

# BRAINWORK

*The Neuroscience Newsletter*

Vol. 14 No. 2

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## News FROM THE FRONTIER

### New Research Stresses the Responses to Stress

BY SANDRA J. ACKERMAN

••• **Normal prion proteins key players in disease?** Mad cow disease and related conditions, such as Creutzfeldt-Jakob disease in humans, are caused by elusive agents known as prions, which cause sponge-like holes in brain tissue. According to R. Anthony Williamson of The Scripps Research Institute in La Jolla, Calif., prion proteins “have a Jekyll and Hyde personality.” They can occur in either of two states: a normal configuration found on the surface of many cells (especially neurons), or the abnormal version that causes disease.

Researchers had believed that “bad” prions bring about cell death by converting their healthy counterparts into a toxic form. But several recent studies suggest that normal prion proteins are themselves active players in the relay that kills neurons. In a report published online January 29 in *Science*, Williamson and colleagues investigated the so-called cellular prion protein (PrP<sup>C</sup>)—the Dr. Jekyll to the protein PrP<sup>SC</sup>, which causes the disease called scrapie.

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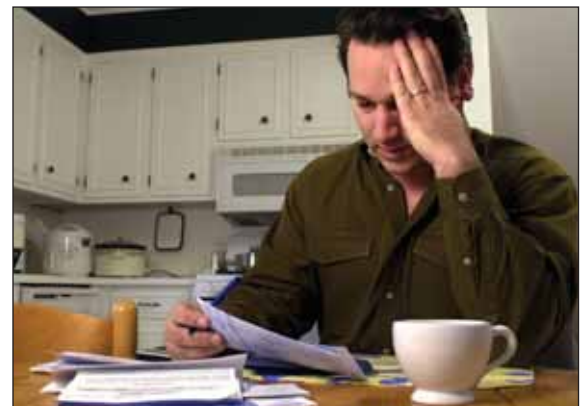
From Thanksgiving through the New Year, and now again with the approach of the mid-April deadline for filing income-tax returns, the air is full of warnings about stress and tips for avoiding it. In fact, according to numerous broadcasts, articles, and workshops, we navigate a minefield of stress throughout the year: finishing school in the spring and beginning again after the summer; preparing for a vacation and returning from a vacation (not to mention any out-of-the-ordinary kinds of stress that may crop up during a vacation); diminishing daylight in the fall; and so on, right around to the winter holidays again. All this stress, we hear, is bad for our health—but why? And what is stress exactly? New studies shed light on these questions and suggest some surprising countermeasures.

“People seem to know what we mean when we say ‘stress,’ but when we look at the term carefully, it seems we’re talking about a lot of different things,” says Bruce McEwen, professor of neuroendocrinology at Rockefeller University in New York. Sonia Lupien, associate director of clinical research at the McGill Centre for Studies in Aging in Verdun, Quebec, says, “The common notion of stress has to do with time pressure or a loss

of control over one’s time, but the scientific definition names three other components instead: The source of the stress must be unpredicted or unpredictable, novel, and beyond the individual’s control.” Whatever this source may be, humans respond by producing the well-known “stress hormones”: adrenalin, which raises blood pressure and heart rate and makes more energy available to the muscles, and glucocorticoids, which enhance memory and immune function and help the body replenish depleted energy stores.

These powerful chemicals serve extremely well in a crisis, allowing us to fight off or escape from various kinds of danger and to learn how to avoid similar dangers in the future. However, if

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*The stress hormones humans produce benefit a body under pressure, but their presence for an extended period of time poses dangers, not least to the brain.*

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they continue to circulate for long periods of time, they themselves become dangerous—particularly in the brain.

Research from animals exposed to continuously high levels of glucocorticoids shows damage in a tiny brain site called the dentate gyrus, which is now known to produce new neurons throughout the human lifespan. Glucocorticoids also wreak havoc among the signal-receiving dendrites of the hippocampus, a key site for memory.

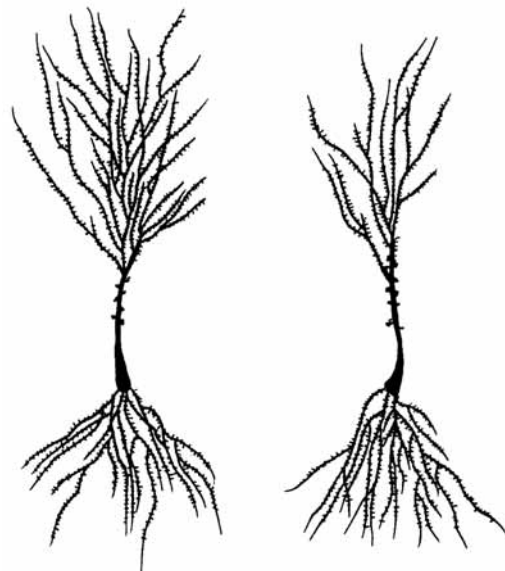
“Normally, dendrites stick out all around the neuronal cell bodies like branches around the trunk of a tree; they take up a lot of space,” says Lupien. “Chronically high levels of stress hormones actually shrink the tree.” Research by Lupien and McEwen has documented a loss of volume—as much as 14 percent—in the hippocampus of men and women in their 70s whose levels of cortisol in the blood stream were chronically higher than average. Clearly,

decades of mental and emotional wear and tear can exert major physical effects on the brain.

Not all the effects appear in medical images, however. In an animal study conducted in the psychology department of the University of Chicago, research fellow Sonia Cavigelli and professor Martha McClintock found that if young rats were fearful of novelty (“neophobic,” or unwilling to explore new spaces or inspect new objects), they produced significantly higher levels of glucocorticoids in response to stress in middle age than did their “neophilic” littermates, those that embraced new things. After stressors such as 30 minutes of physical restraint, neophobic and neophilic rats cleared glucocorticoids from their blood stream at roughly the same rate; however, the higher peak of the neophobic response meant that those rats were exposed to higher-than-baseline levels for a longer time. Perhaps as a consequence, the neophobic rats died earlier: Their median lifespan was 599 days, compared with the neophilic rats’ median of 701 days. These findings hit close to home: Studies in humans, too, suggest a link between a personality trait called “distress proneness” and a shortened lifespan.

### Human Effects

Distress proneness in people, which in everyday conversation goes by labels such as “worrying too much” or “tending to take things hard,” can have grievous consequences even before the end of life. Little by little, it can rob older adults of their episodic memory—that is, the ability to recall recent events that have personal meaning, such as what one had for breakfast or where one went on last weekend’s bicycle ride. “Research into the effects of stress on memory has been going on for some time in animals, but in humans it is quite recent,” says Robert Wilson, director of cognitive neuroscience at Rush University Medical Center in Chicago. In a study of nearly 800 people in their 70s, Wilson and his colleagues found that people prone to distress experienced a tenfold decline in episodic memory over the course of



*Dendrites in the hippocampus become shorter with fewer branches, as these sketches show (from changes observed after a dominant tree shrew experienced the repeated stress of confrontation with an intruder). As a result, cognitive processes such as certain types of learning and memory are impaired.*

about five years. It is possible, however, that the greater anxiety and worry experienced by these individuals was a *response* to the decline in their power of memory rather than a *cause* of it.

The same study offers evidence that distress proneness increases an individual’s risk of developing Alzheimer’s disease, independent of the role played by pathologic features such as cortical plaques or tangles. In the people with the greatest degree of distress proneness (those in the 90th percentile), the risk of Alzheimer’s disease was twice as high as in those with the lowest degree of distress proneness (10th percentile). That a personality trait could be a risk factor for Alzheimer’s disease is still a new idea for neurologists, Wilson says: “It hasn’t reached broad consensus yet.”

### What Is Stress?

Looking at the matter from a different perspective, psychologists have little trouble recognizing that various states of mind may bring distinct physical effects, but they consider terms such as “stress” or “distress proneness” too vague for meaningful study.

## BRAINWORK

### The Neuroscience Newsletter

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“You have to unpackage the word ‘stress,’” says Jerome Kagan, professor of psychology at Harvard University. Kagan argues that although people and animals produce chemical signals of heightened alertness in response to perceiving imminent harm, encountering novelty, or being separated from a loved one, each kind of event causes a different form of stress. “You can’t equate separation with the threat of imminent harm,” he says.

Kagan’s own work, based on the close observation of hundreds of children, concerns the human response to novelty, an important dimension of an individual’s lifelong temperament. Over several decades of study, Kagan has established that when presented with an unfamiliar sight or sound,

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***Psychologists have little trouble recognizing that various states of mind may bring distinct physical effects, but they consider terms such as “stress” or “distress proneness” too vague for meaningful study.***

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infants as young as 16 weeks begin to show one of two typical responses—an uncomfortably high sensitivity to the new stimulus or a calm interest in exploring it—and that the infant’s response can partially predict the timidity or boldness of that individual as an adolescent and even into adulthood. Of course most people settle somewhere in the middle of the reactivity spectrum as they grow up, but, Kagan says, “About one in four of the infants who show extreme reactivity to novelty will carry this trait throughout their childhood, and not one of the individuals who lack the trait in infancy will develop it later on.”

In birds, fish, mice, and foxes, as well as in humans, the individuals within a species vary considerably in their response to novelty, Kagan says. The biological basis of this variance has long been a subject for debate. This much is clear: In the human brain, novel events or perceptions stimulate several sites near the hippocampus that are unaffected by anything familiar. These sites transmit

their signals to the amygdala, which then sets off the bodily responses that we associate with “stress.” Given that neurological research has established that the *detection* of unfamiliarity precedes by several milliseconds the brain’s *response* to it, Kagan and his colleagues, along with several other research groups, suggest that differential excitability in the amygdala is what produces the two very different styles of response to novelty. In this regard, McEwen says recent studies have shown that the amygdala grows additional neurons as a result of acute and chronic stress and that these changes are accompanied by increased anxiety.

Thus, the psychological states we call distress or fear of imminent harm come to us courtesy of a chemical signaling system that evolved for the rapid distribution of glucocorticoids in the body and remains essential for our survival today. But although this system is ingrained in the body, with the

threshold for reaction in each individual set at birth, the setting is not unalterable. Someone who tends to take things hard is not necessarily doomed to forget more and die sooner; there is more than one way to protect the brain from the long-term toll of a highly reactive amygdala. For example, says McEwen, animal studies over the past 40 years have shown that frequent, gentle handling in infancy can “induce the animals to be more laid-back” throughout their lives—that is, to reset permanently their threshold of reactivity. Later on, even once the threshold is fixed for life, people can still take measures to defend the brain against the effects of long-term overexposure to glucocorticoids; regular exercise, good social support, and higher levels of education can help stave off damage to the hippocampus, although the physical mechanisms that accomplish this are not yet clear.

Most recently, a number of studies have shown that certain drugs already widely used to treat depression can also

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## Surviving Brain Tumors Can Come at a Steep Price

BY HAKON HEIMER

When cancer therapy kills a brain tumor, we expect a happy ending. For some people, however, a new tragedy begins to unfold, as the side effects of radiation therapy rob the patient of memory and other critical cognitive faculties. The heartening news from several recent studies in animal models is that common anti-inflammatory drugs might be able to counteract these harmful side effects.

Only recently have researchers confirmed the sobering observation that most patients who undergo radiation therapy that includes the head and neck will experience some level of decline in mental faculties. “Most children who survive their disease require special education classes following cranial irradiation, and adults who survive have an increased rate of dementia,” says Michelle L. Monje, an M.D./Ph.D. student at Stanford University and lead author of one of the recent animal studies.

Although adult patients are likely to be distressed at the realization that their mental faculties have declined, they can compensate to some extent with the knowledge and experience gained up to that point in life. Not only do children lack that advantage, says Stanford researcher Theo D. Palmer, in whose laboratory Monje conducted her research, “Children who receive radiation therapy before the age of 3 will have a declining IQ that never bottoms out.”

The reality is that there is often no alternative to radiation when tumor cells must be killed. This is especially true in the brain, which has elaborate defense mechanisms to buffer brain cells from large molecules such as toxins, bacteria, or, unfortunately, most therapeutic drugs. Radiation is an

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(BRAIN TUMORS, continued from page 3)

option that can add months or even years to a patient's life.

"As we develop more effective treatment for brain tumor patients, resulting in longer survivals, we can expect to see increases in the number of patients suffering from irradiation-induced cognitive decline, unless we develop a means to offset this side effect," says Myrna R. Rosenfeld, an expert in the treatment and biology of brain tumors at the University of Pennsylvania in Philadelphia.

Rosenfeld says better targeting of radiation to just the site of the tumor should help to protect the brain from the effects of radiation. However, because tumors often intertwine themselves with healthy brain tissue, this approach will not provide complete protection. In a separate approach to the problem, scientists are exploring how irradiation affects brain cells in the hopes of offsetting the damage.

### Inflammatory Research

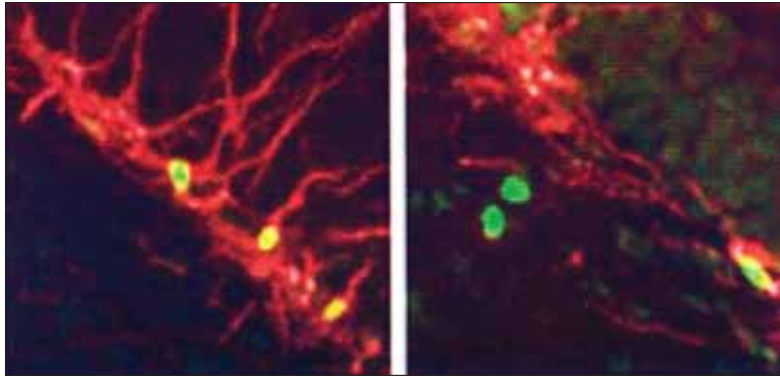
Among the changes noted in the brain following irradiation is an increase in inflammation, one of the immune system's defenses. Inflammation is a complicated process involving the activation of different cells and the release of various chemical messengers. In fact, inflammation probably plays a role in fighting tumors, but it can also damage the normal functioning of the nervous system.

In 2002, Palmer, Monje, and their colleagues published important findings in *Nature Medicine* in which they showed how radiation interferes with cell replacement in the hippocampus, an area of the brain critical for memory and learning. The hippocampus is one of the few areas of the brain where nerve cells are continuously replaced throughout our lifetimes. Any interference with the process called *neurogenesis*, whereby stem cells in the hippocampus mature into nerve cells, can

harm learning and memory.

Working in rats, Palmer and Monje showed that cranial irradiation interferes with this process of hippocampal cell replacement, not by harming the stem cells or the adult nerve cells, but by altering the "microenvironment" surrounding the cells in the hippocampus. The researchers hypothesized that inflammation might be the problem.

In a recent study reported in *Science*, Palmer, Monje, and coauthor Hiroki Toda have found strong evi-



*New neurons in the brain of a rat, left, are significantly reduced by inflammation, as shown in the image on the right. Radiation to wipe out a brain tumor causes this inflammation; survivors of such tumors often experience cognitive decline.*

dence that inflammation is to blame. In order to avoid any other effects of radiation on the brain, they used a chemical stimulus that triggers only inflammation. This led to a significant reduction in the birth of new nerve cells in the hippocampus. When they treated the rats with indomethacin, a common nonsteroidal anti-inflammatory drug (NSAID), they were able to protect the neurogenesis of hippocampal nerve cells.

Surprisingly, about the same time, researchers working on a very different illness had come to the same conclusion. A team led by Olle Lindvall of Lund University in Sweden has been studying how epileptic seizures can lead to inflammation in the brain. In an article published in the *Proceedings of the National Academy of Sciences*, they also demonstrated that inflammation reduces the birth of new nerve cells in the hippocampus. What's more, they were able to restore neuro-

genesis with an NSAID (and antibiotic) called minocycline.

### Unanswered Questions

So if inflammation is the culprit, and we already possess safe drugs, why not start giving them to tumor patients along with radiation therapy? As one might expect, there are some obstacles and unanswered questions. For example, Palmer and Monje are still completing experiments to determine whether the reduced inflamma-

tion and increased neurogenesis in irradiated rats results in higher maze test scores.

And as Palmer points out, inflammation has its benefits. It appears that an immune response works in unison with the radiation therapy to fight the tumor. If inflammation is a necessary part of this process, NSAIDs would not be useful during the period of irradiation. For this reason, Palmer's team has begun research to determine whether NSAIDs could help

patients after they have finished their course of radiation therapy.

Rosenfeld says NSAIDs may help cancer patients in another way. One of the principle effects of this class of drugs is to inhibit an enzyme called cyclooxygenase-2 (COX-2), which is elevated in tumor cells. "There are data that suggest that COX-2 inhibition with NSAIDs increases the sensitivity of tumor cells to radiation, making radiation more effective," says Rosenfeld.

As these different lines of research converge on common processes and molecules, it will be especially gratifying if the silver lining to the dark cloud of cognitive side effects should turn out to be a group of drugs that are inexpensive, safe, and already widely available.

*Hakon Heimer is a science and medical writer in Providence, R.I.*

## Study Raises New Questions about MS

BY ANN MACDONALD

**M**ultiple sclerosis (MS) is thought to develop from some complex interaction between genetic and environmental factors, as yet unknown. Also puzzling is why MS affects twice as many women as men. Now the first large study of twins with MS answers some questions but raises others—chief among them to what degree the hormone estrogen, long a suspect, contributes to development of the disorder.

“That’s probably the most important implication of the study, although it’s not barn door obvious,” says lead author George Ebers, chair of clinical neurology at Oxford University in England. The study was published last fall in *Proceedings of the National Academy of Sciences*.

MS is a progressive autoimmune disorder that impairs the ability of the brain and spinal cord to send and receive messages to peripheral nerves. Manifestations of the disorder vary in severity from one person to the next, but typically include symptoms such as numbness and tingling, weakness, difficulty walking, imbalance, and, at the worst extreme, paralysis. These symptoms develop when a person’s immune system attacks the protective myelin sheath that surrounds nerves, preventing them from sending signals efficiently.

It is believed that the autoimmune attack begins when a susceptible person encounters some type of environmental trigger. It is also likely that several genes interact, perhaps in concert with environmental factors, to create the initial vulnerability. One leading suspect is a gene known as HLA-DR.

Twin studies are considered the gold standard for trying to determine the relative influence of genetic and environmental factors, but most of those done on MS have been small. This latest study is significant because of its

scope and size. The authors partnered with the Canadian Collaborative Study Group to obtain and analyze blood samples and other data from patients at a network of specialized MS clinics. The authors queried nearly 20,000 patients about whether they were a twin or part of a multiple birth. After study criteria were met, 370 twin pairs were included in the final analysis, which the authors estimate represents about 75 percent of the twins with MS in Canada.

The study dispelled one longstanding theory: that being a twin somehow increases risk of MS. The authors found that people with MS were no more likely to be a twin than members of the general population.

To try to determine the relative influence of genes and environment, the authors looked at concordance rates—how often both twins develop MS. When genes alone cause a disorder,

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***“This opens a new door in the research, and suggests that estrogen may not be the answer.”***

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the concordance rate in identical twins—who have virtually identical genes—should be 100 percent. Instead the authors found concordance rates of 25 percent in identical twins, meaning that if one twin develops MS, there is only a one in four chance the other one will. This finding confirms previous studies and provides further evidence that environmental factors contribute to the disorder.

The authors found a slightly higher concordance rate in fraternal twins than in other siblings—about 5 percent compared with 3 percent. Because fraternal twins have different genes but develop in the same womb, Ebers says, “This hints that there may be something early in life, occurring either prenatally or shortly after birth, that affects susceptibility.” Also interesting, says Ebers, is that the highest rate of concordance occurred in female twins: “This suggests that there is something about being female that

puts people at risk for MS.”

What that might be is the \$64,000 question. “Nobody knows why women are more likely than men to suffer from autoimmune disorders,” says rheumatologist Robert Lahita, chairman of medicine at the Jersey City Medical Center and an expert in autoimmune disorders.

Lahita says the development of an autoimmune disorder probably has two phases. The first stage, known as acquisition, probably occurs prenatally or very early after birth. Exposure to female hormones during prenatal development likely plays a role in this phase, Lahita says: “The hormones affect the developing immune system.” The disorder then develops only after a second event later in life. Factors under investigation include environmental triggers such as infectious agents, toxins, or diet, but a leading suspect is the female hormone estrogen—especially, Lahita says, because many autoimmune disorders begin to manifest themselves after puberty.

But this latest twins study challenges the estrogen theory. The researchers found that identical female twins were about 10 times as likely to develop MS as fraternal female twins—a 34 percent concordance rate compared with about 4 percent. “That was the biggest difference in concordance that we found,” says Ebers. “Most people think that autoimmune disorders are more common in women because of estrogen. This is saying, well, maybe not.” He points out that both sets of female twins, identical and fraternal, share the same exposure to female hormones both prenatally and during puberty. “This opens a new door in the research, and suggests that estrogen may not be the answer,” says Ebers. “Some other interesting gene-environment interaction may be at work.”

To determine what that might be, Ebers and colleagues are currently doing further analyses of their data and collecting information from the patients about family history and early life experiences.

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

# What's So Funny?

BY THOMAS S. MAY

Two psychiatrists run into each other at a scientific meeting. "Hello, how am I?" says the first one. "You're fine, how am I?" the other responds.

If you didn't find this joke funny, it doesn't necessarily mean you have an impaired sense of humor. But it might: Advanced age, as well as damage to certain areas of the brain, can result in a decreased ability to understand and/or appreciate humor, according to some studies.

## Never Too Old to Laugh

Ask any comedian, and he'll probably tell you that it is much easier to make a younger audience laugh than an audience full of octogenarians. Research conducted by Prathiba Shammi and Donald Stuss of the University of Toronto, Canada, seems to confirm that older people do not always understand the punch line of a joke.

In a study published in the September 2003 issue of the *Journal of the International Neuropsychological Society*, Shammi and Stuss asked 20 healthy older adults (average age 73) and 17 healthy younger adults (average age 28) to select the correct punch lines for 16 incomplete joke stems. Each joke stem had four different endings, one of which was the correct (humorous) punch line.

In another test, participants were shown 10 different cartoons. Each cartoon consisted of a series of four similar drawings, only one of which had a funny detail. Participants were then asked to select the correct (funny) version.

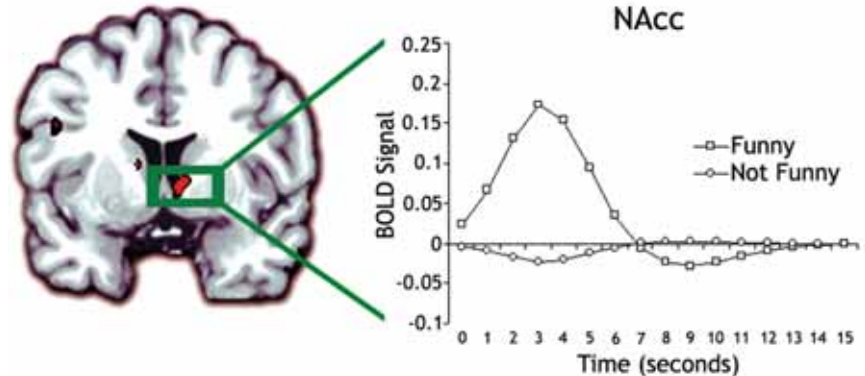
An analysis of the results showed that the older adults made significantly more errors in both of the tests. Despite these deficits in humor comprehension, older adults did not differ from the younger ones in terms of their ability to appreciate humor; they

reacted appropriately, with a smile or laugh, when they understood the joke.

We're never too old to laugh, according to Stuss. "Our sense of humor, the appreciation of a humorous joke or situation that is understood does not diminish with age," he contends. "However, the ability to capture some of the nuances of certain types of humor may alter" in older individuals.

## Right Frontal Lobe Essential

In another paper, Shammi and Stuss examined the effects of brain damage (resulting from stroke, tumor, or head trauma) on people's ability to understand and appreciate humor.



When subjects found cartoons funny, blood flow increased in a small brain structure called the nucleus accumbens. In the graph, "BOLD signal" indicates blood flow. This finding indicates that humor is inherently rewarding and may have evolved as an innate coping mechanism.

The researchers found that subjects with damage to the right frontal lobe area not only had difficulty getting punch lines, but their ability to appreciate humor in general appeared to suffer as well.

According to Frank Rodden of the University of Tübingen, Germany, who coauthored a review article about the neural correlates of laughter and humor that appeared in the October 2003 issue of *Brain*, other studies also have implicated the right frontal lobe in humor perception. "So it is very likely that an intact right frontal lobe is a necessary condition for the perception of humor," he says.

It is important to understand, however, that impaired humor appreciation after brain damage is not an "all

or nothing affair," Stuss points out. "It is a relative change. Indeed there are individual differences of humor appreciation in individuals without known neurological damage."

## Natural Antidepressant?

Although an intact right frontal lobe appears to be essential, it is not the only area of the brain that has an important role to play in the perception and appreciation of humor. A study published in the December 2003 issue of *Neuron* identified several cortical regions that appear to be involved in either the linguistic aspects of "getting the joke" or the motor components of humor (i.e., laughter).

Using functional magnetic resonance imaging, the researchers also found that a small structure deep inside the brain called the nucleus accumbens is activated as well when a person sees or hears something funny. "This region has previously been shown to be activated by rewarding drugs, such as cocaine and amphetamines, suggesting that it is involved in the rewarding aspects of humor," says Dean Mobbs of Stanford University, the study's lead author. These findings indicate that humor is inherently rewarding, Mobbs says, so it may have evolved as an innate coping mechanism or "natural antidepressant."

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

# News

## FROM THE FRONTIER

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The team injected mice with custom-designed, or “monoclonal,” antibodies that attach to PrP<sup>C</sup> at specific locations. Antibodies that cross-linked, or hooked together, two PRP<sup>C</sup> molecules triggered a cascade of neurodegeneration typical of scrapie—even though no scrapie protein was present. But intriguingly, an antibody that latched onto only one PRP<sup>C</sup> molecule did not produce disease. This finding suggests that the cross-linking turns on a series of signaling events, ultimately killing neurons.

The study provides important information for researchers seeking to understand how prions cause disease. It also warns against the use of antibodies to treat prion diseases. Though they powerfully inhibit prions in tissues outside the brain, antibodies cannot cross the blood-brain barrier and would have to be introduced directly into the brain. To judge by the new finding, “This approach might liquefy brain tissue even more effectively than prions do,” Williamson cautions.

••• **Simple sugar may fend off Huntington’s disease.** In Huntington’s disease, a stretch of the gene that encodes the protein huntingtin begins to repeat itself, forming clumps that build up in the nuclei of brain cells and ultimately destroy the neurons. Many scientists are searching for molecules that are small enough to enter the brain and can interfere with this abnormal clumping process. In an article published online January 18 in *Nature Medicine*, a team from the Riken Brain Science Institute in Japan has reported that a type of sugar called trehalose can prevent huntingtin aggregates from forming and can improve motor function in mice with the disease.

After screening some 200 compounds, including simple sugars and small peptides, Nobuyuki Nukina and

colleagues found that trehalose prevented aggregate formation in a test protein that they had developed, as well as in a line of cells containing a similar genetic repeat. Finally the researchers gave trehalose to “transgenic” mice that had both the genes and the symptoms of Huntington’s disease. A 2 percent solution of trehalose prevented brain atrophy and decreased the number of aggregates in neurons. The treated mice showed improvement in movement, taking bigger strides and showing better posture when walking, and completing motor tests more quickly than untreated mice or mice given table sugar (sucrose); they also lived an average of 10 weeks longer.

Trehalose is safe and easy to administer—it was given to the mice in their drinking water—and it’s easily obtained, existing naturally in many foods such as honey and produced from starch for laboratory use. The authors believe that trehalose is a promising candidate for clinical trials in humans. Says Nukina, “We believe that our work opens new treatment avenues, not only for Huntington’s disease but for other related condi-

tions”—the progressive movement disorders known as ataxias, for example.

••• **Block that memory!** Sigmund Freud believed that we can keep unpleasant or unwanted memories out of our awareness. Though the theory may not be his most provocative, the mechanism of “repression” in the brain has proved a mystery. In the January 9 issue of *Science*, a team from the University of Oregon and Stanford University used functional magnetic resonance imaging to observe the brain’s efforts to forget. The researchers asked subjects to memorize pairs of words. Then, in the scanner, the subjects were given one word of the pair and asked to either think of the associated word or make an effort not to think about it.

According to the scans, repressing the memorized word increased activity in a distinct network of brain regions, including two parts of the cortex—an area known to be involved in preventing movements and controlling thought processes. At the same time, activity decreased in the hippocampus—a part of the brain that helps

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### DECIPHERING DEMENTIAS

Although Alzheimer’s disease accounts for the majority of dementia cases, other types of dementia also are common. For example, dementia with Lewy bodies (DLB) is the second most prevalent form of dementia, accounting for about 20 to 35 percent of cases in the United States. Deciphering the different illnesses is not always straightforward, though it can be critical for proper treatment, says Tanis J. Ferman, a neuropsychologist at the Mayo Clinic in Jacksonville, Florida. Now, she and her colleagues have identified a new, statistically significant clinical feature that may help with the task.

Currently, clinicians generally use three criteria to diagnose DLB, including visual hallucinations; symptoms frequently associated with Parkinson’s disease, especially rigidity and freezing; and fluctuating cognitive abilities. Patients with cognitive fluctuations may have several hours or days where they are particularly confused, stare into space, have incoherent speech, and experience daytime drowsiness despite having had a good night’s rest.

But clinicians do not always recognize these symptoms and researchers have debated whether these symptoms really distinguished DLB from AD or normal aging. To find out, Tanis and colleagues, both in Jacksonville and at the Mayo Clinic in Rochester, Minnesota, used a 19-part questionnaire to test 200 healthy elderly volunteers, 70 Alzheimer’s patients, and 70 patients who appeared to have DLB based on visual hallucinations and Parkinson’s-like symptoms, as well as dementia.

Sixty-three percent of the DLB patients had three or four symptoms of cognitive fluctuations, while only 12 percent of Alzheimer’s patients and 0.5 percent of healthy adults did. Therefore, using a standardized questionnaire such as the one Ferman’s group used may allow doctors to decipher DLB patients from those with Alzheimer’s, which is particularly important because some treatments for Alzheimer’s exacerbate the symptoms of DLB.

The new work was published in the January 27 issue of *Neurology*.

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

(STRESS, continued from page 3)

help protect the brain against the effects of an overreactive amygdala. McEwen describes the intriguing results of a study in which animals were subjected to many stressors while being treated with antidepressants. "Behaviorally, the animals still acted as though they were stressed," he says, "but the experience didn't seem to have the same cumulative effects on the brain" as in untreated animals. With enough ways to buffer the brain against the inevitable bumps and spills of everyday life, the worriers among us may soon have one less thing to worry about.

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

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### BEYOND THERAPY

The landmark report of the President's Council on Bioethics on the ethical and social consequences of our use of medical advances to seek perfection. Special foreword for this edition by Leon R. Kass, M.D., Council chairman; added commentary by three council members; introduction by William Safire.



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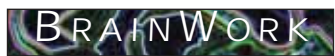
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form and retrieve memories. The researchers found that activity in the "repression" circuits tracked with the participants' success at keeping the unwanted word out of their thoughts. What's more, those who had been able to block the words were less able to remember them after the test was over—indicating that the memory was being dismantled and not just temporarily ignored.

Unpleasant or traumatic memories can be difficult to erase, especially in people suffering from mood disorders; the existence of a brain network devoted to memory repression may shed light on what the authors call "motivated forgetting."

"Our work confirms that there's an active process by which people can prevent awareness of an unwanted past experience," says Michael Anderson of the University of Oregon's Department of Psychology.

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



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