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Japanese Alzheimer's Disease Neuroimaging Initiative: Present status and future

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Abstract Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) was launched in 2008, aiming at conducting a longitudinal workup of a standardized neuroimaging, biomarker and clinico-psychological surveys. The research protocol was designed to maximize compatibility with that of US-ADNI, including structural magnetic resonance imaging analysis for the evaluation of brain atrophy, fluorodeoxyglucose and amyloid positron emission tomography, cerebrospinal fluid sampling, *APOE* genotyping, together with a set of clinical and psychometric tests that were prepared to achieve the highest compatibility to those used in the United States. Japanese ADNI has recruited ~357 participants (142 amnestic mild cognitive impairment, ~134 normal aged and 72 mild Alzheimer's disease (AD), as of April 15, 2010). World-wide ADNI activities will establish the rigorous quantitative descriptions of the natural course of AD in its very early stages. The data, as well as the methodologies and infrastructures, will facilitate the clinical trials of disease-modifying therapies for AD using surrogate biomarkers.

Keywords: ADNI; Neuroimaging; Biomarker; Alzheimer's disease; Disease-modifying therapy

Currently, there is a compelling need to establish novel treatments for Alzheimer's disease (AD), and to demonstrate, as well as track, the efficacy of potential treatments in clinical trials, especially those for disease-modifying drugs that target the pathophysiological mechanism of AD. At this time, clinical trials of AD are conducted in a stage of the disease that is considered late in the trajectory of the pathological process. In addition, clinical studies require large numbers of participants with AD because the statistical power of our currently available measures, that is, clinico-neuropsychological scales, is low because of the large fluctuation in data. Thus, biomarkers, including neuroimaging and body fluid chemistry, hold great promise that would assist in many of these challenges.

To identify such biomarkers, Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in the United States in 2005. US-ADNI already completed the recruitment and is continuing the longitudinal follow-up of ~800 participants including mild cognitive impairment (MCI) as the major target population, a major proportion of which represents the very early stage of AD.

We started discussions about the need for Japanese version of ADNI in 2006 for several reasons. First, there was an urgent need to meet with the requirements for global clinical trials of disease-modifying drugs for AD that were about to start in Japan, although we had little experience in nationwide or global-level clinical studies on AD, despite the relatively high activities of neurologists, psychiatrists, and geriatricians who had been involved in the clinical studies of dementia. Second, we did not have sufficient infrastructures, such as clinical study coordination center like Alzheimer's Disease Cooperative Study or imaging data repository like Laboratory of Neuro Imaging, that are required for clinical studies or trials of AD. Third, we realized that we would be able to improve the Japanese AD clinical sciences to an international level by conducting rigorous and comprehensive clinical study like ADNI, in collaboration with international experts in this field.

In this way, we submitted proposals for Japanese ADNI (J-ADNI) to the two major governmental funding agencies, that is, Ministry of health, labor and welfare (MHLW), and

URL of J-ADNI: http://www.j-adni.org/.

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New Energy and Industrial Technology Development Organization (NEDO; a foundation of Ministry of economy, technology, and industry), and got funded in 2007. Seven domestic pharmas (Astellas, Eisai, Daiichi-Sankyo, Dainippon-Sumitomo, Shionogi, Takeda, Tanabe-Mitsubishi) and four international pharmas (Bristol-Myers Squibb, Eli-Lilly, Merck-Banyu, Pfizer) also decided to contribute one-third of the total budget; the total costs for J-ADNI amounts to ∼500 million yen/year.

We designed the research protocol to maximize the compatibility with that of US-ADNI, including structural magnetic resonance imaging (MRI) analysis, fluorodeoxyglucose (FDG) and amyloid positron emission tomography (PET), cerebrospinal fluid sampling, *APOE* genotyping, combined with a set of clinical and psychometric tests that were prepared to achieve the highest compatibility to those used in US-ADNI. We are going to recruit 300 individuals with amnestic MCI (using logical memory cut off based on education), 150 early AD and 150 cognitively normal individuals by the end of 2010, following them up until 2013 (Fig. 1).

The organization of J-ADNI is shown in Fig. 2. In total, 38 clinical sites participated in J-ADNI.

The clinical core is headed by Takashi Asada (Tsukuba University, Psychiatry) and Hiroyuki Arai (Tohoku University, Gerontology) and is responsible for the registration and clinical evaluation of the participants. The clinical core closely collaborates with the neuropsychology core led by Morihiro Sugishita (Niigata Rehabilitation University). During the preparation stage, Sugishita corrected the Japanese translation as well as the configuration of several major clinical and neuropsychological batteries, including ADAS-COG, MMSE, and Clinical Dementia Rating, to maximize the harmonization between English and Japanese versions. Currently, the compatibility of the test batteries is being demonstrated through the analysis of the baseline data of J-ADNI.

Hiroshi Matsuda (Saitama Medical University, MRI core PI), in collaboration with Fumio Yamashita (National Center for Neurology and Psychiatry) and other core members, has established an algorithm to achieve the standardization of MRI scans among clinical sites using different MRI equipments from various vendors, based on 3D-MPRAGE scan protocol using ADNI phantom. They also have created programs for the correction and calibration of signal equity or distortion of the images, which enabled the rigorous volumetric analysis.

Kengo Ito (National Institute for Longevity Sciences, PET core PI) and Michio Senda (Institute of Biomedical Research and Innovation, PET quality control PI) also have established the standardized protocol for PET imaging in J-ADNI, in collaboration with Kenji Ishii (Tokyo Metropolitan Institute for Gerontology, amyloid PET PI). Twenty-eight sites are conducting FDG-PET, so far covering ∼71% of participants (253 cases). Amyloid PET core has established a standardized protocol for ^{11}C-PiB PET using dynamic scan data acquisition (in addition to late-phase images), as well as that for ^{11}C-BF-227, the latter being developed by Kudo and colleagues in Japan. ^{11}C-PiB PET is being conducted in 15 sites and ^{11}C-BF-227 is used in two sites.

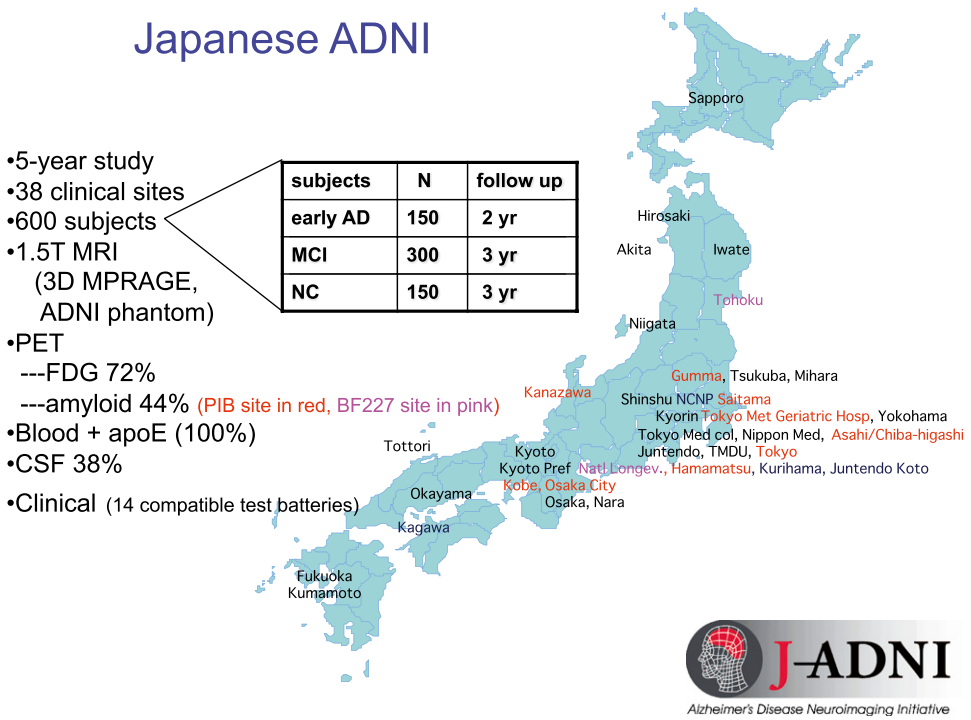

Fig. 1. Overview of J-ADNI.

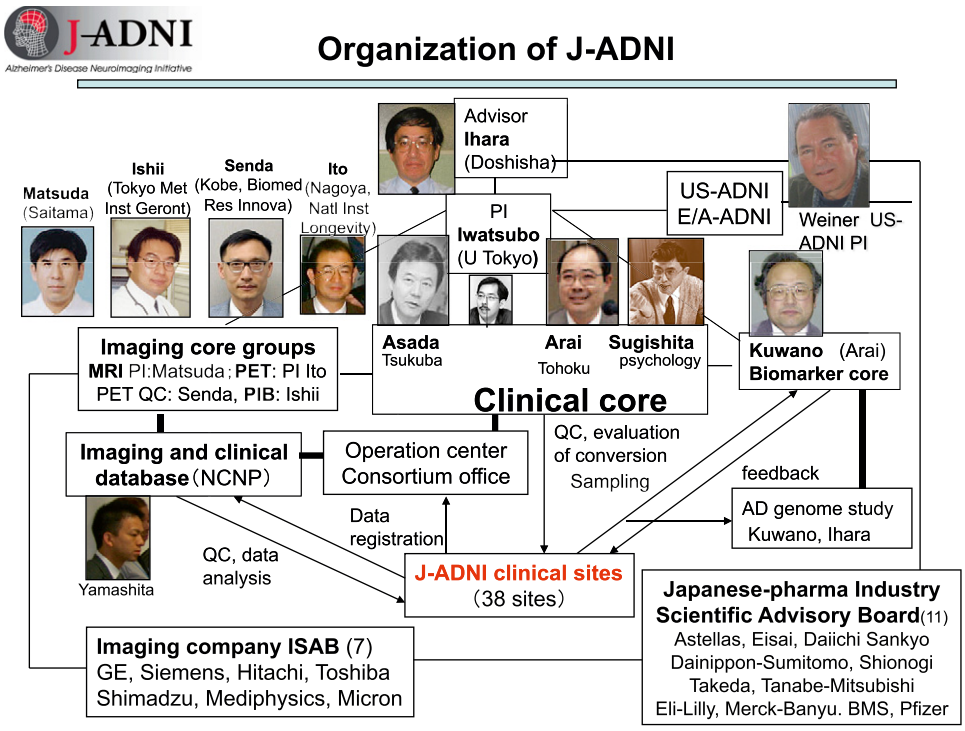

Fig. 2. Organization of J-ADNI.

Currently ~44% of total participants (157 cases) have undergone amyloid PET scan.

Biomarker core is led by Ryozo Kuwano as PI (Niigata University), with the assistance of Hiroyuki Arai as co-PI. They established the J-ADNI biosample repository in Niigata, based on the nationwide collection network of biofluid samples with the assistance of SRL company. Blood samples were collected from all participants upon every visit. So far, 139 participants (~39% of total) had lumber tap and donated cerebrospinal fluid samples. *APOE* genotype also is characterized at the Niigata site.

Until now, 38 clinical sites have screened 483 individuals and enrolled 357 participants who met with the inclusion criteria (151 amnestic MCI, 134 cognitively normal aged, and 72 early AD, as of April 15, 2010). The overall exclusion rate upon screening was 21.0% (8.8% in CN, 27.8% in MCI and 25.0% in AD), which was lower than that in US-ADNI. Currently longitudinal follow-up examination is underway with a relatively low drop-out rate (~6.5%/year).

Use of highly compatible protocols between J-ADNI and US-ADNI will enable us to establish the rigorous quantitative descriptions of the natural course of AD in its very early stages. The data, as well as the methodologies and infrastructures, will facilitate clinical trials of disease-modifying therapies for AD using surrogate biomarkers, enabling the application of effective therapies to AD/MCI patients, and eventually the prevention of AD.

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