Alzheimer's Progression Tracked Prior To Dementia

By Michael C. Purdy
Washington University in St. Louis

Researchers including Anne Fagan, right, and graduate student Courtney Sutphen, have shown that markers in human spinal fluid and other indicators can help track the progression of preclinical Alzheimer's disease.

For years, scientists have attempted to understand how Alzheimer's disease harms the brain before memory loss and dementia are clinically detectable. Most researchers think this preclinical stage, which can last a decade or more before symptoms appear, is the critical phase when the disease might be controlled or stopped, possibly preventing the failure of memory and thinking abilities in the first place.

Important progress in this effort is reported in October in Lancet Neurology. Scientists at the Charles F. and Joanne Knight Alzheimer Disease Research Center at Washington University School of Medicine in St. Louis, working in collaboration with investigators at the University of Maastricht in the Netherlands, helped to validate a proposed new system for identifying and classifying individuals with preclinical Alzheimer's disease.

Their findings indicate that preclinical Alzheimer’s disease can be detected during a person’s life, is common in cognitively normal elderly people and is associated with future mental decline and mortality. According to the scientists, this suggests that preclinical Alzheimer’s disease could be an important target for therapeutic intervention.

A panel of Alzheimer’s experts, convened by the National Institute on Aging in association with the Alzheimer’s Association, proposed the classification system two years ago. It is based on earlier efforts to define and track biomarker changes during preclinical disease.

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According to the Washington University researchers, the new findings offer reason for encouragement, showing, for example, that the system can help predict which cognitively normal individuals will develop symptoms of Alzheimer’s and how rapidly their brain function will decline. But they also highlight additional questions that must be answered before the classification system can be adapted for use in clinical care.

“For new treatments, knowing where individuals are on the path to Alzheimer’s dementia will help us improve the design and assessment of clinical trials,” said senior author Anne Fagan, PhD, research professor of neurology. “There are many steps left before we can apply this system in the clinic, including standardizing how we gather and assess data in individuals, and determining which of our indicators of preclinical disease are the most accurate. But the research data are compelling and very encouraging.”

The classification system divides preclinical Alzheimer’s into three stages:

Stage 1: Levels of amyloid beta, a protein fragment produced by the brain, begin to fall in the spinal fluid. This indicates that the substance is beginning to form plaques in the brain.

Stage 2: Levels of tau protein start to rise in the spinal fluid, indicating that brain cells are beginning to die. Amyloid beta levels are still abnormal and may continue to fall.

Stage 3: In the presence of abnormal amyloid and tau biomarker levels, subtle cognitive changes can be detected by neuropsychological testing. By themselves, these changes cannot establish a clinical diagnosis of dementia.

The researchers applied these criteria to research participants studied from 1998 through 2011 at the Knight Alzheimer Disease Research Center. The center annually collects extensive cognitive, biomarker and other health data on normal and cognitively impaired volunteers for use in Alzheimer’s studies.

The scientists analyzed information on 311 individuals age 65 or older who were cognitively normal when first evaluated. Each participant was evaluated annually at the center at least twice; the participant in this study with the most data had been followed for 15 years.

At the initial testing, 41 percent of the participants had no indicators of Alzheimer’s disease (stage 0); 15 percent were in stage 1 of preclinical disease; 12 percent were in stage 2; and 4 percent were in stage 3. The remaining participants were classified as having cognitive impairments caused by conditions other than Alzheimer’s (23 percent) or did not meet any of the proposed criteria (5 percent).

“A total of 31 percent of our participants had preclinical disease,” said Fagan. “This percentage matches findings from autopsy studies of the brains of older individuals, which have shown that about 30 percent of people who were cognitively normal had preclinical Alzheimer’s pathology in their brain.”

Scientists believe the rate of cognitive decline increases as people move through the stages of preclinical Alzheimer’s. The new data support this idea. Five years after their initial evaluation, 11 percent of the stage 1 group, 26 percent of the stage 2 group, and 52 percent of the stage 3 group had been diagnosed with symptomatic Alzheimer’s.

Individuals with preclinical Alzheimer’s disease were six times more likely to die over the next decade than older adults without preclinical Alzheimer’s disease, but researchers don’t know why.

“Risk factors for Alzheimer’s disease might also be associated with other life-threatening illnesses,” Fagan said. “It’s also possible that the presence of Alzheimer’s hampers the diagnosis and treatment of other conditions or contributes to health problems elsewhere in the body. We don’t have enough data yet to say, but it’s an issue we’re continuing to investigate.”

This research was supported by funding from the National Institute on Aging of the National Institutes of Health (NIH) (P01-AG003991, P50-AG05681, P01-AG02676), Internationale Stichting Alzheimer Onderzoek, the Center for Translational Molecular Medicine, Project Learn, the EU/EFPIA Innovative Medicines Initiative Joint Undertaking, and the Charles F. and Joanne Knight Alzheimer’s Disease Research Initiative.
Study Confirms That Rare Mutations Increase Risk Of Late-Onset Alzheimer’s Disease

MGH researchers have identified and validated two rare gene mutations that appear to cause the common form of Alzheimer’s disease (AD) that strikes after the age of 60. The two mutations occur in a gene called ADAM10, which now becomes the second pathologically-confirmed gene for late-onset AD and the fifth AD gene overall.

By Sue McGreevey
Massachusetts General Hospital Public Affairs Office

Finding how impaired activity of ADAM10 enzyme increases neurodegeneration suggests therapeutic applications

Massachusetts General Hospital (MGH) researchers have identified and validated two rare gene mutations that appear to cause the common form of Alzheimer's disease (AD) that strikes after the age of 60. The two mutations occur in a gene called ADAM10 – coding for an enzyme involved in processing the amyloid precursor protein – which now becomes the second pathologically-confirmed gene for late-onset AD and the fifth AD gene overall.

In their report, which will appear in the October 16 issue of Neuron and has been released online, the investigators from the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND) describe how the two mutations in ADAM10 increase generation and accumulation of the toxic amyloid beta (A-beta) protein in the brains of a mouse model of AD. The mutations also reduce generation of new neural cells in hippocampus, a part of the brain essential to learning and memory.

"This is the first report to document, in animal models, new pathogenic gene mutations for AD since the reports of the original four genes in the 1990s," says Rudolph Tanzi, PhD, director of the Genetics and Aging Research Unit at MGH-MIND and senior author of the Neuron paper. "What we found regarding the many effects of these two rare mutations in ADAM10 strongly suggests that diminished activity of this enzyme can cause AD, and these findings support ADAM10 as a promising therapeutic target for both treatment and prevention."

The process leading to the generation of A-beta – which accumulates in characteristic plaques in the brains of AD patients – begins when the amyloid precursor protein (APP) is cut into smaller proteins by enzymes called secretases. A-beta results if APP is first cut into two segments by an enzyme called beta-secretase, and one of those segments is further cut by a gamma-secretase enzyme to release the toxic A-beta fragment. However, processing of APP by an alpha-secretase enzyme – one of which is ADAM10 – cuts right through the A-beta region in APP. So instead of generating the toxic A-beta fragment, cleavage with alpha-secretase produces a protein fragment that has been reported to protect and stimulate the generation of neurons in brain.

An earlier study by Tanzi's team reported finding that either of two mutations in ADAM10 increased the risk of AD in seven families with the late-onset form of the disease. Since ADAM10 was already known to be important to alpha-secretase processing of APP, along with having a role in early brain development, the researchers set out to investigate how the observed mutations might lead to the pattern of neurodegeneration characteristic of AD.

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Study Confirms That Rare Mutations Increase Risk Of Late-Onset Alzheimer’s Disease continued...

Experiments using several strains of transgenic mice – including lines that express both one of the ADAM10 mutations and an APP mutation that leads to AD-like pathology – revealed the following:

- AD-associated mutations in ADAM10 reduced the release from neurons in the animals' brains of the beneficial protein produced by alpha-secretase processing of APP,
- Reduced ADAM10 activity caused by the mutations increased the generation of A-beta and its accumulation in plaques, along with producing other AD-associated neurodegenerative signs,
- Reduced ADAM10 activity also impaired the generation of new neurons in the hippocampus, one of the areas of the brain most vulnerable to neurodegeneration in AD,
- The AD-associated mutations produce these effects by impairing the correct folding of ADAM10 and interfering with its normal functions.

Jaehong Suh, PhD, of the MGH-MIND Genetics and Aging Research Unit, lead author of the Neuron article, says, "Our current study shows that reducing ADAM10 activity by these AD-associated mutations delivers a 'one-two punch' to the brain – one, decreasing neuroprotective alpha-secretase cleavage products and two, increasing neurotoxic A-beta protein accumulation. Thus, we believe that increasing ADAM10 activity might help to alleviate both genetic and environmental AD risk factors that increase the toxic beta-secretase processing of APP. We're planning to develop optimal ways to increase ADAM10 activity in brain and to further investigate the molecular structure and regulatory mechanism of the ADAM10 enzyme." Suh is an instructor in Neurology, and Tanzi is the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School.

Additional co-authors of the report are Se Hoon Choi, PhD, Donna Romano, Moira Gannon, Andrea Lesinski, and Doo Yeon Kim, PhD, all of the MGH-MIND Genetics and Aging Research Unit. The study was supported by the Cure Alzheimer's Fund and grants from the National Institute on Aging, the National Institute for Mental Health and the American Health Assistance Foundation.

NIH funding boosts new Alzheimer’s research on prevention, novel drug targets

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Alzheimer’s: Newly Identified Protein Pathology Impairs RNA Splicing

By Quinn Eastman
Emory Health Sciences

In Alzheimer's disease, all that tangles is not tau. A protein pathology identified by Emory investigators could have major implications for understanding the disease mechanism.

Tangled string-like structures involving aggregated U1 snRNP splicing proteins can be seen in this image. The darker round structures are cell nuclei.

Move over, plaques and tangles.

Researchers at Emory University School of Medicine's Alzheimer's Disease Research Center have identified a previously unrecognized type of pathology in the brains of patients with Alzheimer's disease.

These tangle-like structures appear at early stages of Alzheimer's and are not found in other neurodegenerative diseases such as Parkinson's disease.

What makes these tangles distinct is that they sequester proteins involved in RNA splicing, the process by which instructional messages from genes are cut and pasted together. The researchers show that the appearance of these tangles is linked to widespread changes in RNA splicing in Alzheimer's brains compared to healthy brains.

The finding could change scientists' understanding of how the disease develops and progresses, by explaining how genes that have been linked to Alzheimer's contribute their effects, and could lead to new biomarkers, diagnostic approaches, and therapies.

The results are published in the Proceedings of the National Academy of Sciences, Early Edition.

"We were very surprised to find alterations in proteins that are responsible for RNA splicing in Alzheimer's, which could have major implications for the disease mechanism," says Allan Levey, MD, PhD, chair of neurology at Emory University School of Medicine and director of the Emory ADRC.

"This is a brand new arena," says James Lah, MD, PhD, associate professor of neurology at Emory University School of Medicine and director of the Cognitive Neurology program. "Many Alzheimer's investigators have looked at how the disease affects alternative splicing of individual genes. Our results suggest a global distortion of RNA processing is taking place."

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This research was led by Drs. Levey, Lah, and Junmin Peng, PhD, who was previously associate professor of genetics at Emory and is now a faculty member at St Jude Children's Research Hospital. They were aided by collaborators at University of Kentucky, Rush University, and University of Washington as well as colleagues at Emory.

Accumulations of plaques and tangles in the brains of patients with Alzheimer's disease were first observed more than a century ago. Investigating the proteins in these pathological structures has been central to the study of the disease.

Most experimental treatments for Alzheimer's have aimed at curbing beta-amyloid, an apparently toxic protein fragment that is the dominant component of amyloid plaques. Other approaches target the abnormal accumulation of the protein tau in neurofibrillary tangles. Yet the development of Alzheimer's is not solely explained by amyloid and tau pathologies, Lah says.

"Two individuals may harbor similar amounts of amyloid plaques and tau tangles in their brains, but one may be completely healthy while the other may have severe memory loss and dementia," he says.

These discrepancies led Emory investigators to take a "back to basics" proteomics approach, cataloguing the proteins that make up insoluble deposits in the brains of Alzheimer's patients.

"The Alzheimer's field has been very focused on amyloid and tau, and we wanted to use today's proteomics technologies to take a comprehensive, unbiased approach," Levey says.

The team identified 36 proteins that were much more abundant in the detergent-resistant deposits in brain tissue from Alzheimer's patients. This list included the usual suspects: tau and beta-amyloid. Also on the list were several "U1 snRNP" proteins, which are involved in RNA splicing. These U1 proteins are normally seen in the nucleus of normal cells, but in Alzheimer's brains they accumulated in tangle-like structures. Accumulation of insoluble U1 protein was seen in samples from patients with mild cognitive impairment (MCI), a precursor stage to Alzheimer's, but the U1 pathology was not seen in any other brain diseases that were examined.

According to Chad Hales, MD, PhD, one of the study's lead authors, "U1 aggregation is occurring early in the disease, and U1 tangles can be seen independently of tau pathology. In some cases, we see accumulation of insoluble U1 proteins before the appearance of insoluble tau, suggesting that it is a very early event."

For most genes, after RNA is read out from the DNA (transcription), some of the RNA must be spliced out. When brain cells accumulate clumps of U1 proteins, that could mean the process of splicing is impaired. To test this, the Emory team examined RNA from the brains of Alzheimer's patients. In comparison to RNA from healthy brains, more of the RNA from Alzheimer's brain samples was unspliced.

The finding could explain how many genes that have been linked to Alzheimer's are having their effects. In cells, U1 snRNP plays multiple roles in processing RNA including the process of alternative splicing, by which one gene can make instructions for two or more proteins.

"U1 dysfunction might produce changes in RNA processing affecting many genes or specific changes affecting a few key genes that are important in Alzheimer's," Lah says. "Understanding the disruption of such a fundamental process will almost certainly identify new ways to understand Alzheimer's and new approaches to treating patients."

The research was supported by the National Institute on Aging (P50AG025688, P50AG005136), the National Institute of Neurological Disorders and Stroke (P30NS055077) and the Consortium for Frontotemporal Dementia Research.
Alzheimer's disease affects more than 26 million people worldwide. It is predicted to skyrocket as boomers age—nearly 106 million people are projected to have the disease by 2050. Fortunately, scientists are making progress towards therapies. A collaboration among several research entities, including the Salk Institute and the Sanford-Burnham Medical Research Institute, has defined a key mechanism behind the disease's progress, giving hope that a newly modified Alzheimer's drug will be effective.

In a previous study in 2009, Stephen F. Heinemann, a professor in Salk's Molecular Neurobiology Laboratory, found that a nicotinic receptor called Alpha7 may help trigger Alzheimer's disease. "Previous studies exposed a possible interaction between Alpha-7 nicotinic receptors (α7Rs) with amyloid beta, the toxic protein found in the disease's hallmark plaques," says Gustavo Dziewczapolski, a staff researcher in Heinemann's lab. "We showed for the first time, in vivo, that the binding of this two proteins, α7Rs and amyloid beta, provoke detrimental effects in mice similar to the symptoms observed in Alzheimer's disease."

Their experiments, published in The Journal of Neuroscience, with Dziewczapolski as first author, consisted in testing Alzheimer's disease-induced mice with and without the gene for α7Rs. They found that while both types of mice developed plaques, only the ones with α7Rs showed the impairments associated with Alzheimer's.

But that still left a key question: Why was the pairing deleterious?

In a recent paper in the Proceedings of the National Academy of Sciences, Heinemann and Dziewczapolski here at Salk with Juan Piña-Crespo, Sara Sanz-Blasco, Stuart A. Lipton of the Sanford-Burnham Medical Research Institute and their collaborators announced they had found the answer in unexpected interactions among neurons and other brain cells.

Neurons communicate by sending electrical and chemical signals to each other across gaps called synapses. The biochemical mix at synapses resembles a major airport on a holiday weekend—it's crowded, complicated and exquisitely sensitive to increases and decreases in traffic. One of these signaling chemicals is glutamate, an excitatory neurotransmitter, which is essential for learning and storing memories. In the right balance, glutamate is part of the normal functioning of neuronal synapses. But neurons are not the only cells in the brain capable of releasing glutamate. Astrocytes, once thought to be merely cellular glue between neurons, also release this neurotransmitter.

In this new understanding of Alzheimer's disease, there is a cellular signaling cascade, in which amyloid beta stimulates the alpha 7 nicotine receptors, which trigger astrocytes to release additional glutamate into the synapse, overwhelming it with excitatory ("go") signals.

This release in turn activates another set of receptors outside of the synapse, called extrasynaptic-N-methyl-D-aspartate receptors (eNMDARs) that depress synaptic activity. Unfortunately, the eNMDARs seem to overly depress synaptic function, leading to the memory loss and confusion associated with Alzheimer's.

Now that the team has finally determined the steps in this destructive pathway, the good news is that a drug developed by the Lipton's Laboratory called NitroMemantine, a modification of the earlier Alzheimer's medication, Memantine, may block the entry of eNMDARs into the cascade.
"Thanks to the joint effort of our colleagues and collaborators, we seem to finally have a clear mechanistic link between a key target of the amyloid beta in the brain, the Alpha7 nicotinic receptors, triggering downstream harmful effects associated with the initiation and progression of Alzheimer’s disease," says Dziewczapolski. "This is a clear demonstration of the value of basic biomedical research. Drug development cannot proceed without knowing the details of interactions at the molecular and cellular level. Our research revealed two potential targets, α7Rs and eNMDARs, for future disease-modifying therapeutics, which Dr. Heinemann and I both hope will translate in a better treatment for Alzheimer’s patients."

Other researchers on the study were Maria Talantova, Xiaofei Zhang, Peng Xia, Mohd Waseem Akhtar, Shu-ichi Okamoto, Tomohiro Nakamura, Gang Cao, Alexander E. Pratt, Yeon-Joo Kang, Shichun Tu, Elena Molokanova, Gary Tong, Scott R. McKercher, James Parker, Emily A. Holland, Traci Fang-Newmeyer, Dongxian Zhang, Nobuki Nakanishi, H.-S. Vincent Chen and Rajesh Ambasudhan of the Sanford-Burnham Medical Research Institute; Samuel Andrew Hires of the Howard Hughes Medical Research Institute; Herman Wolosker and Hagit Sason of the Technion-Israel Institute of Technology in Israel; Yuqiang Wang of Jinan University in China and Panorama Research Institute in California; Loren H. Parsons, David G. Stouffer, Matthew W. Buczynski, Amanda Roberts, James P. Solomon, Evan T. Powers and Jeffery W. Kelly of the Scripps Research Institute; Sarah Michael and Eliezer Masliah of UCSD School of Medicine.

This work was supported by the National Institutes of Health, Department of Defense, National Institute of Neurological Disorders and Stroke, American Heart Association and the Ministry of Education and Science of Spain.
Alzheimer’s disease has proven to be a difficult enemy to defeat. After all, aging is the No. 1 risk factor for the disorder, and there’s no stopping that.

Most researchers believe the disease is caused by one of two proteins, one called tau, the other beta-amyloid. As we age, most scientists say, these proteins either disrupt signaling between neurons or simply kill them.

Now, a new UCLA study suggests a third possible cause: iron accumulation.

Dr. George Bartzokis, a professor of psychiatry at the Semel Institute for Neuroscience and Human Behavior at UCLA and senior author of the study, and his colleagues looked at two areas of the brain in patients with Alzheimer’s. They compared the hippocampus, which is known to be damaged early in the disease, and the thalamus, an area that is generally not affected until the late stages. Using sophisticated brain-imaging techniques, they found that iron is increased in the hippocampus and is associated with tissue damage in that area. But increased iron was not found in the thalamus.

The research appears in the August edition of the Journal of Alzheimer’s Disease.

While most Alzheimer’s researchers focus on the buildup of tau or beta-amyloid that results in the signature plaques associated with the disease, Bartzokis has long argued that the breakdown begins much further "upstream." The destruction of myelin, the fatty tissue that coats nerve fibers in the brain, he says, disrupts communication between neurons and promotes the buildup of the plaques. These amyloid plaques in turn destroy more and more myelin, disrupting brain signaling and leading to cell death and the classic clinical signs of Alzheimer’s.

Myelin is produced by cells called oligodendrocytes. These cells, along with myelin, have the highest levels of iron of any cells in the brain, Bartzokis says, and circumstantial evidence has long supported the possibility that brain iron levels might be a risk factor for age-related diseases like Alzheimer’s. Although iron is essential for cell function, too much of it can promote oxidative damage, to which the brain is especially vulnerable.

In the current study, Bartzokis and his colleagues tested their hypothesis that elevated tissue iron caused the tissue breakdown associated with Alzheimer’s disease. They targeted the vulnerable hippocampus, a key area of the brain involved in the formation of memories, and compared it to the thalamus, which is relatively spared by Alzheimer’s until the very late stages of disease.

The researchers used an MRI technique that can measure the amount of brain iron in ferritin, a protein that stores iron, in 31 patients with Alzheimer’s and 68 healthy control subjects.

In the presence of diseases like Alzheimer’s, as the structure of cells breaks down, the amount of water increases in the brain, which can mask the detection of iron, according to Bartzokis.

"It is difficult to measure iron in tissue when the tissue is already damaged," he said. "But the MRI technology we used in this study allowed us to determine that the increase in iron is occurring together with the tissue damage. We found that the amount of iron is increased in the hippocampus and is associated with tissue damage in patients with Alzheimer’s but not in the healthy older individuals — or in the thalamus. So the results suggest that iron accumulation may indeed contribute to the cause of Alzheimer’s disease."

But it’s not all bad news from this study, Bartzokis noted.
"The accumulation of iron in the brain may be influenced by modifying environmental factors, such as how much red meat and iron dietary supplements we consume and, in women, having hysterectomies before menopause," he said.

In addition, he noted, medications that chelate and remove iron from tissue are being developed by several pharmaceutical companies as treatments for the disorder. This MRI technology may allow doctors to determine who is most in need of such treatments.

Other authors of the study included Erika Raven, Po Lu, Todd Tishler and Panthea Heydari. Funding was provided by National Institutes of Health grants MH 0266029, AG027342 and T32 NS041231 and by the RCS Alzheimer’s Foundation.

Alzheimer’s Missing Link Found: Is A Promising Target For New Drugs

By Bill Hathaway
Yale School of Medicine

Yale School of Medicine researchers have discovered a protein that is the missing link in the complicated chain of events that lead to Alzheimer’s disease, they report in the Sept. 4 issue of the journal Neuron. Researchers also found that blocking the protein with an existing drug can restore memory in mice with brain damage that mimics the disease.

“What is very exciting is that of all the links in this molecular chain, this is the protein that may be most easily targeted by drugs,” said Stephen Strittmatter, the Vincent Coates Professor of Neurology and senior author of the study. “This gives us strong hope that we can find a drug that will work to lessen the burden of Alzheimer’s.”

Scientists have already provided a partial molecular map of how Alzheimer’s disease destroys brain cells. In earlier work, Strittmatter’s lab showed that the amyloid-beta peptides, which are a hallmark of Alzheimer’s, couple with prion proteins on the surface of neurons. By an unknown process, the coupling activates a molecular messenger within the cell called Fyn.

In the Neuron paper, the Yale team reveals the missing link in the chain, a protein within the cell membrane called metabotropic glutamate receptor 5 or mGluR5. When the protein is blocked by a drug similar to one being developed for Fragile X syndrome, the deficits in memory, learning, and synapse density were restored in a mouse model of Alzheimer’s.

Strittmatter stressed that new drugs may have to be designed to precisely target the amyloid-prion disruption of mGluR5 in human cases of Alzheimer’s and said his lab is exploring new ways to achieve this.

Other Yale authors are Ji Won Um, Adam C. Kaufman, Mikhail Kostylev, Jacqueline K. Heiss, Massimiliano Stagi, Hideyuki Takahashi, Meghan E. Kerrisk, Alexander Vortmeyer, Thomas Wisniewski, Anthony J. Koskne, Erik C. Gunther and Haakon B. Nygaard.

The research was funded by the National Institutes of Health.
The researchers have identified a protein—RbAp48—that, when increased in aged wild-type mice, improves memory back to that of young wild-type mice. In the image, yellow shows the increased RbAp48 in the dentate gyrus. Image credit: Elias Pavlopoulos, PhD/Columbia University Medical Center

“Our study provides compelling evidence that age-related memory loss is a syndrome in its own right, apart from Alzheimer’s. In addition to the implications for the study, diagnosis, and treatment of memory disorders, these results have public health consequences,” said Dr. Kandel, who is University Professor & Kavli Professor of Brain Science, co-director of Columbia’s Mortimer B. Zuckerman Mind Brain Behavior Institute, director of the Kavli Institute for Brain Science, and senior investigator, Howard Hughes Medical Institute, at CUMC. Dr. Kandel received a share of the 2000 Nobel Prize in Physiology or Medicine for his discoveries related to the molecular basis of memory.

The hippocampus, a brain region that consists of several interconnected subregions, each with a distinct neuron population, plays a vital role in memory. Studies have shown that Alzheimer’s disease hampers memory by first acting on the entorhinal cortex (EC), a brain region that provides the major input pathways to the hippocampus. It was initially thought that age-related memory loss is an early manifestation of Alzheimer’s, but mounting evidence suggests that it is a distinct process that affects the dentate gyrus (DG), a subregion of the hippocampus that receives direct input from the EC.

“Until now, however, no one has been able to identify specific molecular defects involved in age-related memory loss in humans,” said co-senior author Scott A. Small, MD, the Boris and Rose Katz Professor of Neurology and director of the Alzheimer’s Research Center at CUMC.
A Major Cause Of Age-Related Memory Loss Identified continued...

The current study was designed to look for more direct evidence that age-related memory loss differs from Alzheimer’s disease. The researchers began by performing microarray (gene expression) analyses of postmortem brain cells from the DG of eight people, ages 33 to 88, all of whom were free of brain disease. The team also analyzed cells from their EC, which served as controls since that brain structure is unaffected by aging. The analyses identified 17 candidate genes that might be related to aging in the DG. The most significant changes occurred in a gene called RbAp48, whose expression declined steadily with aging across the study subjects.

To determine whether RbAp48 plays an active role in age-related memory loss, the researchers turned to mouse studies. “The first question was whether RbAp48 is downregulated in aged mice,” said lead author Elias Pavlopoulos, PhD, associate research scientist in neuroscience at CUMC. “And indeed, that turned out to be the case—there was a reduction of RbAp48 protein in the DG.”

When the researchers genetically inhibited RbAp48 in the brains of healthy young mice, they found the same memory loss as in aged mice, as measured by novel object recognition and water maze memory tests. When RbAp48 inhibition was turned off, the mice’s memory returned to normal.

The researchers also did functional MRI (fMRI) studies of the mice with inhibited RbAp48 and found a selective effect in the DG, similar to that seen in fMRI studies of aged mice, monkeys, and humans. This effect of RbAp48 inhibition on the DG was accompanied by defects in molecular mechanisms similar to those found in aged mice. The fMRI profile and mechanistic defects of the mice with inhibited RbAp48 returned to normal when the inhibition was turned off.

In another experiment, the researchers used viral gene transfer and increased RbAp48 expression in the DG of aged mice. “We were astonished that not only did this improve the mice’s performance on the memory tests, but their performance was comparable to that of young mice,” said Dr. Pavlopoulos.

“The fact that we were able to reverse age-related memory loss in mice is very encouraging,” said Dr. Kandel. “Of course, it’s possible that other changes in the DG contribute to this form of memory loss. But at the very least, it shows that this protein is a major factor, and it speaks to the fact that age-related memory loss is due to a functional change in neurons of some sort. Unlike with Alzheimer’s, there is no significant loss of neurons.”

Finally, the study data suggest that RbAp48 protein mediates its effects, at least in part, through the PKA-CREB1-CBP pathway, which the team had found in earlier studies to be important for age-related memory loss in the mouse. According to the researchers, RbAp48 and the PKA-CREB1-CBP pathway are valid targets for therapeutic intervention. Agents that enhance this pathway have already been shown to improve age-related hippocampal dysfunction in rodents.

“Whether these compounds will work in humans is not known,” said Dr. Small. “But the broader point is that to develop effective interventions, you first have to find the right target. Now we have a good target, and with the mouse we’ve developed, we have a way to screen therapies that might be effective, be they pharmaceuticals, nutraceuticals, or physical and cognitive exercises.”

“There’s been a lot of handwringing over the failures of drug trials based on findings from mouse models of Alzheimer’s,” Dr. Small said. “But this is different. Alzheimer’s does not occur naturally in the mouse. Here, we’ve caused age-related memory loss in the mouse, and we’ve shown it to be relevant to human aging.”

The paper is titled, “A Molecular Mechanism for Age-Related Memory Loss: The Histone Binding Protein RbAp48.” The other contributors are Sidonie Jones, Stylianos Kosmidis, Maggie Close, Carla Kim, and Olga Kovalerchik, all at CUMC.

The study was supported by grants from the Howard Hughes Medical Institute, the James S. McDonnell Foundation, the Broitman Foundation, the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc., the McKnight Brain Research Foundation, and the National Institute on Aging (AG034618).
Scientists at UC San Francisco are reporting that they have found a way to reverse some of the negative effects of aging on the brain, using a video game designed to improve cognitive control.

The findings, published on Sept. 5 in *Nature*, show that a specially designed 3-D video game can improve cognitive performance in healthy older adults, they said. The researchers said the study provides a measure of scientific support to the burgeoning field of brain fitness, which has been criticized for lacking evidence that such training can induce lasting and meaningful changes.

The ability to multitask – or switch rapidly between tasks – declines rapidly over the adult lifespan, something that researchers refer to as “multitasking cost.” But after just one month of training on the NeuroRacer game, researchers found significant improvement in study participants.

In the game, which was developed by the UCSF researchers, participants race a car around a winding track while a variety of road signs pop up. Drivers are instructed to keep an eye out for a specific type of sign, while ignoring all the rest, and to press a button whenever that particular sign appears.

The need to switch rapidly from driving to responding to the signs – i.e. multitasking – generates interference in the brain that undermines performance. The researchers found that this interference increases dramatically across the adult lifespan.

But after receiving just 12 hours of training on the game, spread over a month, the 60- to 85-year-old study participants improved their performance until it surpassed that of 20-somethings who played the game for the first time.
The training also improved the participants’ performance in two other important cognitive areas: working memory and sustained attention. And participants maintained their skills at the video game six months after the training had ended.

“The finding is a powerful example of how plastic the older brain is,” said Adam Gazzaley, MD, PhD, UCSF associate professor of neurology, physiology and psychiatry and director of the Neuroscience Imaging Center. Gazzaley co-founded the company, Akili Interactive Labs, which is developing the next generation of the video game.

Gazzaley, who has made a career out of studying how distraction affects cognitive performance, said his game, NeuroRacer, does more than any ordinary game – be it bridge, a crossword puzzle, or an off-the-shelf video game – to condition the brain. Like a good teacher, he said, NeuroRacer undermines people’s natural tendency to go on automatic pilot once they’ve mastered a skill, and pushes them further than they think they can go.

“Normally, when you get better at something, it gets easier,” he said. But with this game, “when you get better, it gets harder.”

Adam Gazzaley, MD, PhD

Brain Training Reverses Age-Related Decline

Evidence that the adult brain is capable of learning has been accumulating for more than a dozen years. A study of London taxi drivers, for example, found that their brains had changed as they learned to navigate the city’s notoriously complicated streets.

Nevertheless, Gazzaley said the brain’s function often erodes steadily over time in many areas, with some exceptions, like wisdom.

Given this, Gazzaley said it’s encouraging that even a small amount of brain training can reverse some of the age-related decline.

Gazzaley’s group found evidence of a possible brain mechanism that may explain the improvements he saw in his older subjects, and why these gains transferred to other cognitive areas. Electroencephalograph (EEG) recordings point to changes in a neural network involved in cognitive control, which is necessary to pursue goals.

The scientists measured midline frontal theta – or low frequency oscillations – in the prefrontal cortex, as well as the coherence in these waves between frontal and posterior regions of the brain. As the older “drivers” became more adept at the multitasking challenges of NeuroRacer, their brains modulated this key neural network and its activity began to resemble that of young adults.
Both of these measures – midline frontal theta and theta coherence – are well established neural markers of cognitive control that have been associated with many of the processes that enable people to pursue their goals.

"We see this as evidence that the training may have improved our study participants’ ability to stay in an engaged, active state for a longer period of time," said Joaquin A. Anguera, the paper’s first author and a post-doctoral fellow in Gazzaley’s lab.

Indeed, the researchers found that the training-induced changes in this neural network predicted how well participants would do on a different test, called the Test of Variables of Attention (TOVA), which measures sustained attention.

“The amount that midline frontal theta went up was related to something that was untrained, this other measure, the TOVA,” Anguera said. “It implies there’s something that changed that was common to the training and to the task we tested afterwards.”
Wider Applications for Cognitive Control

Gazzaley said these findings point toward a common neural basis of cognitive control that is enhanced by the challenging and high-interference conditions of the video game, and this might explain how racing a car in 3-D could improve something as seemingly unrelated as memory.

This graphic shows increased brain activity for older adults who underwent multi-tasking training (bottom left) versus those who only did single-task training (bottom center) or no training at all (bottom right). Credit: Joaquín A. Anguera/UCSF

If the finding holds, it could have wide application. Other brain disorders like ADHD, depression and dementia are also associated with deficits in cognitive control.

“Follow up studies using functional Magnetic Resonance Imaging and transcranial electrical stimulation are still needed to better understand exactly how this network is involved in the performance changes,” Gazzaley said.

Other authors of the article, “Video game training enhances cognitive control in older adults,” include Jacqueline Boccanfuso, Jean Rintoul, Omar Al-Hashimi, Farshid Faraji, Jacki Janowich, Erwin Kong, Yudy Larraburo, Cammie Rolle and Eric Johnston.

Gazzaley is co-founder and chief science advisor of Akili Interactive Labs, which is developing cognitive video game software as diagnostic and therapeutic tools, and has a patent pending on a game-based cognitive intervention he developed from the research presented in the paper.

The study was funded under Health Games Research, a program of the Robert Wood Johnson Foundation and by the National Institute on Aging. Anguera is also supported by a UCSF Institutional Research and Career Development Award.

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Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

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