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NEW WAYS TO DETECT AND TREAT ALZHEIMER'S DISEASE

Specific brain changes suggest new diagnostic markers and therapeutic targets

SAN DIEGO — New studies identify brain changes in people with Alzheimer's disease. The results give researchers a greater understanding of the disease and may help at-risk individuals by improving early detection. New animal research also shows a novel approach to Alzheimer's vaccine design that may avoid dangerous side effects. These new results were reported at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

About 5.3 million people have Alzheimer's disease, according to the Alzheimer's Association. With the aging baby boomer population, Alzheimer's will continue to affect more people worldwide. Better diagnostic techniques may help identify the disease at earlier, potentially more treatable stages.

Today's new findings show that:

- People with Alzheimer's disease show structural changes in the caudate nucleus, a brain structure typically associated with movement disorders such as Parkinson's disease, suggesting that the disease produces broader damage in the brain than previously thought (Sarah Madsen, abstract 348.4, see attached summary).
- People at risk for Alzheimer's disease exhibit a structural change in portions of the cerebral cortex, which is largely responsible for reasoning, memory and other "higher function" tasks. The findings may help identify those who would most benefit from early intervention (Sarah George, abstract 756.9, see attached summary).
- A new vaccine, which was tested in mice, could protect against memory problems associated with Alzheimer's disease without potentially dangerous side effects. The vaccine targeted a non-human protein that may make it a safer alternative to previous vaccine approaches that caused inflammation in human clinical trials (Charles Glabe, PhD, abstract 725.6, see attached summary).
- Too many small aggregates of a protein called tau in the brain can directly interfere with memory, according to new animal research. The findings are important because they suggest that tau may be a good target for developing therapies against Alzheimer's and related diseases (Ottavio Arancio, MD, PhD, abstract 527.8, see attached summary).

"Identifying those at risk for Alzheimer's and developing new treatments for nervous system disorders is a social imperative," said press conference moderator Sam Sisodia, PhD, of the University of Chicago, an expert on the cellular biology of proteins implicated in Alzheimer's disease. "These studies are evidence that we're making real progress to overcome this tragic epidemic."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

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Related Presentation:

Special Lecture Session: **Amyloid Imaging: Impact on the Study of Alzheimer's Disease**
Wednesday, Nov. 17, 10–11:10 a.m., Ballroom 20
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Abstract 348.4 Summary

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Brain Tissue Loss in People with Alzheimer's Disease and Mild Cognitive Impairment

Study investigates another possible marker for the progression of the disease

People with Alzheimer's disease exhibit striking structural changes in the caudate nucleus, a brain structure typically associated with movement disorders such as Parkinson's disease, a new study has found. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our finding suggests that Alzheimer's disease produces broader damage in the brain than previously thought, including damage to areas not usually associated with the disease," said lead author Sarah Madsen, a graduate student working with Paul Thompson, PhD, of the University of California, Los Angeles.

For the study, Madsen and her colleagues analyzed the brains of 400 elderly participants. Of this group, 100 were healthy, 100 had diagnosed Alzheimer's disease, and 200 had mild cognitive impairment, a condition that sometimes serves as a precursor to Alzheimer's disease.

Compared with healthy individuals, the caudate nucleus was seven percent smaller in those with Alzheimer's disease and four percent smaller in those with mild cognitive impairment. It was also smaller in older and in overweight individuals.

"Our finding suggests a gradual progression of brain tissue loss in the caudate nucleus as dementia becomes more severe," said Madsen. "This brain area, which is associated with certain forms of learning and memory as well as motor control, is an important factor to consider when studying Alzheimer's disease and in predicting how the disease will progress," she said.

Research was supported by the National Institutes of Health Roadmap for Medical Research and Alzheimer's Disease Neuroimaging Initiative, National Institute on Aging, National Heart, Lung, and Blood Institute, National Institute of Neurological Disorders and Stroke, National Institute of Biomedical Imaging and Bioengineering, and the Dana Foundation.

Scientific Presentation: Monday, Nov. 15, 11–12 p.m., Halls B–H

348.4, Caudate atrophy and its clinical correlates in 400 Alzheimer's disease, MCI, and healthy elderly subjects
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TECHNICAL ABSTRACT: Caudate atrophy is typical of motor disorders such as Parkinson's disease, but it also occurs in Alzheimer's disease (AD), where amyloid and tau pathology accumulate in the caudate. Caudate atrophy is rarely studied in AD, so we mapped 3D profiles of atrophy and correlations with clinical measures in 100 healthy elderly, 200 MCI, and 100 AD subjects (age: 75.8 years+/-6.6 SD). All subjects were scanned with 3D structural brain MRI as part of the Alzheimer's Disease Neuroimaging Initiative. We tested associations of caudate atrophy with: (1) clinical scores (MMSE, CDR) and their change over a one-year follow-up interval; (2) conversion from MCI to AD; (3) CSF amyloid-beta, tau, p-tau levels; and (4) age, sex, ApoE genotype, and body mass index (BMI). We identified the caudate head in each scan, with an automated method using adaptive boosting, based on thousands of features in a training set of expertly labeled images. 3D maps of p-values at each surface point revealed regions where atrophy correlated with clinical measures; all maps were corrected for multiple comparisons by permutation testing. Versus controls, caudate volumes were lower in MCI (2.64 percent L, 4.43 percent R) and AD (4.7 percent L, 8.5 percent R). Caudate atrophy was associated with age, sum-of-boxes CDR, Delayed Logical Memory scores, conversion from MCI to AD, future decline in MMSE scores 1 and 2 years later, and body mass index (BMI; greater atrophy with higher BMI). Reduced right caudate volume was associated with conversion from MCI to AD, baseline global CDR, Immediate and Delayed Logical Memory scores, one-year decline in MMSE scores, and with CSF tau and p-tau levels. The right caudate was 3.9 percent larger than the left in controls and 2.1 percent larger in MCI - an asymmetry not found in AD. Caudate nucleus atrophy was associated with poorer performance on standard clinical and cognitive tests, and with higher BMI - perhaps reflecting heightened vascular risks for AD. Assessment of the caudate nucleus, along with other AD biomarkers, may identify individuals who will soon decline to AD, boosting power in drug trials.

Abstract 756.9 Summary

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Structural Brain Changes in People at Risk for Alzheimer's Disease

Study suggests an early marker for dementia, might identify candidates for early treatment

People at risk of developing Alzheimer's disease exhibit a specific structural change in the brain that can be visualized by brain imaging, according to new research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings may help identify those who would most benefit from early intervention.

"Our findings support the notion that structural imaging techniques can be used to identify people at risk for developing Alzheimer's disease," said Sarah George, a graduate student who co-authored the study with Leyla deToledo-Morrell, PhD, of Rush University Medical Center.

The researchers followed people with mild cognitive impairment, a condition that may be a precursor to Alzheimer's disease and other forms of dementia. Some of the participants went on to develop Alzheimer's disease, others did not.

The researchers used magnetic resonance imaging (MRI) to look for structural changes in the substantia innominata (SI), a region deep within the brain that sends chemical signals to the cerebral cortex, the brain's outer layer that is largely responsible for reasoning, memory and other "higher function" tasks. Although no structural changes were found in the SI, the MRI showed a thinning of the cortical areas that receive input from the SI in those who went on to develop Alzheimer's disease.

"MRI screening appears to be a strong candidate for an early biomarker of Alzheimer's disease," George said.

Research was supported by the National Institute on Aging and the Illinois Department of Public Health Regional Alzheimer's Disease Assistance Center of Northeastern Illinois Grant.

Scientific Presentation: Wednesday, Nov. 17, 8–9 a.m., Halls B–H

756.9, Cortical thinning in the substantia innominata projection sites in incipient Alzheimer's disease
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TECHNICAL ABSTRACT: The substantia innominata (SI) contains cholinergic neurons of the nucleus basalis of Meynert, which innervate the entire cortical mantel and degenerate during the progression of Alzheimer's disease (AD). Using high-resolution structural magnetic resonance imaging (MRI), we previously reported that SI volume is reduced in patients with mild AD, but preserved in individuals with amnestic mild cognitive impairment (aMCI) who are at high risk of developing AD (George et al., Neurobiol. Aging, 2009). The lack of SI volumetric changes in aMCI could be due to the inclusion of both individuals who progress to a diagnosis of AD over time (converters) and those who remain stable (non-converters). In the present study, we separated aMCI converters and non-converters to determine if SI volume is reduced in converters. The study included 47 individuals who entered into an ongoing longitudinal project with a clinical diagnosis of aMCI at baseline. All subjects were followed annually (mean follow-up period = 5.9 ± 3.5 years) with clinical evaluations and MRI scans acquired on a 1.5T scanner using a T1-weighted 3D SPGR protocol. Based on clinical follow-up, 22 converted to AD (mean age = 80 ± 5.2 years) and 25 remained stable (non-converters; mean age = 77 ± 9.2 years). Baseline MRI scans were used to derive SI volume from 3 coronal slices taken perpendicular to the AC-PC line. To correct for individual differences in brain size, SI volume was normalized with total intracranial volume. SI volume did not differ between converters and non-converters. Next, the FreeSurfer software was used to identify cortical regions that show significant thinning in aMCI converters compared to non-converters. We then focused on cortical regions that receive projections from the SI and found significant thinning in the following sites: bilateral superior and middle frontal, bilateral superior and inferior parietal, left superior and inferior temporal, right precuneus and posterior cingulate. SI volume was found to be positively correlated with the thickness of the right inferior parietal ($r = 0.61$, $p<0.01$), right superior frontal ($r = 0.51$, $p<0.05$), and right precuneus ($r = 0.44$, $p<0.05$) among converters. There was no relationship between cortical thinning and SI volume among non-converters. Therefore, although SI volume is preserved in aMCI, its cortical projection sites exhibit cortical thinning in incipient AD. These findings suggest that cortical thinning precedes SI volumetric changes, supporting the concept that the process of retrograde degeneration impacts neuronal survival within the SI during the progression of AD.

Abstract 725.6 Summary

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Development of a Safer Vaccine for Alzheimer's Disease

Mouse study suggests new vaccine approach that may avoid side effects

A new vaccine protects against memory problems associated with Alzheimer's disease, but without potentially dangerous side effects, a new animal study reports. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Vaccines against amyloid-beta accumulation in the brain, one of the hallmarks of Alzheimer's disease, have long been considered a promising approach to developing a treatment. But finding a vaccine that is both safe and effective has been challenging. Previous research in mice showed that a vaccine that targets the human version of amyloid-beta reduces learning and memory loss associated with the disease. However, the vaccine caused dangerous autoimmune inflammation of the brain during human clinical trials.

In the current study, researchers at the University of California, Irvine tested a vaccine developed against a non-human protein that had the same shape as amyloid-beta, but a different sequence of amino acid building blocks. The Alzheimer's mice that received the vaccine showed improved performance on memory and other cognitive tests. The vaccine also reduced the clumps of amyloid-beta and tau protein that may be toxic to brain cells.

"This finding is important because it shows that you don't need a human protein to get an immune response that will neutralize the toxic amyloid oligomers associated with Alzheimer's disease," said senior author Charles Glabe, PhD. Because the protein was not human, Glabe and his colleagues believe it is unlikely to cause the dangerous autoimmune response.

"We've demonstrated a promising approach to developing a safe, active vaccine — and one potentially cheaper and easier to distribute than the manufactured vaccines currently in human trials," Glabe said.

Research was supported by Cure Alzheimer's Fund and the Larry L. Hillblom Foundation.

Scientific Presentation: Wednesday, Nov. 17, 9:15–9:30 a.m., Room 32B

725.6, Non human amyloid oligomer epitope reduces Alzheimer's-like neuropathology in 3xTg-AD transgenic mice
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TECHNICAL ABSTRACT: Accumulation of beta-amyloid (Aß) is an important molecular event in Alzheimer's disease (AD). It is now well known that vaccination against fibrillar Aß prevents amyloid accumulation and preserves cognitive function in transgenic mouse models. To study the effect of vaccination against generic oligomer epitopes, Aß oligomers, islet amyloid polypeptide (IAPP) oligomers, random peptide oligomer (3A) & Aß fibrils were used to vaccinate 3xTg-AD, which develop a progressive accumulation of plaques and cognitive impairment. It was found that all vaccinated mice have a significant improvement in cognitive function compared to controls. Subcutaneous administration of these antigens markedly reduced total plaque load (Aβ burden) in the 3xTg-AD mouse brains. We demonstrated that vaccination with this non human amyloid oligomer generated high titers of oligomer specific antibodies recognizing Aβ oligomers, which in turn inhibited accumulation of Aß pathology in mice. In addition to amyloid plaques, another hallmark of AD is tau pathology. It was found that there was a significant decline in the levels of total tau and hyperphosphorylated tau. We conclude that amyloid Aß sequence is not necessary to produce a protective immune response as the random peptide (3A) gives rise to an oligomer-specific immune response. The critical epitope is a pathology-specific conformation of the peptide backbone that is independent of the specific amino acid sequence. It is therefore suggested that vaccination against a non-human amyloid oligomer epitope may be useful for clearing both hallmark lesions of AD. It may be an effective strategy for developing a vaccine that circumvent auto-inflammatory immune complications.

Abstract 527.8 Summary

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Small Clumps of Tau Protein Disrupt Memory

Animal study suggests possible target for Alzheimer's disease therapies

Too many small aggregates of a protein called tau in the brain can directly interfere with memory, according to new animal research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our findings are important because they suggest that tau may be a good target for developing therapies against Alzheimer's and related diseases," said senior author Ottavio Arancio, PhD, of Columbia University.

Many neurodegenerative diseases are marked by an accumulation of protein aggregates in the brain, and Alzheimer's disease is no exception. The two most common aggregating proteins associated with Alzheimer's disease are amyloid-beta and tau, which form the neural plaques and tangles that are hallmarks of the disease. Recently, scientists have begun to focus on some of the smaller, still-soluble forms of these protein aggregates, called oligomers, which may be especially toxic to neurons.

Arancio and his colleagues found that tau oligomers impaired fearful memories in mice. Tau oligomers also disrupted synaptic plasticity — cellular events important for memory formation.

"Our findings suggest that tau is critically involved in the development of Alzheimer's disease — and that reducing the abnormal aggregation of the protein may prove to be an effective treatment approach," Arancio said.

Research was supported by the Alzheimer's Drug Discovery Foundation, the National Institutes of Health, and Oligomerix, Inc.

Scientific Presentation: Tuesday, Nov. 16, 9:45–10 a.m., Room 32B

527.8, Validation of extracellular tau oligomer target for drug discovery in a novel animal model
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TECHNICAL ABSTRACT: Tau protein is found primarily associated with axons in differentiated neurons where it functions to stabilize microtubule structure and regulate transport. However, during Alzheimer's disease (AD) and other tauopathies tau loses its normal function and gains toxic activity. Tau protein aggregates and is sequestered into filaments and higher order neurofibrillary tangles (NFT), a pathological hallmark of AD, and is modified by multiple mechanisms (Ballatore C et al. Nat Rev Neurosci. 2007 8:663-72). Studies using mouse models of AD and tauopathies show a strong correlation between the accumulation of soluble oligomeric species of tau and neuronal loss and memory impairment (Berger Z et al. J Neurosci. 2007 27:3650-62; Brunden KR et al. J Alzheimers Dis. 2008 14:393-9), and have challenged the assumption that NFT are the neurotoxic structures of tau. As AD progresses, tau pathology reproducibly spreads through the hippocampal structure to the cortex in a contiguous, highly selective and orderly fashion (Braak, H. and E. Braak. J Neural Transm Suppl, 1998. 53:127-40; Schönheit B et al. Neurobiol Aging. 2004 25:697-711) suggesting that aberrant tau protein may be involved in transmitting pathology to neighboring neurons during disease progression. Tau pathology may be transmitted to neighboring healthy neurons through muscarinic receptors I and III (Gómez-Ramos A et al. Eur Neuropsychopharmacol. 2009 19:708-17) or by directly entering cells and functioning as a template for intracellular tau to misfold, aggregate and cause neurodegeneration (Clavaguera F et al. Nat Cell Biol. 2009 11:909-13; Frost B et al. J Biol Chem. 2009 284:12845-52). In AD the levels of extracellular tau increase in cerebrospinal fluid, presumably due to release of intracellular proteins during cell death; hence its use as a biomarker for AD (Trojanowski JQ et al. Alzheimers Dement. 2010 6:230-8). Tau secretion to the extracellular space and to postsynaptic neurons was shown to be dependent on the N-terminus of tau and tauopathy mutations facilitating tau aggregation (Kim W et al. J Alzheimers Dis. 2010 19:647-64). Here, we show that extracellular tau oligomers have a causative effect on disrupting memory in studies of synaptic function in hippocampal slices and behavior in mice. Extracellular tau oligomers, but not monomeric tau, reduced long-term potentiation (LTP) (IC50 5 nM) and impaired associative fear memory in normal mice. These results strongly support extracellular tau oligomers as a target for drug discovery for AD and related tauopathies.