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Reviews

Introduction to special issue: Overview of Alzheimer's Disease Neuroimaging Initiative

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Abstract The Alzheimer's Disease Neuroimaging Initiative (ADNI), designed as a naturalistic longitudinal study to develop and validate magnetic resonance, positron emission tomography, cerebrospinal fluid, and genetic biomarkers for use in AD clinical trials, has made many impacts in the decade since its inception. The initial 5-year study, ADNI-1, enrolled cognitively normal, mild cognitive impairment (MCI) and AD subjects, and the subsequent studies (ADNI-GO and ADNI-2) added early- and late-MCI cohorts. The development of standardized methods allowed comparison of data gathered across multiple sites, and these data are available to qualified researchers without embargo. ADNI data have been used in >600 publications including those describing relationships between biomarkers, improved methods for disease diagnosis and the prediction of future decline, and identifying novel genetic AD risk loci. ADNI has provided a framework for similar initiatives worldwide.

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Established in 2004 in response to a need for improved biomarkers in clinical trials of Alzheimer's disease (AD) therapies, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has made and continues to make a profound impact on nearly all aspects of AD pathobiology and patient-oriented research over the past decade. The ADNI team is now looking forward to continuing its work as a longitudinal study incorporating the latest advances in AD research. At

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the beginning of this century, details of the pathophysiological changes leading to neuronal degeneration in AD were lacking [1], mild cognitive impairment (MCI) had just been recognized as a prodromal state of the disease [2], and clinical trials of disease modifying treatments were limited by the lack of sensitivity of clinical and cognitive outcome measures to detect subtle treatment effects. The primary goal of ADNI, therefore, was to develop and validate biomarkers that could function as surrogate outcome measures with greater statistical power than clinical or cognitive measures alone in addition to advancing understanding of the pathobiology of AD [3,4].

1. History and governance

ADNI was initially funded by a combination of public, private, and foundation sources as a 5-year study of normal cognitive aging, MCI, and early AD, enrolling more than 200 elderly control subjects, 400 MCI patients, and 200 early AD patients across 56 sites in the United States and Canada [3]. The initiative was structured as a series of eight cores (Clinical, Magnetic Resonance Imaging [MRI], Positron Emission Tomography [PET], Biomarker, Genetics, Neuropathology, Biostatistics, and Informatics) under the direction of an Administrative Core and was overseen by a Steering and Executive Committee consisting of representatives from all funding sources as well as principal investigators of the ADNI sites [5]. In addition, a Private Partner Scientific Board convened by the Foundation for the National Institutes of Health provided an opportunity for industry partners to exchange study-related scientific data in a precompetitive manner, and a Data And Publications Committee monitored scientific publications arising from ADNI research and data [5]. A subsequent Grand Opportunities grant funded ADNI-GO which enrolled a new cohort of 200 early MCI patients, and a competitive renewal of ADNI-1 in 2011, termed ADNI-2, enrolled 150 elderly controls, 100 early MCI, 150 late MCI, and 150 AD patients in addition to existing ADNI-1 and ADNI-GO cohorts. Successive studies added new technologies such as functional MRI, amyloid imaging using ^{11}C-Pittsburg compound and then ^{18}F-AV45 radioligands, and MRI techniques to detect microhemorrhages. Some subjects have now been monitored for 10 years, providing critical longitudinal data.

2. Data sharing

A groundbreaking feature of ADNI from its beginning was the resolve to make all data generated available to qualified researchers worldwide. This open data sharing was unprecedented for NIH-funded studies. To achieve this, the Informatics Core constructed a sophisticated infrastructure based at the Laboratory of Neuroimaging, currently at the University of Southern California, to facilitate the storage, curating and sharing of ADNI imaging, biomarker, clinical, and genetic data [6].

3. Relationships between biomarkers

ADNI data have been used in >600 publications spanning multiple scientific areas ranging from epidemiology to computer science to genetics and beyond. Two early studies established a biomarker "signature" for AD that defined a series of cut points for cerebrospinal fluid (CSF) biomarkers beyond which a patient would be considered to have a high probability of the disease [7,8]. Combining low $A\beta_{42}$ and high t-tau or p-tau_{181} levels, these signatures identified AD pathology in AD patients as expected [7], but also suggested that cognitively normal participants could harbor abnormal tau and Aβ brain pathology [8]. Early longitudinal biomarker data contributed to a provocative model for the temporal ordering of pathophysiological changes occurring during the progression of AD by Jack et al. [9], which has been subsequently refined based on analysis of further ADNI data [10,11], and which is supported by many studies [12]. Perhaps the most influential ADNI article, the Jack et al. [9] temporal ordering of ADNI biomarkers is the most widely accepted working model of AD biomarker dynamics.

4. Diagnosis

The rich and continually growing ADNI data set has provided opportunities for researchers to investigate new approaches to the challenges of diagnostic classification and the prediction of future clinical change in subjects ranging from those who are cognitively normal to those with MCI or who have manifest AD. Vemuri et al. [13] first combined MRI and CSF biomarkers for AD diagnosis and the prediction of future clinical decline [14], finding that CSF biomarkers increased the diagnostic accuracy and predictive ability of MRI measures. Subsequently, a multimodal classifier that selected MRI and fluorodeoxyglucose PET regions of interest and combined them with CSF biomarker data proved highly accurate [15]. This marked the transition to the use of the full breadth of ADNI data for these tasks, and recent studies have continued to improve accuracy by focusing on the selection of features that are most AD like across multiple modalities and by incorporating longitudinal data [12].

5. Genetics

As of the end of 2014, there were 2065 distinct *APOE* genotype data results available, and genome-wide association study (GWAS) data were available for 1252 participants within ADNI. Over 200 publications have used ADNI genetic data, representing a contribution to AD genetics that extends far beyond the original mandate of the initiative. In 2009, Potkin et al. [16] reported the first ADNI GWAS using MRI hippocampal volume as quantitative trait. Since then, the ADNI Genetics Core has pioneered the first GWAS using measures of CSF Aβ and tau [17], whole brain region of interests [18], longitudinal hippocampal MRI