BRAIN WORK

The Neuroscience Newsletter

Vol. 12 No. 6 November-December 2002

News FROM THE FRONTIER

••• **Baby Memories.** Ever wonder why you don't remember being a baby? It is because frontal lobe development for long-term memory does not begin until about the first birthday. And full development of long-term memory takes until the second birthday, according to Conor Liston and Jerome Kagan of Harvard University, who reported their study of infant memory in the October 31 issue of *Nature*.

Conor and Kagan used props and verbal cues to demonstrate simple action sequences, then asked if babies could imitate the actions four months later. For example, they would announce, "Cleanup time!", wipe a table with a paper towel, then toss it in the trash. Four months later, babies received paper towels and heard, "Cleanup time!", but demonstrations were not repeated. At what ages would babies imitate wiping and tossing?

Babies were shown action sequences at 9, 17 and 24 months of age. The 9-month olds could not imitate the actions four months later, but older infants could. Their research, the scientists say, bolsters the evidence that

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How Do We Remember? Let Us Count the Ways.

BY RABIYA S. TUMA

Memory, or the loss of it, is a frequent topic in the media. But how many of us really know the difference between working memory and long-term memory? Or what ailments afflict which function? To get a better handle on this complex area of neurobiology, *Brain Work* interviewed Howard Eichenbaum, a leader in the field of memory research, and asked him to break down the different memory types for us. Here is what he had to say.

First off, it is important to recognize that a driving principle in much of cognitive neuroscience is that there are multiple memory systems, or multiple forms of memory, and they are each mediated by different physical regions in the brain or different wiring systems. And along with that separation, each has distinct operating characteristics that affect how and when things can go wrong.

One of the major lines along which to break down memory types is to distinguish long term versus short term. Within short term memory, researchers often talk about immediate short term memory, which refers to the amount of information a person can respond to or repeat back immediately. A longer form of short term memory is called working memory. This is the memory function that works as the thinking part of the brain, the part that allows us to do math or take advantage of stored facts for logical deduction. However, even though working memory may rely on some stored information, the data it is currently processing does not necessarily get stored in any long term way.

To distinguish between short term and working memory, Howard Eichenbaum, a professor of psychology at Boston University, uses the example of someone looking up a phone number in a phone book. For a very short time, the person might be able to remember quite a bit about the page on which they found the number, its color, surrounding names, etc. That information is stored in short term memory and disperses rapidly. But working memory will take over, repeating, for example, the seven digit phone number as one walks from

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The ability to do math is one function of working memory.

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the book to the phone.

Long term memory, on the other hand, is that information that sticks with you for a long time, on the order of days, weeks and years.

Long Term Memory

However, because we are talking about the complex classification of a complex system, you have probably already guessed what comes next: long term memory is itself subdivided into two broad categories, declarative or conscious memory and non-declarative or unconscious memory, which holds information that cannot usually be accessed by the conscious mind but is present and used nonetheless.

Within declarative long term memory there are also subcategories, episodic and semantic being the main ones. Episodic memory refers to personal life memories, events you took part in, what you had for breakfast yesterday, childhood experiences and the like. Semantic memory is more general knowledge about the world and language, such as who was the first President or that Paris is the capital of France. Although one could argue that all semantic memory is gained through personal experiences, such as in a classroom or during a conversation with a friend, somehow this sort of factual knowledge seems to be filed in a system distinct from episodic memory. Some scientists think that the distinction between the two is not complete and that episodic memory may be something of a gateway to the storage of semantic memories because such facts were first encountered during a personal experience of one kind or another. Interestingly though, episodic memories are organized by experience, in something of a time sequence ("I went to dinner with Joe before I left for Paris"), whereas semantic memories are organized around the logical structure of the subject (the government's organizational tree or grammar rules) and is relatively timeless.

In addition, within long term memory there is emotional memory, which is centralized in the amygdala of the brain. It is emotional memory that makes you nervous when you enter a dark alley; even though nothing has gone wrong at that moment, your brain associates the situation with danger and you may feel fear. Similarly, when you hear the thumping of the musical score to a scary scene from the movie *Jaws*, you expect to see a shark and your heart may start beating a little faster.

As for nondeclarative memory, this includes things like procedural memory, certain habit learning or skills learned that have now become totally unconscious. Much of our life is run by such activities, like driving that familiar route to work, which is such a routine that you often do not even remember the drive because you were thinking consciously about something else while relying on habit to navigate the trip. The skills required for more common tasks like speaking, typing, riding a bike, also rely on procedural memory. These types of memories are controlled largely by the regions of the brain that control motor function, but may also intermittently interact with declarative systems.

A final caveat to all of this? The experts warn that distinguishing between one or another system is a bit arbitrary and not all researchers use the terms in exactly the same way. So if you are discussing memory and need a specific definition, it might be best to define your terms with your conversation partners.

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

Memory systems disorders

As one can imagine given the complexity of the different memory systems, each has its own set of disorders or dysfunctions that go along with it.

Alzheimer's disease first affects *episodic memory*, which is largely contained in the hippocampus of the brain. But as the disease progresses, it begins to also affect *semantic memory*, which is controlled by the cortex region just outside of the hippocampus. Furthermore, Alzheimer's disease may affect *working memory*, both in a person's ability to remember what they are trying to do and in their ability to retrieve the information from other parts of their brain that are required for the task.

Both *episodic* and *semantic* memory can be involved in classic amnesia cases, depending on where the damage is in the brain.

Problems with *working memory* can result from attention problems like attention deficit and hyperactivity disorder (ADHD).

Patients with post-traumatic stress disorder (PTSD) have an exaggerated sense of *emotional memory*, such that their fear or nervousness is disproportionately triggered relative to the actual danger in a situation.

Early in Parkinson's disease patients often lose their ability to acquire new motor skills or habits, which is a deficit in their *procedural memory*.

BRAINWORK

The Neuroscience Newsletter

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When Genetic Hyde Turns Jekyll, It Protects Neurons

BY ANN MACDONALD

In the past few years, scientists sifting through clues to determine what causes neurodegenerative diseases have puzzled over something unexpected in the brains of people with Alzheimer's disease. Along with the hallmark plaques and tangles, researchers found markers of cell cycle activity littering post-mortem brain tissue. This suggested that before they died, neurons tried to re-enter the cell cycle, an orderly process in which cells copy their genetic material and then divide. Yet this made no sense. Neurons are among the few cells in the body that do not divide after maturing.

Meanwhile, evidence has also mounted that oxidative stress, which contributes to aging, heart disease, and cancer, might also play a role in neurodegenerative disorders such as Alzheimer's, amyotrophic lateral sclerosis, and Parkinson's disease. Cells suffer oxidative stress when assaulted by free radicals, highly reactive molecules that are the byproduct of normal cellular activity. Free radicals perform some helpful roles in the body (such as attacking bacteria), but in excess amounts they can damage healthy cells. Scientists have speculated that oxidative stress in the brain might cause cells to commit suicide, contributing to neurodegeneration.

But it has been unclear how oxidative stress, the cell cycle, and neurodegeneration might be linked. In the September 26th issue of *Nature,* scientists at The Jackson Laboratory in Bar Harbor, Maine, suggest a way to connect the dots. In doing so, they propose that a gene formerly thought of as a destructive "Mr. Hyde" can also function as a helpful "Dr. Jekyll."

The Dual Role of the Aif Gene

Susan L. Ackerman heads a team at the Jackson Laboratory that focuses on development and survival of neurons in the cerebellum, the part of the brain that controls movement and coordination. In this study, Ackerman and her colleagues describe their research on Harlequin mice, which lose muscle coordination as they age because neurons in their cerebella and retinas degenerate.

The Jackson scientists used various genetic techniques to determine that the mice have a mutated form of the apoptosis-inducing factor (Aif) gene. This gene is active, or "expressed," throughout the body, and earlier research had shown that it induces cells to commit suicide in the process known as "apoptosis." Researchers also suspected that the gene had other roles, but it was difficult to study.

"The normal strategy in understanding a gene's function is to over-express it or knock it out," explains Valina Dawson, a professor of neurology at Johns Hopkins University School of Medicine. But over-expressing a "death" gene kills the very cells under study. Attempts to knock out Aif function in animals failed because the embryos die early in development (suggesting that the gene has a prenatal role).

The Jackson researchers analyzed the sequence of the Aif gene and found that Harlequin mice have a mutation that scrambles the gene's DNA code and reduces its expression by 80 percent. "Essentially these are 'knock-down' mice," explains Dawson. As such, "they offer a window of insight into what other roles the gene might have."

In a series of laboratory experiments, the Jackson team compared Aif functioning in normal mice with its malfunctioning mutant form in Harlequin mice. In the nucleus, Aif induces apoptosis (showing that it can continue to function in this role even when its expression is reduced). But in the mitochondria (the cell's internal energy generators), Aif has an additional and previously unknown role: it acts as an "anti-oxidant" that protects against damage by hydrogen peroxide, a type of free radical.

"This research shows that Aif is essential for life, but can also initiate the molecular cascade that leads to cell death," says Dawson. Its exact function depends on where it is expressed in the cell, at what level, and what other proteins it interacts with.

By sifting through telltale markers of cell cycle activity, the Jackson scientists also discovered that stressed neurons re-enter the cell cycle before dying. Based on their findings, the scientists propose that the Harlequin mouse provides the first living model of how oxidative stress can trigger re-entry into the cell cycle and eventually lead to neurodegeneration.

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As it ages, the Harlequin mouse loses muscle coordination as neurons in its brain deteriorate. This phenomenon makes it a good animal model to study human neurodegenerative diseases such as Alzheimer's disease, ALS, and Parkinson's disease.

Brain Roots of Addiction and Memory Converge as New Understandings Emerge:

A Conversation with Eric J. Nestler

BY BRENDA PATOINE

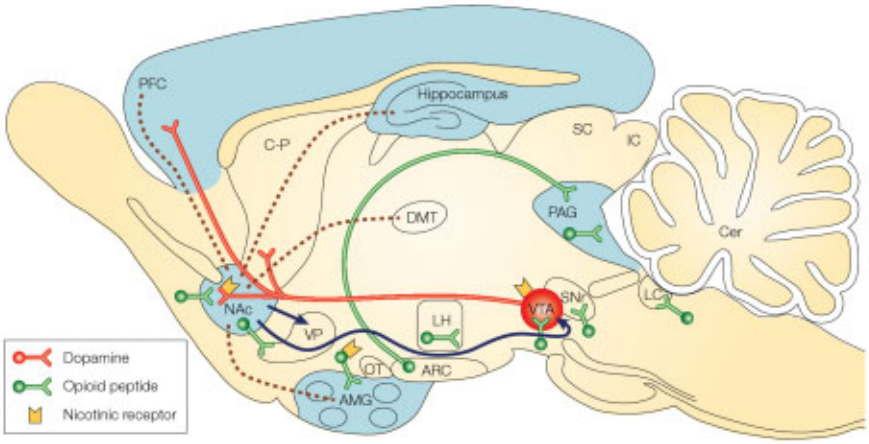
As recognition grows that addiction is a brain disorder with biological roots, and as scientists progress in unraveling those roots, they are finding intriguing similarities with yet another of neuroscience's deepest mysteries: how the brain learns and remembers. In fact, over the past ten years or so, understandings about the brain pathways involved in drug addiction have converged with the growing knowledge about the processes of learning and memory.

It is a well-accepted tenet of addiction research that memory plays an important role in the continued use of drugs of abuse, and particularly in the cravings that can lead to relapse. This is true whether the drug is cocaine, heroin or other illicit "street drugs", or "legalized drugs" like nicotine and alcohol.

"Some of the most striking aspects of addiction are the phenomena where people will have powerful cravings when they meet people with whom they used to get high or go back to an environment where they used to do drugs," says Eric J. Nestler, chairman of the psychiatry department at The University of Texas Southwestern Medical Center. "Something about the situation reminds them of the drug, and that elicits very strong cravings and risk for relapse."

The brain changes that underlie those memories are probably very similar to the changes in the brain that encode other kinds of memories, Nestler says, whether it's a long-lasting image of a kindergarten teacher you adored, or "lessons never forgotten," such as touching a hot stove. Emotionally charged memories tend to have longer staying power than those that are more run-of-the-mill. The now-classic example is that most people remember clearly what they were doing on September 11 when they first heard the news of the attacks. In the same way that bad things can strengthen memories, it is now clear that "good" things—like the high produced by a drug of abuse—can also strengthen memories.

While no one would suggest that drugs of abuse are "good" for you, the brain sees them as intensely rewarding. That is because all addictive drugs act on the brain's reward pathways (see diagram). Through the actions of dopamine and other brain chemicals, they trigger a switch that seems to say "That's great. Do it again." These same pathways, which have been highly conserved throughout evolution, are also implicated in behaviors such as obesity and sex drive. That the brain has evolved with such a reward system makes sense, Nestler says, because it has always been in an animal's best interest to remember where to find food for survival or mates for procreation. The commonality among all of these types of "reward-seeking behaviors" is that they activate brain reward pathways that use dopamine, as well as other biochemical transmitters in the brain.



Nature Reviews | Neuroscience

***Key neural circuits of addiction**: The intense high of a drug of abuse floods the brain's reward pathways with dopamine and other neurochemicals, which seem to strengthen the memory of the high. Environments that trigger memories of earlier highs can induce powerful cravings and increase the risk for relapse. In the complex circuits, researchers have implicated the hippocampus, prefrontal cortex (PFC), the nucleus accumbens (NAc), and amygdala (AMG) both in addiction and in learning and memory.*

The "Nerve" Root of the Problem

The real question now before scientists is, what are the changes in the brain that encode very stable memories, whether they are bad ones like September 11, or "good" ones like a first rush of heroin? How does the brain change in a way that can last a lifetime? On those fronts, "we really have very little insight," Nestler says. "We don't even know what the type of mechanism is, let alone the specifics."

Sorting out the specifics is a major challenge now before addiction research, and there are intriguing leads already. Nestler reviewed these clues recently in the journal *Neurobiology of Learning and Memory*. They include so-called morphological changes—changes in the structure and shape of nerve cells—as well as actions of nerve

growth factors like BDNF and protein factors like CREB, which induce changes in the nuclei of nerve cells, where DNA is encoded. It is more than coincidental that these same types of changes are seen in models of memory and learning, nor is it surprising to experts such as Nestler.

"Nerve cells can only change in a finite number of ways," he says. Whether it is a nerve cell in the nucleus accumbens, a pivotal brain structure in the reward circuit, or a hippocampal neuron in the brain's memory center, the underlying processes are likely to be the same, "even though the stimulus and the consequences of the changes can be very different."

For scientists like Nestler, it is never enough to just be able to describe the changes that occur when a drug of abuse bombards a nerve cell, or what happens to a nerve cell when a particular experience is laid down as memory. They want to know how these changes are created. His laboratory and many other scientific teams worldwide are now aiming their sights at the nuclei of nerve cells deep in the pleasure circuit of the brain to nail down the specific molecular events that are causing lasting changes in the brain.

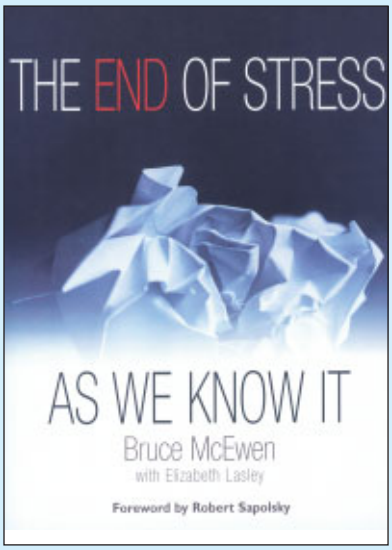
"In order to understand addiction, you need to understand it at this level," says Nestler. I think it's likely that as we understand addiction better, we'll understand memory better, and vice versa. There is so much convergence, the two fields will really assist each other."

Brenda Patoine is a medical and science writer based in LaGrangeville, New York.

Editor's Note: Please look for a follow-up report on addiction and memory in BrainWork's next issue, when we report on a series of lectures on the topic at the 2002 annual meeting of the Society for Neuroscience.

New From THE DANA PRESS

The End of Stress As We Know It



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With Elizabeth N. Lasley

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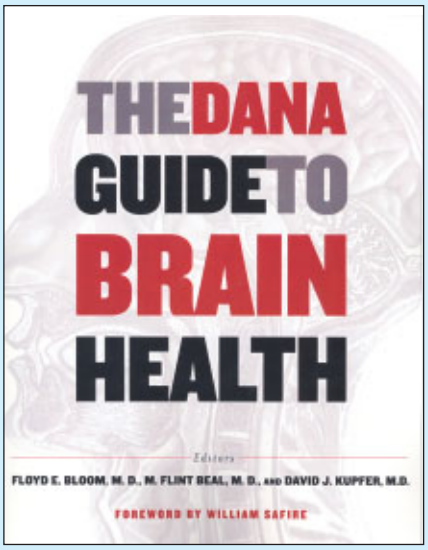


Painkiller Surrenders a Secret

BY TOM HOLLON

The man-in-the-street may be forgiven for assuming that when a home medicine cabinet pain remedy is gobbled by tens of millions of people every day all across the globe, doctors know how it works. But as pain researchers will tell you, acetaminophen, better known as Tylenol, has always combined commercial success with scientific enigma. Knowing how it worked, in fact, was never a requirement when acetaminophen came into medicine; it was enough that it was safe and effective. It was so successful that it was taken for granted. Even in scientific circles it could be forgotten that behind the veneer of familiarity was something mysterious.

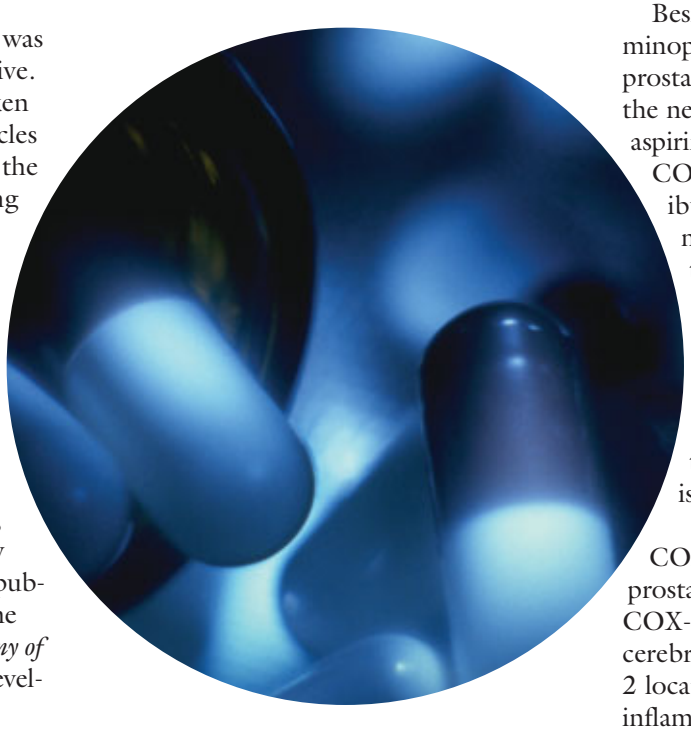
Mysterious until now. At Brigham Young University in Provo, Utah, Daniel L. Simmons and his colleagues have shone light on how acetaminophen works and, in doing so, uncovered additional complexity in the painkiller class of drugs to which aspirin and acetaminophen belong, the nonsteroidal anti-inflammatory drugs (NSAIDs). Their research, published in the October 15 issue of the *Proceedings of the National Academy of Sciences*, opens a new avenue for developing better painkillers.

The Out-of-Step NSAID

Acetaminophen relieves pain and fever, but in one respect it is not a full-fledged NSAID—it is not anti-inflammatory. Its failure to inhibit cyclooxygenase (COX) enzymes that convert arachidonic acid into a prostaglandin called PGH_2 is also unusual. PGH_2 is a precursor for a variety of prostaglandins, including prostaglandins that sensitize nerves to pain at sites of inflammation.

It was not clear that aspirin (acetylsalicylic acid) affected more than one cyclooxygenase until the 1990s, when it was discovered that aspirin reduced pain of inflammation by inhibiting an enzyme called COX-2. Gastrointestinal toxicity, a risk for arthritis sufferers dependent on aspirin to reduce chronic pain, was found to be caused by the aspirin inhibition of COX-1. These discoveries led to the development of painkillers such as Vioxx and Celebrex, which inhibit COX-2 without inhibiting COX-1.

"Since the discovery of COX-2, we have learned an enormous amount about how aspirin drugs work," says Simmons. Acetaminophen, though, did not inhibit COX-1 or COX-2, so "the mechanism of acetaminophen remained elusive."



Extending the COX Family

As Simmons and his team report, acetaminophen does have a COX connection, one that came to light when they cloned COX genes active in the brains of dogs. One clone represented an unsuspected alternate splicing of COX-1 mRNA and produced a new cyclooxygenase which they named COX-3. COX-3 possessed additional amino acids not found in COX-1. The addition endowed COX-3 with a remarkable property: It was strongly inhibited by acetaminophen. The discovery confirmed a claim in the scientific literature of the 1970s that the canine brain possesses a cyclooxygenase sensitive to acetaminophen.

The team soon discovered two other proteins arising from COX-1 gene variants. Neither had cyclooxygenase activity, so the researchers called them *partial* COX proteins PCOX-1a and PCOX-1b. Their physiological roles are unclear. What is clear is that COX genes are more complex than previously realized. The discovery sets the stage for years of work as researchers unravel how the genes and their enzymes affect pain, fever and inflammation.

Next Steps

Besides suggesting that acetaminophen works by reducing prostaglandin production in the brain, the new discovery leaves the roles of aspirin and ibuprofen unsettled. Is COX-3 inhibition by aspirin and ibuprofen important? They are far more potent COX-3 inhibitors than acetaminophen, but neither easily penetrates the blood-brain barrier. On the other hand, doses of aspirin and ibuprofen for pain relief are considerably lower than doses to reduce inflammation. So the issue is open.

So far there is no evidence that COX-3 produces novel prostaglandins. But the fact that COX-3 predominately occurs in the cerebral cortex and heart, while COX-2 locates to the CNS and sites of inflammation suggests that details of how the enzymes influence pain will prove different. It will also be important to compare COX-3 to COX-1. COX-1 is now understood to do more than produce prostaglandins that protect the stomach. COX-1 also plays a role in pain: Drugs that inhibit COX-1 prove better than COX-2 inhibitors for controlling visceral pain caused by chemical pain stimulators.

Another area of investigation is whether overlapping COX enzyme functions explain why individuals response to NSAIDs differently.

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News
FROM THE FRONTIER

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acquiring long-term memory depends on frontal lobe development during the second year after birth.

••• **Iron Deficiency and Neurodegeneration**. Brain cell loss may not be inevitable as we grow older, according to Bruce N. Ames and his colleagues at the University of California, Berkeley. Neuronal death, possibly including neuronal death in Alzheimer's disease, may be due to a treatable condition—deficiency of the iron-carrier molecule called heme.

Heme is best known for enabling hemoglobin to bind to oxygen and giving blood its color, but heme occurs in many cell types. Ames and his team wondered if there might be a link between age-related decline in heme synthesis and neurodegeneration. To find out, they blocked heme synthesis in cultured human and rat neurons. Starved for heme, the cells acquired metabolic characteristics resembling those of Alzheimer's disease neurons. When they tried to make the heme-deficient cells grow, the cells died.

The research, published in the November 4 issue of the *Proceedings of the National Academy of Sciences*, does not prove that lack of heme is the cause of devastating neurodegenerative disorders like Alzheimer's disease. But to the extent heme deficiency may contribute to neurodegeneration, there is reason for optimism: Some causes of heme deficiency, such as iron and vitamin B6 deficiency, are not only treatable, but preventable.

••• **Secretin and Autism.** Neuroimaging shows that a peptide called secretin is active in the amygdala, a brain region associated with social integration and implicated in autism. Deborah Yurgelun-Todd of McLean Hospital in Belmont, Massachusetts, described her finding in an address to the International Meeting of Autism Research in November.

Autistic children are noted for impaired social responses, including lack of eye contact and difficulty reading emotions from facial expressions. These problems are believed connected to reduced amygdala activation. Yurgelun-Todd investigated another autism characteristic, lack of amygdala activation upon viewing a fearful face, by using functional magnetic resonance imaging (fMRI) to study secretin and amygdala activation in 12 healthy men. In a double-blind trial, the men received placebo or secretin before viewing a series of facial expressions. Neither secretin nor placebo activated the amygdala when subjects viewed happy or neutral faces. But fMRI showed that secretin activated the amygdala when subjects viewed fearful faces; placebo had no effect.

The study suggests that secretin influences social behavior. Repligen Corporation, of Waltham, Massachusetts, supplied secretin for Yurgelun-Todd's study and is conducting a phase III clinical trial to see if secretin improves social interaction in young autistic children.

••• **Recurring Depression.** An unusual pattern of brain activity may explain the risk of recurrent depression. The pattern, called a "depression trait marker," by discoverers Mario Liotti of the University of Aberdeen, Scotland, and Helen Mayberg of the Baycrest Centre for Geriatric Care in Toronto, Canada, may help develop therapies to prevent recurring depressions. Even when people recovered from depression continue antidepressant medication, recurrence remains a risk.

The depression trait marker is an unusual activity pattern of two frontal lobe regions, the subgenual cingulate and the medial frontal cortex. The subgenual cingulate is associated with the experience of intense sadness and is a site of action for antidepressants; the medial frontal cortex is associated with emotional processing for reward and positive reinforcement.

The scientists used positron emission tomography (PET) to monitor brain activity of subjects who were asked to recall extremely sad experiences—deaths of loved ones, for example. Liotti and Mayberg compared subgenual cingulate and medial frontal cortex activity of patients actively depressed, patients fully recovered for over a year, and subjects who had never experienced depression. They found that activity patterns of fully recovered patients were closer to patterns of depressed patients than patterns of the never-depressed group. Liotti and Mayberg suggest that the recovered patients' abnormal patterns may explain vulnerability to relapse. Their research is described in the November issue of the *American Journal of Psychiatry.*

••• **Seafood Reduces Dementia Risk.** The list of health benefits of fish and seafood fatty acids grows. An aging study published in the October 26th issue of the *British Medical Journal* suggests that in addition to lowering risk of atherosclerosis, thrombosis and inflammation, fish and seafood fatty acids lower the risk of dementia.

Conducted by Pascale Barberger-Gateau and colleagues at Universite Victor Segalen Bordeaux, France, the study followed the fish, seafood and meat consumption habits of 1,674 residents of southwestern France. Fish and seafood are high in polyunsaturated fatty acids; meat is high in saturated fatty acids. Study participants were without dementia and at least 68 years old.

At the end of seven years the researchers analyzed the data for links between fatty acid consumption and dementia, adjusting for the influence of age, sex, and education. They found no evidence that meat affected risk of dementia. But according to Barberger-Gateau, eating fish and seafood at least once a week significantly lowered the risk of Alzheimer's disease and other dementias.

Education accounted for part of the reduced risk. Higher education was associated with eating fish and seafood at least once a week. The researchers suggest that higher education prompts closer adherence to recommendations to eat fish, or that healthy dietary habits are associated with more education.

—Tom Hollon

(PAIN KILLERS, continued from page 6)

"Hopefully, COX-3 is the [acetaminophen] target that inhibits pain and fever," says Simmons. COX-3, however, may not end the story. Simmons and his group are trying to isolate a second COX enzyme inhibited by acetaminophen; it may be a variant of COX-2. In addition they will investigate the role of PCOX proteins and study the COX-3 enzyme of humans.

It has not gone unnoticed that COX-3 has practical applications. "We are enlisting the aid of the pharmaceutical industry," says Simmons, "to apply this discovery in a way that benefits people suffering from pain and fever." One possibility is a painkiller without the risk of liver toxicity associated with acetaminophen.

Tom Hollon writes about science and medicine in Rockville, MD.

(Aif GENE, continued from page 3)

How It Works

The theory goes like this: Reduced levels of Aif protein set off a domino-like chain of events in the cerebellum. With less Aif protein to protect them, neurons become vulnerable to damage by hydrogen peroxide. As the assault continues, levels of hydrogen peroxide increase in the affected neuron. That stimulates mitogenic signals, which function a bit like "on" and "off" switches when it comes to the cell cycle. The mitogenic signals turn on and the neuron re-enters the cell cycle, duplicating its genetic material. But the neuron dies as it attempts to divide during the final phase of the cycle. Neurodegeneration begins.

The authors note that Harlequin mice do not suffer neurodegeneration in areas outside the cerebellum. This suggests that neurons located elsewhere may be less susceptible to damage by hydrogen peroxide, or have other internal anti-oxidant defenses.

Carlos Pena, a program assistant in the neurodegeneration group at the National Institute of Neurological Disorders and Stroke, calls the study "provocative," and says it suggests that "…cells continuously maintain a balance between pro- and anti-apoptotic factors. Exploring the contribution of Aif in other oxidative stress related models may further understanding … of neuronal degeneration."

Ann MacDonald writes about science and medicine in Wakefield, RI.

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