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# BRAINWORK

The Neuroscience Newsletter

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## Imaging Reveals Alzheimer's Clues both Before and After Disease Develops

*BY CARL SHERMAN*

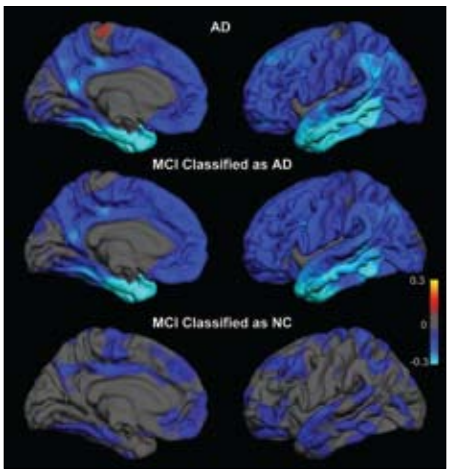
Years of research have failed to generate effective treatments for Alzheimer's disease (AD). Now, scientists are employing diverse neuroimaging and analytical approaches to examine brain structure and function years to decades before symptoms might emerge, in an effort to develop treatments that could stave it off.

"We have all the evidence we need that pathology starts well before clinical symptoms appear," says William Klunk, a professor of psychiatry and neurology at the University of Pittsburgh. "We need to use techniques that can show us that pathology, identify people who are going to develop the disease and treat them before the symptomatic phase, when it may be too late."

To this end, researchers are employing imaging in brains diseased and healthy, old and younger.

### MCI or Early Alzheimer's?

Much of this research has focused on people with mild cognitive impairment (MCI), mental decline including memory loss that is noticeable but not severe enough to interfere with life.




*A study of people with mild cognitive impairment (MCI) found that on average, more than half (middle pair) resembled patients with Alzheimer's (top) in terms of cortical thinning. Blue areas represent thinning relative to healthy controls.*

Research indicates that 10 to 15 percent of people with MCI will develop Alzheimer's disease within a year.

Researchers working to identify which cases of MCI are actually Alzheimer's disease at an early stage have found clues in the loss of brain tissue recorded by magnetic resonance imaging (MRI). Most have focused on the hippocampus, a memory center hit early by Alzheimer's. But one recent study, reported in the April 2009 *Radiology*, found that widespread atrophy—a pattern of tissue loss in temporal, cingulate and orbitofrontal regions—clearly differentiated Alzheimer's patients from healthy

*(Continued on page 2)*

### Inside:



## 'Neuroeducation' Emerges as Insights into the Brain and Learning Grow

*BY AALOK MEHTA*

"Neuroeducation"—an interdisciplinary field that combines neuroscience, psychology and education to create improved teaching methods and curricula—is moving increasingly close to prime time as researchers gain a more sophisticated understanding of how young minds develop and learn, leading education and brain experts say.

Johns Hopkins University's "Learning, Arts, and the Brain" educational summit in Baltimore and the "Learning and the Brain" meeting in Washington, D.C., last month shed new light on links between arts education and general learning, how learning physically alters the brain, and what goes wrong in students with learning disabilities. These findings are beginning to directly influence how classes are organized and taught, speakers at the meetings said.

"The interest among educators in neuroscience is enormous," Ken Kosik, a professor of neuroscience at the University of California, Santa Barbara, said during Learning and the Brain. "We need neuroscientists in schools. Just like we have teaching hospitals, we need teaching schools."

The many signs of neuroeducation's

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**BRAINWORK**

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control subjects.

"This pattern could be specific to AD," says Linda McEvoy, a researcher in the multimodal imaging laboratory at University of California, San Diego, and an author of the paper. "There are other disorders that affect the hippocampus, but with these multiple cortical areas [involved], it's more likely to be Alzheimer's."

When McEvoy examined people with MCI, she found the Alzheimer's pattern of atrophy in more than half. A year later, their mental status had worsened significantly, on average, and the atrophy had progressed, while those with healthy-looking brains had remained stable. Of the 33 participants with MCI who were diagnosed with AD during that year, 26 had had the telltale brain loss pattern when first tested.

Other researchers have analyzed chemicals in cerebrospinal fluid (CSF). In a paper in the April 2009 *Annals of Neurology*, a team led by Leslie Shaw of the University of Pennsylvania reported a distinctive "biomarker signature" in the CSF of people with mild AD, which involved two proteins strongly associated with the disease: beta-amyloid and tau. The researchers found a similar concentration of these proteins in the CSF of 33 of 37 people with MCI who went on to develop AD by one year later.

"This is a very important paper," says Neil Buckholtz, chief of the dementias branch at the National Institute on Aging. The changing concentrations of beta-amyloid fragments and tau protein in CSF, he says, may reflect the actual disease process.

### Imaging a Telltale Protein

Since 2002, amyloid in the living human brain has been visible thanks to a tracer called Pittsburgh compound B (PiB), which binds to amyloid deposits and lights up on positron emission tomography (PET) scans. But because the isotope with which PiB is labeled, carbon-11 (11C), has only a 20-minute half-life, research with the tracer has been limited to institutions with a cyclotron on site.

Amyloid-binding compounds now under development should extend the reach of this technique. These compounds employ fluoride-18 (18F), whose half-life is 110 minutes, allowing use by scientists in any lab within a two-hour radius of a cyclotron, says Dean Wong, professor of psychiatry, neuroscience and environmental health sciences at Johns Hopkins University, who has been testing one of the compounds.

***Scientists ultimately hope to be able to identify the Alzheimer's disease process before any symptoms occur.***

Little research involving these compounds has been published, but ongoing research presented at scientific conferences such as the April 2009 Human Amyloid Imaging Meeting in Seattle have documented their accuracy as amyloid markers. Several are in clinical trials, and FDA approval—likely within a few years, Wong and others believe—could make amyloid detection possible virtually anywhere in the country.

"The widespread availability of 18F amyloid imaging agents would be paradigm-shifting," predicts Michael Weiner, director of the Center for Imaging of Neurodegenerative Diseases at the San Francisco Veterans Affairs Medical Center and principal investigator for the Alzheimer's Disease Neuroimaging Initiative (see box). Beyond Alzheimer's, "it will reveal a lot of new things about role of amyloid in normal aging, late-life depression and the impact on the brain of traumatic injury and diseases like diabetes."

### Spotting Alzheimer's Before It Happens

Scientists ultimately hope to be able to identify the Alzheimer's disease process before any symptoms occur—when the brain is presumably

### ADNI

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a five-year, $60 million project, financed by a public-private partnership, that supports research at sites across the country. ADNI is collecting neuroimaging and cerebrospinal fluid (CSF) biomarker data on 800 people ages 55 to 90 (200 with Alzheimer's disease, 400 with mild cognitive impairment (MCI) and 200 without symptoms), and making it available to researchers, including several whose studies are reported in this article.

undamaged and treatment would have the best chance of success. Research toward this goal has focused on people who carry a gene, apoE4, strongly associated with increased risk. Those with one copy of apoE4 are twice as likely as noncarriers to develop AD; those with two copies are 10 times as likely.

In research reported in the April 21 issue of *Proceedings of the National Academy of Sciences*, Eric Reimer of the University of Arizona and colleagues used PiB PET to examine 28 cognitively normal people with an average age of 64. They found more beta-amyloid, on average, in the brains of those who carried one apoE4 allele than in noncarriers, and even more in those who had two alleles.

Another study, published one week later in the same journal, used functional MRI to examine brain activity in healthy young adults ages 20 to 35. A memory task caused greater hippocampal activation in those who carried at least one copy of the apoE4 allele than those who had none—an indication, the authors say, that the genetic variant affects brain function long before symptoms of neurodegeneration would appear.

How (or even whether) changes in brain function at age 30 are linked to the development of Alzheimer's many years later is unclear; nor is it certain that apoE4 carriers with extra amyloid are the ones who will develop the disease.

"The time line is a long one," says Mony de Leon, director of the Center for Brain Health in the department of psychiatry at New York University. "What will ultimately be needed are studies targeting normal individuals in high-risk groups that take observations [of several types] forward over an extended period."

### On the Cusp of Change

Neuroimaging and biomarker findings have given researchers a coherent, if tentative, map of how Alzheimer's develops, says Ronald Petersen, director of the Alzheimer's Disease Research Center at the Mayo Clinic. Amyloid deposition is detectable decades before clinical symptoms appear. Metabolic decline in the cortex starts to show up on scans as the disease begins to affect brain function. Areas of atrophy on MRI represent further and possibly irreversible deterioration, which grows more pronounced as the disease progresses.

"Different imaging tests might have utility at different points in the clinical spectrum," he says.

On a practical level, the research has produced "a boatload of data, probably enough to establish revision of diagnostic criteria of AD and make [the diagnosis] earlier," says de Leon.

Discussions about how neuroimaging and biomarkers might be integrated into diagnostic protocols have begun, says Buckholtz, of the National Institute on Aging. "If we get agreement within the scientific community, this could happen in the next couple of years."

On the research front, "more and more companies and academic investigators are incorporating imaging and biomarkers in clinical trials," he says. By making it possible to track therapeutic effects more quickly and precisely, "this data may clear the way for developing drugs with disease-modifying effects."

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*(NEUROEDUCATION, continued from page 1)*

growing potential include research programs on the subject that have been established at Harvard University, Johns Hopkins and the University of Texas, Arlington. Other academic departments around the country also now look to recruit faculty in the area.

Meanwhile, the Learning and the Brain conferences, held two or three times a year, continue to attract hundreds of educators interested in learning how neuroscience might affect their profession. In fact, the D.C. meeting marked the series' 10th anniversary with a program revolving around arts and creativity.

***Studies involving school-age children are difficult to design and conduct.***

Many of the speakers there were doing double duty, also having participated in Hopkins' Learning, Arts, and the Brain summit. At that meeting—the first of planned annual gatherings—scientists and educators expressed strong optimism about neuroeducation and called for more studies that could directly impact classroom practices. (Both the summit in Baltimore and the conference in D.C. were sponsored in part by the Dana Foundation.)

But experts also warn that, so far, the transition from laboratory to classroom has been slow, a circumstance likely to continue because studies involving school-age children are difficult to design and conduct. In addition, many education-focused companies have made grandiose assertions about the science behind their commercial products, "burning" the scientists evaluating their potential and increasing the burden for researchers working in the field.

Current research with potential neuroeducation applications follows

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*(NEUROEDUCATION, continued from page 3)*
two disparate but related strands, says Kurt Fischer, a professor of education at Harvard's Graduate School of Education and director of the school's Mind, Brain, and Education Program. Most scientists in the field are working on specific developmental conditions that can cause learning problems, such as dyslexia or autism. Though such research is geared toward specific treatments for these conditions, Fischer says, the findings often have implications for how to help normal students learn as well. On the other hand, insights into how the brain works and develops in general also sometimes offers insights specific to teaching.

He points out recent work that has found that children with dyslexia suffer from two specific problems: trouble analyzing and processing sound and difficulties with rapid naming of objects. Addressing those problems specifically and early in development seems more effective than later, more general treatments.

"Phonological intervention in kids—before they get into trouble in school—appears to prevent dyslexia in kids," Fischer says. "The old finding was that dyslexia was a hole in brain, a deficit in mental capacities. But no, that may not be the case. Dyslexic kids show the brain patterns of people who haven't learned to read well. We all have a range of capabilities, arranged on a normal distribution …. These kids may just be on the low end of the distribution, instead of having some problem in their brains."

As for the alternative approach, he mentions a forthcoming study showing that children from troubled family situations show a drop in abnormally high levels of cortisol, a stress hormone, while in preschool. "This suggests that we might encourage placing children from troubled families in preschool, where they can be in a safer environment," he says.

Another example is work done by Mariale Hardiman, co-organizer of the Learning, Arts, and the Brain summit, when she was simultaneously principal of Baltimore's Roland Park Elementary/Middle School and a graduate student in education at Johns Hopkins. A paper Hardiman wrote eventually blossomed into a book, *Connecting Brain Research with Effective Teaching: The Brain-Targeted Teaching Model*, outlining a six-point strategy for incorporating general neuroscience and psychology principles in schools to foster learning and achievement. The strategies include connecting kids emotionally, creating enriched physical learning environments, designing curricula based on big-picture concepts, teaching for mastery, teaching how to apply knowledge, and evaluating learning outcomes periodically.

*Mariale Hardiman, chair of interdisciplinary studies at the Johns Hopkins School of Education, has developed a strategy for encouraging learning by incorporating neuroscience and psychology principles in schools. Hardiman co-organized the "Learning, Arts, and the Brain" summit May 6 in Baltimore.*

***"We have to conduct that research—on what children learn and remember, on the practical needs of teachers."***

"I applied six elements that I had identified as really important to long-term learning and included what we needed to do as educators," says Hardiman, who applied the program at her school before moving on to become chair of interdisciplinary studies at the Johns Hopkins School of Education. To this day, the model garners interest at both Roland and other schools nationwide, and she continues to lecture and revise her book as new information becomes available.

"We can say that we are learning more and more every day—for example, what influences memory, the importance of sleep," she says. "But we have to conduct that research—on what children learn and remember, on the practical needs of teachers …. That [was] part of the reason for the summit."

At the Hopkins summit and elsewhere, researchers are continuing to incorporate several aspects from Hardiman's model, particularly the importance of emotion. Education in the arts, to which children often respond emotionally, is by extension also an important area of study.

For instance, seven groups of scientists involved in the Dana Arts and Cognition consortium recently showed tight correlations between artistic endeavors and cognitive abilities. New findings by Michael Posner, a professor of psychology at the University of Oregon, suggest that studying the arts may be an effective way to train attention, which in turn can cause general increases in intelligence. And an extended imaging study comparing young children who take up music instruction with those who do not has shown "profound changes" in brain connections, says Gottfried Schlaug, a neurology professor at Beth Israel Deaconess Medical Center and Harvard Medical School.

"Research in the field is now extending into the realm of normal abilities, and that's exciting," says Mary Helen Immordino-Yang, an assistant professor of psychology at the University of Southern California's Brain and Creativity Institute. "There are general principles that you can take from that and apply across fields, and that have implications for way we teach math, reading and more normative pathways."

*Aalok Mehta is a Web journalist for Dana Press. He may be reached at amehta@dana.org.*

# Brain Training May Help Stroke Victims Recover Vision

*BY TOM VALEO*

Researchers are developing a form of visual therapy that may help people blinded or partially blinded by stroke to regain at least some vision.

Krystel R. Huxlin of the University of Rochester Eye Institute hopes to exploit the phenomenon of blindsight, in which people who cannot see display an uncanny ability to guess what is going on in their visual field. A case study published in *Current Biology* last year, for example, described a South African man blinded by a stroke that destroyed both sides of his visual cortex. Yet, when researchers asked him to walk down an obstacle-filled hallway, he walked around them all. (See the video at **www.youtube.com/watch?v=GwGmWqX0MnM**.)

Vision relies on signals from the retina, at the back of each eye, traveling to the first visual area at the back of the brain, known as V1, and on to higher brain regions that detect motion, color and other aspects of vision. People with damage to "downstream" visual areas can still see, but they often display deficits. They may lose color vision, for example, or their ability to recognize familiar faces.

"V1 is kind of the bottleneck," says Huxlin. "By damaging V1 you're starving most of visual system of its primary visual input."

In a paper published in the April 29 *Journal of Neuroscience*, Huxlin and her colleagues described how they tested seven patients who had suffered strokes to one side of the primary visual cortex, causing hemianopia, or vision loss in half of their visual field. The patients fixed their gaze on the middle of a computer screen and tried to determine whether flickering dots displayed within their damaged visual field were drifting right or left. When they guessed correctly a chime sounded.

At first patients succeeded only about 50 percent of the time—no better than guessing—but after practicing for about 30 minutes once or twice a day for 9 to 18 months, some developed the ability to correctly detect and discriminate the direction of motion of the dots 80 to 90 percent of the time.

"Some of the patients are fully aware of changes and improvement in their vision," Huxlin says. "Some develop an actual sense of seeing, but it doesn't reach consciousness in everyone."

### Exercises Strengthen Visual Pathways

Huxlin believes that patients with damage to V1 detect motion thanks to visual signals bound for V1 that are normally diverted to higher visual areas as they travel through the thalamus, a relay station for sensory information. Strengthening those pathways may provide some ability to see.

*Richard Farrands of Fulton, N.Y., undergoes extensive visual testing as part of a study by Krystel R. Huxlin, background, of visual retraining after stroke.*

"There's significant plasticity in the adult brain," Huxlin says. "If you retrain the system … then you can actually improve function over time, and this is accompanied by changes in particular areas of the brain."

Huxlin and her colleagues hope to develop a type of therapy that will improve visual function in people with damage to the visual cortex, and they recently received a patent for the idea of retraining vision with the type of exercises described in her paper.

Some vision experts believe this may lead to the recovery of useful vision in people whose visual cortex has been damaged.

"I think this is a very motivating paper," says Melissa Saenz, a researcher at the California Institute of Technology who studies the relationship between brain activity and consciousness. "It motivates researchers to develop training methods, and it must be very motivating for someone with a significant blind spot to learn that some visual ability is available and can be improved with training."

### Some Remain Skeptical

Others are not so confident.

"I wouldn't say I'm pessimistic; I'm realistic," says Eli Peli, a senior scientist at the Schepens Eye Research Institute and a professor of ophthalmology at Harvard Medical School.

Peli points out that research on blindsight usually involves people like Huxlin's subjects, who suffer from hemianopia due to a stroke on one side of the brain. Peli says they may be able to respond correctly to visual stimuli presented to their blind spot by using vision cues received by the functional part of their visual field. People with extensive damage to V1 on both sides of the brain cannot see because the visual cortex is no longer capable of processing signals, much less sending them on to higher regions of the visual system, Peli adds.

"I will start to believe in blindsight when they show me a few totally blind people who can perform these tasks," he says. He does not believe that the man sidestepping obstacles in his path is demonstrating genuine blindsight.

"That patient simply sees," Peli says. "I work with low-vision patients, and they often say, 'I have no vision in that eye,' but they actually have some vision when tested carefully."

But Huxlin points out that some signals from the retina are diverted to higher visual areas before they reach V1. "These are the pathways we are trying to target and strengthen with our form of visual motion discrimination training," she says.

Also, training decreases the size of the blind area, which means some blindsight is transformed into sight. "Not fully normal sight," Huxlin says, "but conscious and usable sight."

*Tom Valeo is a science and medical writer based in St. Petersburg, Fla. He can be reached at tom.valeo@gmail.com.*

# News
## FROM THE FRONTIER

**••• REM sleep stimulates creativity.** Sleep has often been associated with creative insights, but its role in the process has remained unclear. A new study into the effects of napping suggests that rapid eye movement (REM) sleep may help the brain to create associations between unrelated ideas, enhancing creative problem solving.

Researchers led by Sara Mednick, an assistant professor of psychiatry at the University of California, San Diego, tested 77 people using a creativity task called the Remote Associates Test (RAT). After taking the test, study participants were randomly assigned to take a nap or to rest quietly without sleeping. Those who napped were further divided based on whether they entered REM sleep or not. The three groups showed similar improvements upon retaking the test, indicating that the passage of time alone increased creative problem solving.

Researchers then looked at the effect of "priming" on the results. Study participants completed analogy tests after taking the test in the morning, the answers to which contained words that, unbeknownst to participants, would later appear on an afternoon test. The REM-sleep group scored significantly higher on the afternoon test than the non-REM and quiet-rest groups.

"Only the REM group was able to answer more of the questions with answers from the analogy test," says Mednick. "They were able to take those words and generalize them to a completely different test, which is the creative leap."

The study authors hypothesize that modulation of norepinephrine and acetylcholine that occurs during REM sleep may help incorporate information into associative pathways in the brain. Levels of these two neurotransmitters are higher when we are awake and inhibit recurrent connections in the neocortex.

The study was published in the June 8 early online edition of the *Proceedings of the National Academy of Sciences.*

**••• Active brain and body help maintain cognitive function.** Remaining active—physically, mentally, and socially—can help maintain cognitive function in older adults, according to a study published June 9 in *Neurology.*

Alexandra Fiocco, a postdoctoral fellow at the University of California, San Francisco, and colleagues followed 2,509 well-functioning seniors, age 70 to 79 at recruitment, for eight years. Cognitive function was measured at the beginning of the study and again at three, five and eight years using the Modified Mini-Mental State Examination, which consists of a 100-point questionnaire designed to assess cognitive function.

Researchers identified three distinct groups: those who maintained cognitive function (30 percent), those with minor cognitive decline (53 percent) and those with major cognitive decline (16 percent). The study focused on those who maintained cognitive function to determine the psychosocial, health and biological factors associated with successful cognitive aging.

"Not everyone declines, and there are factors that characterize those who don't decline," says Fiocco. "And those factors are mostly modifiable in nature."

The main factors found to be associated with maintaining cognitive function were: age, being white, having at least a high school education, having a ninth-grade or greater literacy level, weekly exercise, and not smoking. On average, this group also was more socially engaged, living with someone and working or volunteering; had a lower body mass index; and drank alcohol in moderation. The researchers suggest that the association between race and cognitive maintenance seen in the study could be related to education and literacy.

Biological factors that have been previously associated with cognitive function, such as glucose levels in the blood and levels of interleukin-6, a protein involved in the body's inflammatory response, were not statistically significant predictors of cognitive maintenance. Study authors suggest that the impact of the biological factors may have been overpowered by the other factors examined in the study.

**••• Synchronized Brain Waves Focus Attention.** Focusing attention on a visual stimulus causes neurons in the visual cortex to fire in unison. The synchronous firing appears to help tune out distractions and focus our attention. A new study suggests that the prefrontal cortex may initiate this neural activity.

In the study, published May 29 in *Science*, neuroscientist Robert Desimone and colleagues from the McGovern Institute for Brain Research at the Massachusetts Institute of Technology used electrodes to measure the brain activity of two monkeys engaged in an attention task. They discovered synchronous firing of neurons in the frontal eye field area of the prefrontal cortex and in a part of the visual cortex called the V4 ventral stream area.

The response in the frontal eye field occurred significantly earlier than in area V4, suggesting that the activity in the visual cortex was prompted by the activity in the prefrontal cortex. Study researchers also found an increase in high-frequency gamma oscillations between the two, indicating that the two regions were communicating. Such oscillations in the prefrontal cortex have been shown to accompany a variety of cognitive processes, including attention.

The results came as a surprise. "We certainly had reasons to believe the prefrontal cortex played an important role in controlling attention in the visual cortex, but we had no idea it actually synchronized the activity there," Desimone says.

In addition, the exact time it took the two brain areas to communicate was reflected by the time difference in the onset of neural activity in each area—another surprise. The researchers postulate that this may be a general feature of communication across brain regions. If so, the finding could open up new

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# Safer than Marijuana, a Natural Chemical Strengthens Memories

*BY ELIZABETH NORTON LASLEY*

When an experience packs an emotional wallop, it burns itself instantly into the memory. A new study shows that endocannabinoids—the brain's natural equivalents of marijuana—are among the substances that help shore up emotionally charged memories.

"We're not recommending that anyone smoke pot to enhance memory," study author Jim McGaugh of the University of California, Irvine, is quick to point out. "But our finding does provide a clue toward developing new compounds that activate the same system [as marijuana] more safely."

The process takes place in the basolateral complex of the amygdala, a region targeted by a variety of chemical messengers. Stress hormones, for example, activate this region to ensure that we avoid dangerous situations in the future.

Important memories form quickly in the amygdala, and the basolateral complex in particular is a target site for several chemical messengers involved in emotion, stress and memory, such as adrenalin. Other hormones called glucocorticoids, which are important in the body's response to stress, trigger a biochemical chain of events in the basolateral amygdala and contribute indirectly to memory formation.

Recent research suggests that endocannabinoids, too, work through receptors in this part of the brain. These brain chemicals contribute to many functions including movement, appetite, mood, and pain control. Full-scale overstimulation of the endocannabinoid receptors—from smoking marijuana, for example—can cause severe memory problems. But in animal experiments, certain receptors known as CB1 receptors have been shown to influence neuronal firing.

In the March 24 *Proceedings of the National Academy of Sciences*, McGaugh, lead author Patrizia Campolongo and colleagues show that endocannabinoids help solidify emotionally significant memories. In the experiment, rats explored a box with a white-walled section and a darkened area with a mildly electrified floor. When a rat entered the dark chamber, it got a brief shock. After 48 hours the rats visited the box again; the strength of their memories was measured by their reluctance to enter the darkened area.

Rats with CB1 receptors stimulated with an experimental compound took far longer to re-enter the dark section, indicating that they remembered the shock with more aversion. Conversely, rats treated with a compound that blocked the receptors ventured more readily into the dangerous area.

Another phase of the experiment showed that endocannabinoids bring about the well-known reinforcing effects of glucocorticoids. Normally, animals treated with the hormone corticosterone will form stronger memories, but when rats were given corticosterone along with a CB1 blocker, they showed less aversion to the place where they received the shock.

McGaugh says growing evidence suggests that the basolateral amygdala helps mark recently acquired information as important—good news too. Reporting in the May 12 *Proceedings of the National Academy of Sciences*, another group led by Campolongo and McGaugh found that a hormone fat cells secrete in response to feelings of satiety or "fullness" also enhances memory in the basolateral amygdala.

"If you're an animal, remembering where you found something good to eat is as important as remembering where you ran into trouble," McGaugh says.

The finding that glucocorticoids need the help of endocannabinoids is also significant, says Rafael Roesler, who heads the department of pharmacology at the Federal University of Rio Grande do Sul in Brazil and was not involved in the recent research. Because long-term stress can lead to impairments in memory and cognition, he says, the cannabinoid system might be an avenue to explore in treating stress-related disorders.

"Disruption of the cannabinoid system is also implicated in neurodegenerative disorders affecting memory, such as Alzheimer's and Parkinson's disease," Roesler says. "Drugs acting on the CB1 receptor are potential next-generation treatments for these and other disorders."

*Elizabeth Norton Lasley is a science writer in Woodbury, Conn.*

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approaches to treating disorders that affect attention, from attention-deficit/hyperactivity disorder to schizophrenia.

••• **Animal model gives insight into antidepressants.** A new experimental mouse model that uses glucocorticoids, a class of steroid hormone, to induce anxiety and depression in mice has shown that the effects of antidepressants are mediated through both neurogenesis-dependent and -independent mechanisms.

Neuroscientist René Hen and colleagues from Columbia University, along with Denis David and colleagues from the University of Paris-Sud, first tested the model by administering corticosterone to mice and then treating them with different antidepressants, including fluoxetine (Prozac). Treatment with the antidepressants reversed behavioral dysfunctions induced by the hormone, suggesting that corticosterone exposure is a reliable and simple method to model a state of anxiety/depression in mice.

The researchers then investigated potential ways in which fluoxetine worked in the mice, looking in particular at treatment effects on neurogenesis in the hippocampus. Previous research has suggested that hippocampal neurogenesis is linked to antidepressant action.

Corticosterone decreased neurogenesis, but the effect was completely reversed by three weeks of fluoxetine treatment. When neurogenesis was completely inhibited in the hippocampus by irradiation before corticosterone exposure, the positive treatment effect of fluoxetine was blocked in some, but not all, of the behavioral tests. This suggests that some aspects of the treatment response to fluoxetine are dependent on neurogenesis, while others are independent of it.

In the research, published May 28 in *Neuron*, investigators also found that expression of the gene beta-arrestin 2 in the hypothalamus, which was decreased by corticosterone, was normalized by fluoxetine. Mice that were missing this gene had a reduced response to the antidepressant, indicating that beta-arrestin 2 is necessary for fluoxetine to work.

"We don't know at present which of these effects are critical for the therapeutic results of these drugs in humans," says Hen. "Now the question is, if you stimulate just one of the processes—the one we're most interested in is neurogenesis—what is the behavioral impact?"

*"News" was written by Maria Schamis Turner, a freelance writer based in Montreal.*

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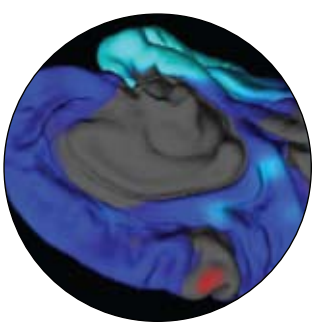
CREDITS: *Page 2: Image courtesy of Linda McEvoy. Reprinted from McEvoy LK, Fennema-Notestine C, Roddey JC, et al. "Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment,"* Radiology *2009; 251:195-205, with permission of the Radiological Society of North America. Page 4: Photo courtesy of Johns Hopkins University. Page 5: Photo by Richard Baker.*

*Imaging and Alzheimer's*



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