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**Contact:** Alzheimer's Association media line: 312-335-4078, [media@alz.org](mailto:media@alz.org)  
AAIC 2011 press room, July 16-21: +33 (0)1 57 25 20 35

**TWO STUDIES ADVANCE GLOBAL STANDARDIZATION OF  
BIOMARKERS FOR ALZHEIMER'S DISEASE**

**- First time international collaborations move the field closer to harmonized protocols -**

PARIS, July 17, 2010 – As the Alzheimer's field moves closer to new and earlier tests for the disease, innovative global research initiatives are taking the first important steps to standardize Alzheimer's biomarkers, as evidenced by two presentations made today at the Alzheimer's Association International Conference 2011 (AAIC 2011) in Paris.

One study compared, for the first time, results of brain amyloid imaging and the impact of genetics and ethnicity on those results across countries on three different continents as part of a worldwide Alzheimer's disease imaging study. The other takes a significant step forward in creating a standard international method for measuring the size of a key memory center in the brain (the hippocampus) – which often is one of the first brain areas affected by Alzheimer's.

“We need to identify people in the earliest stages of Alzheimer's, even those without outward evidence of memory and thinking symptoms, for treatment and prevention trials,” said Maria Carrillo, PhD, senior director of Medical and Scientific Relations at the Alzheimer's Association. “It is very important that the tests are accurate and effective, and that they are delivered and measured in the same way across the world so that measures are comparable.”

“For example, if you get your blood tested for cholesterol levels in Budapest, Bangalore or Boston, the methods are the same and the results are comparable. That is not yet the case for Alzheimer's disease, especially for assays that detect Alzheimer's proteins in blood or cerebrospinal fluid,” Carrillo said. “To ensure comparable results, the methods used for gathering and evaluating samples must be consistent. As an illustration, spinal fluid gathered or stored in a plastic container may give different results than a sample gathered or stored in a glass container.”

The Alzheimer's Association is taking the lead in a number of global efforts to standardize Alzheimer's biomarkers, in particular with the creation and management of the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI) and the Alzheimer's Association Cerebrospinal Fluid (CSF) Quality Control Program.

WW-ADNI is the umbrella organization for neuroimaging initiatives being carried out through the North American ADNI, European ADNI (E-ADNI), Japanese ADNI, Australian ADNI (AIBL), and Taiwan ADNI. The overall goals of WW-ADNI are to better understand the physical changes that occur in healthy individuals compared with individuals with mild cognitive impairment (MCI) and Alzheimer's, and to develop improved methods for identifying the appropriate patient populations for clinical trials. WW-ADNI also aims to standardize the methods used for conducting imaging scans and gathering and testing fluid samples so that data from all sites can be readily combined and easily understood by researchers. Data from WW-ADNI are expected to play a key role in identifying effective treatments for Alzheimer's, as well as methods that may prevent or slow the progression of the disease. [www.alz.org/research/funding/partnerships/WW-ADNI\\_overview.asp](http://www.alz.org/research/funding/partnerships/WW-ADNI_overview.asp)

Launched in fall 2009, the Alzheimer's Association Cerebrospinal Fluid (CSF) Quality Control Program brings together laboratories across the globe with the aim of standardizing the measurement of potential Alzheimer biomarkers. More than 60 labs in North and South America, Asia, Australia and Europe are participating in the program. CSF biomarkers may be useful not only in aiding early detection of Alzheimer's and improving diagnostic accuracy, but also in identifying and monitoring the effects of drugs in clinical trials, understanding the molecular changes that lead to Alzheimer's, and helping to ensure that individuals recruited into Alzheimer clinical trials are on a path toward developing the disease. The program is fully supported by a gift from the Dana and Dave Dornsife family.

"To enable people to live their lives without the dementia caused by Alzheimer's, early detection of the disease and effective treatment are essential," Carrillo said. "These two research efforts, and others like them, will be instrumental in getting us there."

### **Alzheimer's Disease Neuroimaging Data from Three Countries**

It has not been established whether the association between a well-established Alzheimer's risk gene – apolipoprotein E (APOE)  $\epsilon 4$  – age, and amyloid deposition is consistent among ethnic groups.

Kenji Ishii, MD, of Tokyo Metropolitan Institute of Gerontology, and colleagues, used data from three multi-center studies of Alzheimer's that are using a harmonized protocol – the Alzheimer's Disease Neuroimaging Initiative (US-ADNI), Australian Imaging Biomarker and Lifestyle Flagship Study of Aging (AIBL), and Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) – to evaluate the influence of APOE  $\epsilon 4$  and age on the accumulation of amyloid in the brain as measured by PET scan with  $^{11}\text{C}$ -Pittsburgh compound B (PiB). This is the first report of an international ADNI data analysis including these three different national populations, all three of which include people with Alzheimer's, MCI, and cognitively normal individuals.

The researchers found that:

- The effect of age and APOE- $\epsilon 4$  on amyloid deposition in the Japanese population is similar to Caucasians, despite a lower  $\epsilon 4$  allele frequency in the Japanese population.
- In the cognitively normal people in the study, having a single copy of the APOE- $\epsilon 4$  gene is roughly equivalent to 12 additional years of age for PiB positivity.
- Perhaps most importantly, for the Alzheimer's research field, the results suggest that the three multi-national ADNI data sets are feasible for combined analysis.

"This is one of the first demonstrations of the great value of open data sharing in the worldwide ADNI initiative," Ishii said. "Combined analysis enlarges and diversifies the study population and the data set. It increases the power of the results, decreases ethnicity effects and makes the findings more broadly applicable. This is very important as we identify and verify biomarker tests for Alzheimer's disease."

## **Towards a Harmonized Protocol for Measuring the Hippocampus**

The earliest Alzheimer's related brain changes are usually seen in the hippocampus, the "control center" of memory-related activity in the brain. In previous studies, MRI measurement of shrinkage of the hippocampus over time has shown value for diagnosis of Alzheimer's and tracking the progression of the disease. But harmonization (greater standardization) in assessing volume change is needed as researchers work to move hippocampal measurement from research centers into wider clinical use.

A variety of published protocols now exist for assessing hippocampal volume. These protocols differ because they rely on various techniques of "segmentation" - that is, assigning the electronic image voxels (volumetric pixels) to specific structures, such as the hippocampus, within the brain.

As a first phase of the standardization process, Giovanni Frisoni, MD, of San Giovanni di Dio Fatebenefratelli, Brescia, Italy, and colleagues surveyed the various available segmentation protocols to identify underlying reasons why they result in different volume estimates. This work was funded by the Alzheimer's Association.

"The next step will be to create, test and verify a single protocol for MRI-based evaluation of Alzheimer's disease-related hippocampal shrinkage," Frisoni said. "This initial quantification will help our international panel of experts define which key components should be included in an international harmonized protocol."

### **About AAIC**

The Alzheimer's Association International Conference (AAIC) is the world's largest conference of its kind, bringing together researchers from around the world to report and discuss groundbreaking research and information on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

### **About the Alzheimer's Association**

The Alzheimer's Association is the leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit [www.alz.org](http://www.alz.org) or call 800-272-3900.

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- Kenji Ishii, MD; et al. Age, APOE ε4, and Ethnic Effect on [C-11]PiB in Multi-national ADNI Studies - Direct Comparison of J-ADNI, US-ADNI and AIBL Data. (Funders: New Energy and Industrial Technology Development Organization, Kanagawa, Japan; Ministry of Health Labor and Welfare, Tokyo, Japan)
- Giovanni Frisoni, MD; et al. Estimating the Impact of Differences among Protocols for Manual Hippocampal Segmentation on Alzheimer's Disease-Related Atrophy: Preparatory Phase for a Harmonized Protocol. (Funders: Mike & Barbara Urbut, Stuart & Amy Savitz, Harriet K. Burnstein)

**All materials to be presented at the Alzheimer's Association International Conference on Alzheimer's Disease 2011 are embargoed for publication and broadcast until the date and time of presentation at the conference, unless the Alzheimer's Association provides advance written notice of change of date and/or time.**

Session: Sunday, July 17, 2011 Posters

Presentation: P1-378; 12:30-3:00 pm

### **Age, APOE $\epsilon$ 4, and Ethnic Effect on [C-11]PiB in Multi-national ADNI Studies - Direct Comparison of J-ADNI, US-ADNI and AIBL Data**

Presenting author: Kenji Ishii, MD; Tokyo Metropolitan Institute of Gerontology, Japan

Contact e-mail: ishii@pet.tmig.or.jp

**Background:** It has not been established whether the association between apolipoprotein E (APOE)  $\epsilon$ 4 allele, age, and amyloid deposition is similar or different between ethnic groups. In this study, we evaluated the influence of APOE  $\epsilon$ 4 and age on the cortical accumulation of  $^{11}\text{C}$ -Pittsburgh compound B (PiB) in three multi-center studies of Alzheimer's disease (AD) with harmonized protocol; Alzheimer's Disease Neuroimaging Initiative (US-ADNI, U), Australian Imaging Biomarker and Lifestyle Flagship Study of Aging (AIBL, A), and Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI, J).

**Methods:** We analyzed the initial  $^{11}\text{C}$ -PiB scan data from

- US-ADNI: 19 cognitively normals (NL), 64 mild cognitive impairment (MCI) subjects, and 19 AD patients,
- AIBL: 119 NL, 41 MCI, 27 AD, and
- J-ADNI: 46 NL, 32 MCI, and 21 AD.

All the  $^{11}\text{C}$ -PiB PET images were acquired 50-70 min post-injection. The mean cortical standardized uptake value ratio (mcSUVR) in reference to cerebellar cortex was measured with the same platform of data analysis. The cut-off mcSUVR value for PiB-positivity was set at 1.5 for all the studies.

**Results:** The PiB-positive rate (%) in each group with or without  $\epsilon$ 4 allele ( $\epsilon$ 4+/ $\epsilon$ 4-) were:

- NL (80/57), MCI (83/52), AD (100/88) in US-ADNI;
- NL (56/23), MCI (88/31), AD (100/100) in AIBL; and
- NL (59/7), MCI (100/44), AD (100/80) in J-ADNI.

General linear model and logistic regression model were constructed to predict the mcSUVR and PiB positivity based on age, gene dose of  $\epsilon$ 4 allele (0, 1, 2), and study (U, A, or J) as explanatory variables. Significant positive contribution ( $p < 0.001$ ) was estimated in age and  $\epsilon$ 4, but no significant effect of the study group was observed for either mcSUVR value or PiB positivity in the data set of NL category and overall subjects. A single dose of  $\epsilon$ 4 has equivalent contribution to 11.8 years of age for PiB positivity in NL group (Table 1).

**Conclusions:** Our results suggest that the three multi-national ADNI data are feasible for combined analysis. Study effect or ethnic effect was estimated to be limited, however, age and  $\epsilon$ 4 effect on amyloid deposition is similar in Japanese population to those in Caucasians, despite the lower  $\epsilon$ 4 allele frequency in the Japanese population.

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Session: Sunday, July 17, 2011 Posters  
Presentation: P1-299; 12:30-3:00 pm

**Estimating the Impact of Differences among Protocols for Manual Hippocampal Segmentation on Alzheimer's Disease-Related Atrophy: Preparatory Phase for a Harmonized Protocol**

Presenting author: Giovanni Frisoni, MD; San Giovanni di Dio Fatebenefratelli, Brescia, Italy  
Contact e-mail: gfrisoni@fatebenefratelli.it

**Background:** To quantify the impact of the differences among Magnetic Resonance Imaging (MRI)-based hippocampal segmentation protocols on volume estimates of Alzheimer's disease (AD)-related atrophy, in order to support evidence-based decisions for an internationally harmonized protocol. A harmonized procedure is required, since quantitative MRI should help diagnosis and tracking of AD. A survey of segmentation protocols allowed to operationalize the landmarks variability into segmentation units (SUs) (Figure), and their impact on volume estimates has been preliminarily quantified.

**Methods:** A power analysis was carried out on a preliminary sample, to define the sample size allowing reliable computation. Then, we manually traced each SU within the right and left hippocampi of a larger sample of Alzheimer's Disease Neuroimaging Initiative (ADNI) participants, which included Mild Cognitive Impairment (MCI) patients who subsequently converted to AD and AD patients, all with abnormal Cerebrospinal Fluid (CSF) A $\beta$  levels, and controls (CTRL), with normal CSF A $\beta$  levels.

**Results:** The power analysis indicated a required sample size for the quantification of SUs impact on AD-related volume differences of n=77 (31 CTRL, 23 MCI, 23 AD). So far, 40 subjects (16 CTRL, 12 MCI, 12 AD) have been traced and analyzed. The minimum hippocampal body (red SU in Figure) accounted for over 62% of AD-related volume difference across groups (left: 68.5%, right: 62%, p<0.001); the left alveus/fimbria (yellow SU in Figure) for 7.5% (p=0.01) and the right alveus/fimbria for 3% (p=0.7); the subiculum (green SUs in Figure) for 5% bilaterally (left: p=0.08; right: p=0.03); the left tail (blue SUs in Figure) for 19% (p=0.003), and the right tail for the 30% (p=0.001) of the global difference across groups.

**Conclusions:** The informative value for identifying AD-related atrophy differs across SUs. Its quantification may help a panel of experts to define which SU should be included in a harmonized protocol.

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