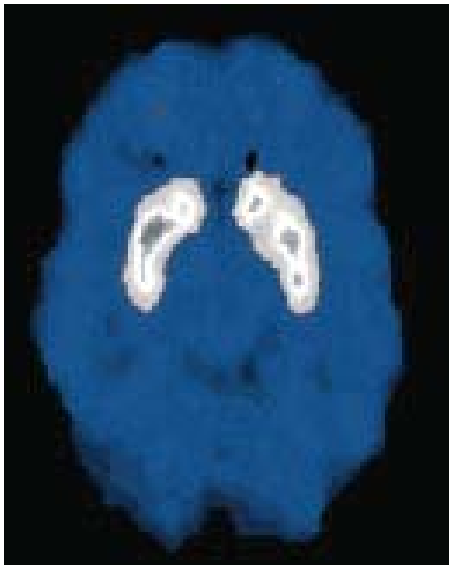
One protein that fits that description is the dopamine receptor. Dopamine is one of the major neurotransmitters in the brain and is involved in pathways that sense pleasure and reward. The dopamine receptor, D2, lies on the far side of neural synapses in the brain and binds dopamine as it is released by the presynaptic neuron; binding of dopamine by the receptor transmits the electrical activation of one neuron to the next.

But when Volkow's team used a brain imaging technique called positron emission tomography (PET), which enables them to detect the level of a specific molecule such as the D2 receptor, they saw substantial differences between addicts and nonaddicts. Addicts generally have less D2 in their brains than do healthy controls. Interestingly, though, there is overlap, suggesting that D2 levels are not an absolute indicator of addiction. The levels of D2 appear to play a role in addiction, but are not sufficient to cause it, says Volkow.

The level of D2 plays an important role in how someone senses reward or value for a stimulus. At normal levels of D2, most people will feel a sense of pleasure or reward from food, social interaction, or sex. If the level of D2 is too low, however, then this sense of reward (or salience, as the scientists term it,) wouldn't occur in response to such natural stimuli.

Addictive drugs, however, increase the amount of dopamine that is released in the synapse relative to natural stimuli. These unusually high levels of dopamine make up for the lower levels of D2 receptor and induce a sense of salience for the addict, salience they may feel only when they take the drug because other stimuli do not induce adequate stimulation of the dopamine system.

To test this model, Volkow asked healthy, nonaddicted people to participate in a study. In the first part of the experiment the researchers determined the level of D2 receptor in each participant's brain via PET imaging. The volunteers were then given a nonaddictive drug that activates dopaminergic neurons. Half of the subjects liked how it felt and half thought it was unpleasant. When the researchers compared each participant's emotional response to the drug with his or her level of D2, they found a strong correlation: The people with lower levels of D2 liked the drug, those with higher levels did not.



Positron emission tomography (PET) can be used to evaluate and compare the distribution and density of receptor or transporter sites in drug abusers and nonusers; this image highlights the dopamine D2 receptors, which may play a role in addiction.

Volkow says the natural variation in D2 levels in the population may be important for who becomes an addict. For those people with higher D2 levels, the drug stimulus was so strong that they felt uncomfortable and would not be inclined to try it again, but for those with a lower receptor level, the drug created a pleasant sensation.

These data, though interesting, show correlation, not causation, so the team turned to animal studies where they can actively alter the levels of D2 receptor in an animal's brain and look at the effects. In this study mice were given access to alcohol, which they could drink as they desired. The team then injected a gene into the animals' brains that encodes the D2 receptor. With this gene delivery system, the amount of D2 in the brain increases 50 percent four days after injection, and by day 10 the level has dropped back to normal. The investigators reinjected the animals on day 20, and again by day 30 levels were normal.

"We see a dramatic change in alcohol consumption," says Volkow: The 50 percent increase in D2 resulted in a 70 percent drop in alcohol consumption by the animals. "An increase in the D2 receptor has a profound effect on the pattern of alcohol consumption."

Volkow says that this and other work is beginning to draw a picture of why some people become addicted while others do not, and of what happens when they do. Such research, Volkow says, may enable clinicians not only to treat addiction but to prevent it.

—R.S.T.

••• **Feeding the Hunger**. In an area of neuroscience where brain

chemistry meets up with the regulation of body weight, a small molecule called leptin burst onto the field in the mid 1990s and has been drawing attention ever since. A hormone secreted in fat cells, distributed through the bloodstream, and active in the brain, leptin appeared at first to be a direct on-off switch for appetite and thus to fulfill many a dieter's dream: nature's own tool for fending off unwanted weight gain. With further research, however, the understanding of leptin has become more complicated—appropriately so, says Jeffrey Friedman, professor and Howard Hughes Medical Investigator at The Rockefeller University. As he sees it, "Feeding behavior offers a unique opportunity to learn how such a complex behavior is regulated."

Friedman, who first discovered the leptin molecule and traced the neural circuits upon which it acts, now sees it as a major but not sole factor in a signaling system through which the brain and body continuously fine-tune the balance of energy expenditure, appetite, and eating. Leptin carries vital information in what is known as a negative feedback loop. When an individual is at his normal weight, or set point, the concentration of leptin in his blood remains steady. If his weight creeps up beyond the set point, the level of leptin rises; the brain then takes measures to return the level to normal, for example by curbing appetite and burning calories stored in the fat cells. Conversely, when a loss of weight brings the level of leptin down, the brain sends out signals to stimulate the appetite. Thus the dieter's complaint of always feeling hungry, even while eating enough to meet normal calorie requirements, arises not from conscious thought ("This is my 12th salad this week") or perception ("All broiled fish tastes the same") but from a signaling pathway that was built into the human brain and body from the beginning.

The specifications for an individual's set point and for the amount of weight gain or loss that triggers the leptin alarm system are carried in each person's unique set of genes, but the system itself is hard-wired in the brain. Receptor sites for leptin are clustered most densely on neurons of the hypothalamus, a small but powerful site that regulates appetite along with other essential functions from deep within the brain. Of course, leptin is not the only source of information that guides our intake of food. The senses of vision and smell and the state of our emotions, not to mention our conscious will to eat or to avoid food, each send their own signals to the hypothalamus. Although there is apparently no single site at which all the information is weighed together, Friedman has observed a considerable amount of "cross-talk" among the brain sites that originate the various signals. The leptin-receptor neurons appear to carry out some processing and integrating of signals as well.

If the negative feedback loop is so sensitive to leptin as an index of body weight, why do some people put on extra pounds up to a point that is clearly unhealthy? Among the most stubborn of medical misperceptions is the belief that obesity arises from a simple lack of willpower, "a view favored by lean people, in my experience," Friedman says. In fact, a large number of twin, adoption, and family genetic studies have established that genes play a major role in the development of obesity.

Genetic mutations that disrupt the negative feedback loop might seem a reasonable way to explain obesity, but Friedman points out that obese people generally have high levels of leptin, which suggests the feedback loop is working normally. "In some cases, the problem may be an intrinsic insensitivity to leptin, that is, less signal getting through," Friedman says. But he adds that "leptin resistance" is currently little more than a vague concept, similar to the idea of insulin resistance in the 1950s. (This condition, a reduced sensitivity to insulin that interferes with the body's normal uptake of glucose, was later found to be typical of type-2 diabetes.)

"Among the most stubborn of medical misperceptions is the belief that obesity arises from a simple lack of willpower, 'a view favored by lean people, in my experience...' "

Currently, evidence from animal and human studies points toward mutations in some of the signaling pathways that run to the hypothalamus. Friedman and his colleagues are now tracing various signaling pathways back to their sites of origin in other parts of the brain, including sites responsible for emotional behavior and for the higher mental functions. Long regarded as a minor topic of medical inquiry, "Obesity research is now one of the most active areas around," says Friedman, "because it lies at the nexus of whole-animal biology, genetics, physiology, nutrition, behavior, neuroscience, and even free will." **—S.J.A.**

(NO FEAR, continued from page 3)

stimulated these neurons while simultaneously exposing the animal to the conditioning stimulus, which in this case was a sound that had been previously paired with a light electric shock, the animal would immediately learn not to fear the sound. In their experiments, the animal experienced extinction with a single episode of the sound and the intralimbic neural stimulation and did not require the repetitions normally necessary for extinction of fear. Furthermore, the extinction was still in place the next day.

When the team looked at the timing of the electrical stimulation of the intralimbic neurons relative to the timing of the conditioning stimulus, they found that the neurons had to be activated within a fraction of a second of the sound. If neural stimulation occurred one second before or after the sound, no extinction occurred.

Based on this finding and the knowledge that extinction does not undo the previously encoded fear but rather overlays a new pattern, the team hypothesizes that the intralimbic neurons stimulated by extinction training (or by the electrical stimulus in Quirk's experiment) send an inhibitory signal to the neurons in the amygdala that are activated by the conditioned fear. If the inhibitory signal gets there at the right time, it blocks the fear response and gives an all clear signal instead.

Quirk suggests that people who experience post-traumatic stress disorder (PTSD) cannot activate this all clear signal adequately and therefore continue to respond to previous conditioning stimuli in a heightened manner, even though they are no longer in actual danger. Interestingly, the area in the medial prefrontal cortex that appears to be required for consolidating the extinction response in animals is often atrophied in people with PTSD, which supports Quirk's model.

Furthermore, it appears that many of the pathways involved in both conditioned learning and extinction of fear are similar in animals and humans, according to work by Elizabeth Phelps of New York University in New York City. When she uses brain imaging techniques such as functional magnetic resonance imaging (fMRI), which shows blood flow patterns in the brain, during a conditioned learning and extinction experiment with healthy volunteers, she sees that both the amygdala and the prefrontal cortex are very active.

This work indicates that what researchers learn about the extinction of fear in animals may be readily transferable to humans and may help with the development of new and better therapies for PTSD, phobias, and anxiety.

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