

Alzheimer's Disease Information Network

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Alzheimer's Disease Cooperative Study Group Will Undertake Four Clinical Trials Over Five Years

With new research funding from the National Institutes of Health, the nation's premier Alzheimer's disease study network will undertake four major studies aimed at finding new treatments for the disease. The award supports the latest projects of the Alzheimer's Disease Cooperative Study (ADCS), a national consortium of academic medical centers and clinics set up by NIH in 1991 to collaborate on the development of Alzheimer's treatments and diagnostic tools. In this round of studies, the ADCS will test drug and exercise interventions in people in the early stages of the disease, examine a medication to reduce agitation in people with Alzheimer's dementia, and test a cutting-edge approach to speed testing of drugs in clinical trials.

The National Institute on Aging (NIA), the lead institute within NIH for Alzheimer's research, announced the award on Jan. 14, 2013. The ADCS will receive \$11 million in fiscal year 2013, and the effort could total as much as \$55 million over the five years of the project. The consortium, coordinated by the University of California, San Diego and led by Paul Aisen, M.D., is made up of more than 70 research sites in the United States and Canada with a focus on advancing studies of interventions that might not otherwise be tested by industry.

"The ADCS is a key initiative in the federal program to discover, develop and test new Alzheimer's treatments and diagnostic tools. Over the years, it has proved invaluable in advancing our understanding about the disease and how to conduct research in this challenging area," said NIA Director Richard J. Hodes, M.D. "I am particularly excited that this round of studies will use what we have learned by testing interventions pre-symptomatically, as early as we can in the development of the disease, where we now think the best hope lies for keeping Alzheimer's at bay."

The ADCS and this latest round of studies, Hodes noted, are critical to accomplishing the research goals set forth in the National Plan to Address Alzheimer's Disease announced by Health and Human Services Secretary Kathleen Sebelius in May 2012. The plan was developed under the National Alzheimer's Project Act, which calls for a coordinated and concentrated effort in research, care and services for Alzheimer's and related dementias. Its primary research goal is to prevent and effectively treat Alzheimer's disease by 2025.

Continued on next page...

CTAD 2013

6th Conference

Clinical Trials in
Alzheimer's Disease

November
14-16, 2013
San Diego, CA

<http://ctad.fr/>

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This newsletter is prepared monthly by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. Content is intended to educate the public about AD research endeavors and other AD issues.

Questions or
comments?

Please email:
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Alzheimer's Disease Cooperative Study Group Will Undertake Four Clinical Trials Over Five Years continued...

The four studies made possible under the new award are:

- The A4 Trial -- The development of plaques made up of amyloid protein fragments is a key feature of Alzheimer's disease. So far, no clinical trial testing anti-amyloid agents has proven successful in people with mild to moderate Alzheimer's dementia. Because Alzheimer's-related brain changes take place years, even decades, before symptoms appear, scientists are now aiming to test therapies earlier in the disease process. The A4 (Anti-amyloid treatment in asymptomatic Alzheimer's disease) secondary prevention trial will test an amyloid-clearing drug in the pre-symptomatic stage of the disease, in 1,000 symptom-free older volunteers who have had positron emission tomography brain images that show abnormal levels of amyloid accumulation. Cognitive tests over three years are designed to determine if the drug is effective in maintaining cognitive health, and imaging tests will track structural and functional brain changes. The trial, which will also be supported by private sector contributions, will provide important information about the effectiveness of clearing amyloid from the brain in the early stages of the disease and inform future prevention studies. (Principal Investigator: Reisa Sperling, M.D., Harvard Medical School, Boston.)
- Exercise MCI Trial -- Although exercise is widely recommended to maintain physical function and reduce risk of a number of age-related medical conditions like cardiovascular disease and diabetes, it has not been shown in a longer-term clinical trial to improve cognition or alter the hallmarks in the brain of Alzheimer's disease. This randomized, controlled trial seeks to find out if supervised aerobic exercise can influence cognitive decline, slow brain atrophy, or mitigate Alzheimer's pathology in older adults with mild cognitive impairment (MCI), a condition that often leads to Alzheimer's disease. The trial will recruit sedentary older volunteers with MCI to participate in a year-long program in which one group will do high-intensity aerobic exercise and the other stretching. Cognitive testing, cerebrospinal fluid biomarkers and magnetic resonance imaging results will provide critical data on the efficacy of aerobic exercise on improving cognition and Alzheimer's-related pathology. (Principal Investigators: Laura D. Baker, Ph.D., Wake Forest School of Medicine, Winston-Salem, N.C. and Carl Cotman, Ph.D., University of California, Irvine.)
- Prazosin for Treating Agitation Trial --Disruptive agitation is often a chronic problem in people with Alzheimer's, dramatically increasing caregiver burden and patient distress, often leading to long-term care outside the home. Currently, drugs used to treat agitation are not very effective and may even cause additional harm in older people, such as increased risk of stroke or excessive sedation. The ADCS will test the use of the generic drug prazosin as a treatment for agitation that may also be well-tolerated in frail and elderly people. (Principal Investigator: Elaine Peskind, M.D., University of Washington Alzheimer's Disease Research Center, Seattle.)

Alzheimer's Disease Cooperative Study Group Will Undertake Four Clinical Trials Over Five Years continued...

- CSF Pharmacodynamic Trial -- When testing potential new drug therapies, specifically ones that target key Alzheimer's disease pathways, scientists use cerebrospinal fluid and blood plasma biomarkers as a way of knowing that the compound crossed the blood-brain barrier and engaged the relevant target. Additionally, these biomarkers help track the relationship between blood levels and central nervous system effects. To increase the efficacy and speed of drug development, the ADCS will employ advanced methods that sample cerebrospinal fluid and plasma levels over time. These methods will track levels of several Alzheimer's-related proteins to help researchers better understand how a drug influences Alzheimer's pathology and to help guide decisions on whether a drug warrants further clinical testing. (Principal Investigators: Douglas R. Galasko, M.D., University of California, San Diego and Martin Farlow, M.D., Indiana University Alzheimer's Disease Center, Indianapolis.)

"The ADCS has long benefited the wider research community by emphasizing the importance of collaboration and data-sharing and by focusing on trial design and instrument standardization," said Laurie Ryan, Ph.D., NIA Alzheimer's disease clinical trials program director. "With this newly funded work, the goal is to expand the range of individuals participating in ADCS clinical trials from those at risk for the disorder to those with Alzheimer's dementia, so that the full spectrum of the disease is represented."

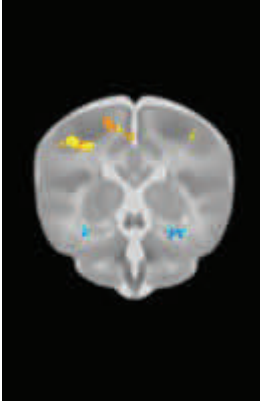
The NIA launched the ADCS in 1991 under a cooperative agreement, in which NIH participates in the management of the studies. Over the past two decades, the ADCS has built an infrastructure emphasizing collaboration and data sharing. It focuses on evaluating interventions that will benefit Alzheimer's patients across the disease spectrum. This includes testing agents that lack patent protection; agents under patent protection that are already marketed for other uses but which might prove useful in treating Alzheimer's; and novel compounds developed by individuals, academia, pharmaceutical companies and small biotech companies.

In addition to testing new therapies, the ADCS mission includes the design of new instruments for use in clinical studies and the development of novel and innovative approaches to Alzheimer's disease clinical trial design and analysis. The ADCS also strives to enhance the recruitment of minority groups into Alzheimer's studies. To date, the ADCS has conducted 30 studies (23 drug studies and seven instrument development protocols).



Risk Genes For Alzheimer's and Mental Illness Linked To Brain Changes At Birth

This study by UNC School of Medicine researchers is the first to report the impact of common gene variants on brain structure in newborns.



Impact of the APOE Alzheimer's risk variant on the newborn brain. Blue clusters show decreased brain volumes in newborns with the risk variant. Similar decreases in this brain area, which is involved in memory, are seen in adults with the same variant.

CHAPEL HILL, N.C. – Some brain changes that are found in adults with common gene variants linked to disorders such as Alzheimer's disease, schizophrenia, and autism can also be seen in the brain scans of newborns.

“These results suggest that prenatal brain development may be a very important influence on psychiatric risk later in life,” said Rebecca C. Knickmeyer, PhD, lead author of the study and assistant professor of psychiatry in the University of North Carolina School of Medicine. The study was published online by the journal *Cerebral Cortex* on Jan. 3, 2013.

The study included 272 infants who received MRI scans at UNC Hospitals shortly after birth. The DNA of each was tested for 10 common variations in 7 genes that have been linked to brain structure in adults. These genes have also been implicated in conditions such as schizophrenia, bipolar disorder, autism, Alzheimer's disease, anxiety disorders and depression.

For some polymorphisms – such as a variation in the APOE gene which is associated with Alzheimer's disease – the brain changes in infants looked very similar to brain changes found in adults with the same variants, Knickmeyer said. “This could stimulate an exciting new line of research focused on preventing onset of illness through very early intervention in at-risk individuals.”

But this was not true for every polymorphism included in the study, said John H. Gilmore, MD, senior author of the study and Thad & Alice Eure Distinguished Professor and Vice Chair for Research and Scientific Affairs in the UNC Department of Psychiatry.

For example, the study included two variants in the DISC1 gene. For one of these variants, known as rs821616, the infant brains looked very similar to the brains of adults with this variant. But there was no such similarity between infant brains and adult brains for the other variant, rs6675281.

Risk Genes For Alzheimer's and Mental Illness Linked To Brain Changes At Birth continued...

"This suggests that the brain changes associated with this gene variant aren't present at birth but develop later in life, perhaps during puberty," Gilmore said.

"It's fascinating that different variants in the same gene have such unique effects in terms of when they affect brain development," said Knickmeyer.

In addition to Knickmeyer and Gilmore, authors of the study were Jiaping Wang, PhD; Hongtu Zhu, PhD; Xiujuan Geng, PhD; Sandra Woolson, MPh; Robert M. Hamer, PhD; Thomas Konneker, BA; Weili Lin, PhD; and Martin Styner, PhD. All are at UNC except Konneker, who was at UNC but is now a PhD student at the University of California, Santa Cruz.

The study was funded by grants from the National Institutes of Health.

Dr. Michael Weiner to Receive 2013 Potamkin Award



Michael Weiner, MD

January 24, 2013

Michael W. Weiner, MD, Director of the San Francisco VA Medical Center's Center for Imaging of Neurodegenerative Diseases and a Professor of Radiology at UCSF will receive the 2013 Potamkin Prize for Research in Pick's, Alzheimer's and Related Diseases from the American Academy of Neurology and the American Brain Foundation. Co-recipients of the prize are William J. Jagust, MD, with the University of California, Berkeley, and Eric M. Reiman, MD, with Banner Alzheimer's Institute in Phoenix. The Potamkin Prize honors researchers for their work in helping to advance the understanding of Pick's disease, Alzheimer's disease and related disorders. The \$100,000 prize is an internationally recognized tribute for advancing dementia research. The award will be presented during the Academy's 65th Annual Meeting, March 16-23, 2013, in San Diego.

Dr. Weiner is receiving the Potamkin Prize for standardizing imaging and biomarker tests to find better ways to detect and diagnose Alzheimer's disease. Weiner helped form the Alzheimer's Disease Neuroimaging Initiative (ADNI), which was the first to perform amyloid PET imaging brain scans at multiple sites across the United States. Today, amyloid PET imaging is widely available for diagnosis and use in clinical trials.

Second Language Shows Benefits to Aging Brain

LEXINGTON, Ky.

Older adults who have spoken two languages since childhood are faster than single-language speakers at switching from one task to another, according to a study conducted at the University of Kentucky College of Medicine.

The study also found that lifelong bilinguals show different patterns of brain activity than their monolingual counterparts when making the switch.

The research was led by Brian Gold, associate professor of anatomy and neurobiology, who specializes in cognitive neuroscience. The article, "Lifelong Bilingualism Maintains Neural Efficiency for Cognitive Control in Aging," was published in the Jan. 9 issue of **The Journal of Neuroscience**.

As people age, cognitive flexibility — the ability to adapt to unfamiliar or unexpected circumstances — and related "executive" functions decline. Recent studies suggest lifelong bilingualism may reduce this decline — a boost that may stem from the experience of constantly switching between languages. However, how brain activity differs between older bilinguals and monolinguals was previously unclear.

Gold and his colleague used functional magnetic resonance imaging (fMRI) to compare the brain activity of healthy bilingual adults, ages 60-68, with that of healthy monolingual adults in the same age group, as they completed a task that tested their cognitive flexibility.

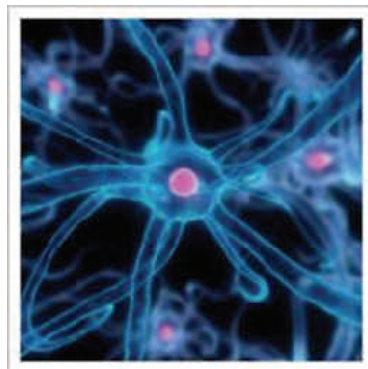
The researchers found that both groups performed the task accurately. However, the bilingual group was faster at completing the task, despite expending less energy in the frontal cortex — an area known to be involved in task-switching.

The researchers also measured the brain activity of younger bilingual and monolingual adults while they performed the cognitive flexibility task.

Overall, the young adults were faster at performing the task. Being bilingual did not affect task performance or brain activity in the young participants. In contrast, older bilinguals performed the task faster than their monolingual peers and expended less energy in the frontal parts of their brain.

"This suggests that bilingual seniors use their brains more efficiently than monolingual seniors," Gold said. "Together, these results suggest that lifelong bilingualism may exert its strongest benefits on the functioning of frontal brain regions in aging."

This research was funded by the U.S. National Institutes of Health and the National Science Foundation.



Study Shows Early Cognitive Problems Among Those Who Eventually Get Alzheimer's

MANHASSET, NY -- People who study or treat Alzheimer's disease and its earliest clinical stage, mild cognitive impairment (MCI), have focused attention on the obvious short-term memory problems. But a new study suggests that people on the road to Alzheimer's may actually have problems early on in processing semantic or knowledge-based information, which could have much broader implications for how patients function in their lives.

Terry Goldberg, PhD, a professor of psychiatry and behavioral science at the Hofstra North Shore-LIJ School of Medicine and director of neurocognition at the Litwin Zucker Center for Research in Alzheimer's Disease and Memory Disorders at The Feinstein Institute for Medical Research in Manhasset, NY, said that clinicians have observed other types of cognitive problems in MCI patients but no one had ever studied it in a systematic way. Many experts had noted individuals who seemed perplexed by even the simplest task. In this latest study, published in this month's issue of the *American Journal of Psychiatry*, investigators used a clever series of tests to measure a person's ability to process semantic information.

Do people with MCI have trouble accessing different types of knowledge? Are there obvious semantic impairments that have not been picked up before? The answer was "yes."

In setting out to test the semantic processing system, Dr. Goldberg and his colleagues needed a task that did not involve a verbal response. That would only confuse things and make it harder to interpret the results. They decided to use size to test a person's ability to use semantic information to make judgments between two competing sets of facts. "If you ask someone what is bigger, a key or an ant, they would be slower in their response than if you asked them what is bigger, a key or a house," explained Dr. Goldberg. The greater the difference in size between two objects, the faster a person -- normal or otherwise -- can recognize the difference and react to the question.

Investigators brought in 25 patients with MCI, 27 patients with Alzheimer's and 70 cognitively fit people for testing. They found large differences between the healthy controls and the MCI and Alzheimer's patients. "This finding suggested that semantic processing was corrupted," said Dr. Goldberg. "MCI and AD (Alzheimer's disease) patients are really affected when they are asked to respond to a task with small size differences."

They then tweaked the task by showing pictures of a small ant and a big house or a big ant and a small house. This time, the MCI and AD patients did not have a problem with the first part of the test -- they were able to choose the house over the ant when asked what was bigger. But if the images were incongruent -- the big ant seemed just as big as the small house -- they were confused, they answered incorrectly or took longer to arrive at a response.

Patients with MCI were functioning somewhere between the healthy people and those with AD. "When the decision was harder, their reaction time was slower," he said.

Would this damaged semantic system have an effect on everyday functions? To answer this question, investigators turned to the UCSD Skills Performance Assessment scale, a tool that they have been using in MCI and AD patients that is generally used to identify functional deficits in patients with schizophrenia. The test taps a person's ability to write a complex check or organize a trip to the zoo on a cold day.

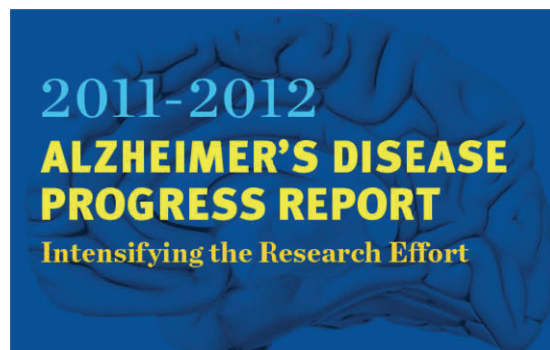
Study Shows Early Cognitive Problems Among Those Who Eventually Get Alzheimer's continued...

This is actually a good test for figure out whether someone has problems with semantic knowledge. Semantic processing has its seat in the left temporal lobe. "The semantic system is organized in networks that reflect different types of relatedness or association," the investigators wrote in their study. "Semantic items and knowledge have been acquired remotely, often over many repetitions, and do not reflect recent learning."

Dr. Goldberg said the finding is critically important because it may be possible to strengthen these semantic processing connections through training. "It tells us that something is slowing down the patient and it is not episodic memory but semantic memory," he said. They will continue to study these patients over time to see if these semantic problems get worse as the disease advances.

In an accompanying editorial, David P. Salmon, PhD, of the Department of Neurosciences at the University of California in San Diego, said that the "semantic memory deficit demonstrated by this study adds confidence to the growing perception that subtle decline in this cognitive domain occurs in patients with amnesic mild cognitive impairment. Because the task places minimal demands on the effortful retrieval process, overt word retrieval, or language production, it also suggests that this deficit reflects an early and gradual loss of integrity of semantic knowledge."

He added that a "second important aspect of this study is the demonstration that semantic memory decrements in patients with mild cognitive impairment may contribute to a decline in the ability to perform usual activities of daily living."



Research shows that Alzheimer's causes changes in the brain years and even decades before the first symptoms appear, so even those who seem free of the disease today may be at risk. The fight against Alzheimer's is urgent because, without new ways to prevent or more effectively treat this age-related disease, it will become increasingly prevalent in our aging population.

This report from the National Institutes of Health (NIH) focuses on research findings reported and projects funded in 2011 and the first half of 2012. These highlights, prepared by NIH's National Institute on Aging (NIA), the lead institute within NIH for Alzheimer's research, covers work by an active scientific community. This work aims to elucidate the basic mechanisms and risk factors of Alzheimer's disease, then apply this knowledge to the development and testing of new interventions to treat or prevent Alzheimer's disease.

The efforts of researchers and clinicians—made possible by the many people who volunteer for clinical studies and trials—may one day lead to a future free of this devastating disorder. This report details some of the recent progress toward that goal.

<http://tinyurl.com/abo4vtu>

Alzheimer's Disease: Inflammation As A New Therapeutic Approach

Researchers discover a signal switch which protects against loss of function of nerve cells

The number of Alzheimer's patients will continue to dramatically increase in the next several decades. Various teams of researchers worldwide are feverishly investigating precisely how the illness develops. A team of scientists under the guidance of the University of Bonn and University of Massachusetts (USA) and with the participation of the German Center for Neurodegenerative Diseases have discovered a new signaling pathway in mice which is involved in the development of chronic inflammation which causes nerve cells in the brain to malfunction and die off. The results are now being published in the renowned scientific journal "Nature".

Alzheimer's disease gradually leads to the destruction of nerve cells and thus to significant losses in memory formation and recall. "Many years before the initial symptoms occur, so-called plaques, which consist of incorrectly folded beta-amyloid peptides, form in the brain of affected persons," says lead author Prof. Dr. Michael T. Heneka, director of the Clinical Neurosciences study group at the Neurology Clinic of the University of Bonn and researcher at the German Center for Neurodegenerative Diseases (DZNE). In addition, there are abnormal tau protein deposits in the brain cells of the patients. "As a result of a signal cascade, there is a chronic inflammatory reaction and the progressive loss of nerve cells," reports Prof. Dr. Eicke Latz from the Institute of Innate Immunity of the Bonn University Hospital, who also performs research for the DZNE and the University of Massachusetts Medical School (USA).

Caspase-1 is increased in the brains of Alzheimer's patients

The scientists from the University of Bonn and the DZNE, in a successful alliance of neurologists and immunologists together with their colleagues from the Caesar Research Center and the Technical University of Braunschweig, have discovered a new signaling pathway which is involved in the development of chronic inflammation of the brain cells. Caspase-1 plays a key role and it is jointly responsible for the activation of the inflammatory reaction. The researchers detected substantially increased amounts of caspase-1 in the brains of Alzheimer's patients in comparison to healthy persons. These increased levels were associated with chronic inflammatory reactions of the immune cells in the brain. The scientists also observed these findings in genetically modified mice who represent a well established model of Alzheimer's disease.

Silent genes prevent inflammation and memory loss

The gene NLRP3 is also crucially involved in the inflammatory signaling pathways which lead to the degeneration and loss of brain cells. The scientists therefore deactivated the NLRP3 gene as well as caspase-1 in the Alzheimer's mice. As a result, there was no inflammation in the brains of these animals and they did not develop any memory loss. In addition, there was shown to be far less beta-amyloid peptide deposited in the brain cells of the genetically silent mice. It is evident that the non-inflamed cells were able to dispose of the deposited plaques much better as "metabolic waste." If the genes for caspase-1 and NLRP3 are muted, the nerve cells and memory are evidently protected from the typical Alzheimer's processes.

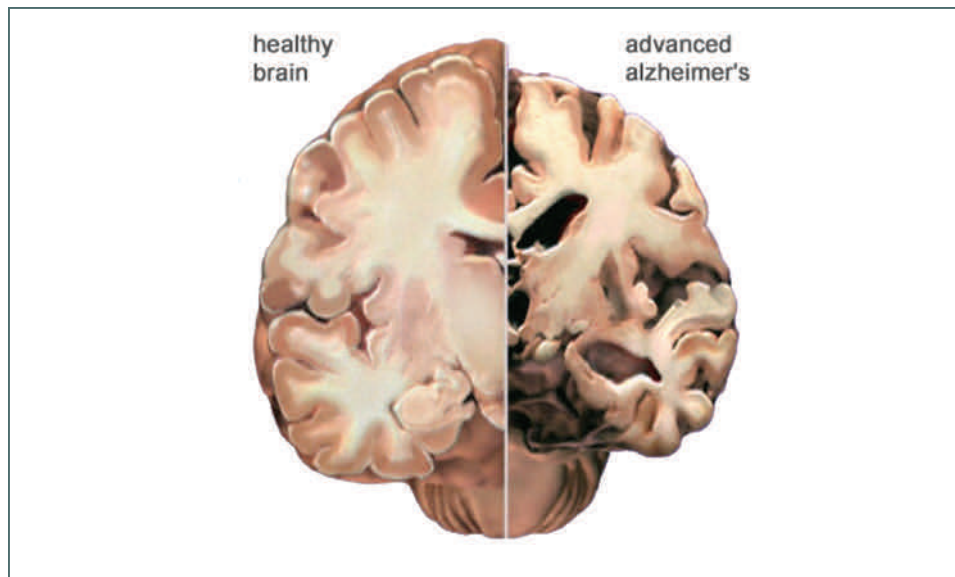
Possible starting point for new therapies

These results indicate a starting point which could possibly aid in the development of new forms of therapy for the treatment of early-stage Alzheimer's disease. "We are still in the basic research stage and thus therapeutic success cannot be foreseen at this time point," says Prof. Heneka. "There is still a long way to go until the first clinical studies."

ADCS Trials Enrolling...

ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments. <http://adcs.org/Studies/ImagineADNI.aspx>.



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