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Review Article

The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception

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Abstract The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD). The study aimed to enroll 400 subjects with early mild cognitive impairment (MCI), 200 subjects with early AD, and 200 normal control subjects; $67 million funding was provided by both the public and private sectors, including the National Institute on Aging, 13 pharmaceutical companies, and 2 foundations that provided support through the Foundation for the National Institutes of Health. This article reviews all papers published since the inception of the initiative and summarizes the results as of February 2011. The major accomplishments of ADNI have been as follows: (1) the development of standardized methods for clinical tests, magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF)

The highlighted text in the PDF version of the article indicate updated text.

Conflicts of interest: please refer to section 9. Disclosures.

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biomarkers in a multicenter setting; (2) elucidation of the patterns and rates of change of imaging and CSF biomarker measurements in control subjects, MCI patients, and AD patients. CSF biomarkers are consistent with disease trajectories predicted by β-amyloid cascade (Hardy, J Alzheimers Dis 2006;9(Suppl 3):151–3) and tau-mediated neurodegeneration hypotheses for AD, whereas brain atrophy and hypometabolism levels show predicted patterns but exhibit differing rates of change depending on region and disease severity; (3) the assessment of alternative methods of diagnostic categorization. Currently, the best classifiers combine optimum features from multiple modalities, including MRI, [^{18}F]-fluorodeoxyglucose-PET, CSF biomarkers, and clinical tests; (4) the development of methods for the early detection of AD. CSF biomarkers, β-amyloid 42 and tau, as well as amyloid PET may reflect the earliest steps in AD pathology in mildly symptomatic or even nonsymptomatic subjects, and are leading candidates for the detection of AD in its preclinical stages; (5) the improvement of clinical trial efficiency through the identification of subjects most likely to undergo imminent future clinical decline and the use of more sensitive outcome measures to reduce sample sizes. Baseline cognitive and/or MRI measures generally predicted future decline better than other modalities, whereas MRI measures of change were shown to be the most efficient outcome measures; (6) the confirmation of the AD risk loci *CLU*, *CR1*, and *PICALM* and the identification of novel candidate risk loci; (7) worldwide impact through the establishment of ADNI-like programs in Europe, Asia, and Australia; (8) understanding the biology and pathobiology of normal aging, MCI, and AD through integration of ADNI biomarker data with clinical data from ADNI to stimulate research that will resolve controversies about competing hypotheses on the etiopathogenesis of AD, thereby advancing efforts to find disease-modifying drugs for AD; and (9) the establishment of infrastructure to allow sharing of all raw and processed data without embargo to interested scientific investigators throughout the world. The ADNI study was extended by a 2-year Grand Opportunities grant in 2009 and a renewal of ADNI (ADNI-2) in October 2010 through to 2016, with enrollment of an additional 550 participants.

Keywords: Alzheimer's disease; Mild cognitive impairment; Amyloid; Tau; Biomarker

1. Introduction to Alzheimer's Disease Neuroimaging Initiative: Goals, history, and organization

1.1. Background

Alzheimer's disease (AD), the most common form of dementia, is a complex disease characterized by an accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles composed of tau amyloid fibrils [1] associated with synapse loss and neurodegeneration leading to memory impairment and other cognitive problems. There is currently no known treatment that slows the progression of this disorder. According to the 2010 World Alzheimer report, there are an estimated 35.6 million people worldwide living with dementia at a total cost of more than US$600 billion in 2010, and the incidence of AD throughout the world is expected to double in the next 20 years. There is a pressing need to find biomarkers to both predict future clinical decline and for use as outcome measures in clinical trials of disease-modifying agents to facilitate phase II-III studies and foster the development of innovative drugs [2]. To this end, Alzheimer's Disease Neuroimaging Initiative (ADNI) was conceived at the beginning of the millennium and began as a North American multicenter collaborative effort funded by public and private interests in October 2004. Although special issues focused on North American ADNI have been published in *Alzheimer's and Dementia* [3] and *Neurobiology of Aging* [4] in addition to a number of other review articles [5–12], the purpose of this review is to provide a detailed and comprehensive overview of the approximately 200 papers that have been published as a direct result of ADNI in the first 6 years of its funding.

1.2. Disease model and progression

One approach toward a greater understanding of the events that occur in AD is the formulation of a disease model [3,12–16]. According to the Aβ hypothesis, AD begins with the abnormal processing of the transmembrane Aβ precursor protein. Proteolysis of extracellular domains by sequential β and γ secretases result in a family of peptides that form predominantly β-sheets, the β-amyloids (Aβ) (Fig. 1). The more insoluble of these peptides, mostly Aβ42, have a propensity for self-aggregation into fibrils that form the senile plaques characteristic of AD pathology. Subsequently, it is thought that the microtubule-associated tau protein in neurons becomes abnormally hyperphosphorylated and forms neurofibrillary tangles that disrupt neurons. However, although ADNI and other biomarker data support this sequence of events, by direct examination of postmortem human brains, Braak and Del Tredici have shown that tau pathology in the medial temporal limbic isocortex precedes the development of Aβ deposits with advancing age in the human brain [17]. Downstream processes such as oxidative and inflammatory stress contribute to loss of synaptic and neuronal integrity, and eventually, neuron loss results in brain atrophy. Jack et al [14,16] presented a hypothetical model for biomarker dynamics in AD pathogenesis. The model begins with the abnormal deposition of Aβ fibrils,