

Alzheimer's کئ Dementia

Alzheimer's & Dementia 6 (2010) 202-211

**Review Articles** 

# The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans

Michael W. Weiner<sup>a,b,\*</sup>, Paul S. Aisen<sup>c</sup>, Clifford R. Jack, Jr.,<sup>d</sup>, William J. Jagust<sup>e</sup>,

John Q. Trojanowski<sup>f</sup>, Leslie Shaw<sup>f</sup>, Andrew J. Saykin<sup>g</sup>, John C. Morris<sup>h</sup>, Nigel Cairns<sup>h</sup>, Laurel A. Beckett<sup>i</sup>, Arthur Toga<sup>j</sup>, Robert Green<sup>k</sup>, Sarah Walter<sup>1</sup>, Holly Soares<sup>m</sup>, Peter Snyder<sup>n</sup>, Eric Siemers<sup>o</sup>, William Potter<sup>p</sup>, Patricia E. Cole<sup>q</sup>, Mark Schmidt<sup>r</sup>; and the Alzheimer's Disease Neuroimaging Initiative

<sup>a</sup>Center for Imaging of Neurodegenerative Diseases, San Francisco VA Medical Center, San Francisco, CA, USA

<sup>b</sup>Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA

<sup>c</sup>Department of Neuroscience, University of California, San Diego, San Diego, CA, USA

<sup>d</sup>Department of Radiology, Mayo Clinic, Rochester, MN, USA

<sup>e</sup>Neuroscience Institute, University of California, Berkeley, Berkeley, CA, USA

<sup>f</sup>Department of Pathology and Lab Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>g</sup>Department of Radiology & Imaging Sciences, Indiana University, Bloomington, IN, USA

<sup>h</sup>Department of Neurology, Washington University, St Louis, MO, USA

<sup>i</sup>Department of Public Health Sciences, University of California, Davis, Davis, CA, USA <sup>j</sup>Department of Neurology-LONI, University of California, Los Angeles, Los Angeles, CA

<sup>k</sup>Department of Neurology School of Medicine, Boston University, Boston, MA, USA

<sup>1</sup>Department of Neuroscience, University of California, San Diego, San Diego, CA, USA

<sup>m</sup>Translational Medicine, Pfizer Global Research and Development, Groton, CT, USA

<sup>n</sup>Department of Bio Med Neurology, Brown University, Providence, RI, USA

<sup>o</sup>Alzheimer's disease research, Eli Lilly and Company, Indianapolis, IN, USA

<sup>p</sup>Translational Neuroscience, Merck Research Laboratories, Rahway, NJ, USA

<sup>q</sup>Imagepace, Cincinnati, OH, USA

<sup>r</sup>Pharmaceutical Research and Development, Johnson & Johnson, Antwerp Area, Belgium

Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in October 2004, is a 6-year research project that studies changes of cognition, function, brain structure and function, and biomarkers in elderly controls, subjects with mild cognitive impairment, and subjects with Alzheimer's disease (AD). A major goal is to determine and validate MRI, PET images, and cerebrospinal fluid (CSF)/blood biomarkers as predictors and outcomes for use in clinical trials of AD treatments. Structural MRI, FDG PET, C-11 Pittsburgh compound B (PIB) PET, CSF measurements of amyloid  $\beta$  (A $\beta$ ) and species of tau, with clinical/cognitive measurements were performed on elderly controls, subjects with mild cognitive impairment, and subjects with AD. Structural MRI shows high rates of brain atrophy, and has high statistical power for determining treatment effects. FDG PET, C-11 Pittsburgh compound B PET, and CSF measurements of A $\beta$  and tau were significant predictors of cognitive decline and brain atrophy. All data are available at UCLA/LONI/ADNI, without embargo. ADNI-like projects started in Australia, Europe, Japan, and Korea. ADNI provides significant new information concerning the progression of AD. © 2010 The Alzheimer's Association. All rights reserved.

### Keywords: ADNI; Alzheimer's disease; MRI; PET; Amyloid; Memory; Tau

This article is dedicated to Leon Thal, who passed away 1 year after ADNI began. His vision was critical in the creation and successful funding of ADNI. \*Corresponding author. Tel.: 415-221-4810 x3642; Fax: 415-668-2864. E-mail address: michael.weiner@ucsf.edu

E-mail address: michael.weiner@ucsi.edu

 $<sup>1552\</sup>text{-}5260/\$$  – see front matter 0 2010 The Alzheimer's Association. All rights reserved. doi:10.1016/j.jalz.2010.03.007

# 1. Introduction

# 1.1. Historical background and rationale for ADNI

Alzheimer's disease currently affects more than five million patients in the U.S. and will rise to 16 million by 2050 [1], costing the U.S. economy more than \$140 billion/yr [1,2]. Globally, an estimated 35.6 million people have dementia (largely because of AD), which is expected to reach 65.7 million in 2030 and 115.4 million in 2050 [3]. It is generally accepted that there is a pressing need to develop effective disease-modifying treatments to slow or halt progression of AD pathology to be used in subjects with dementia, mild cognitive impairment (MCI), and in control subjects at risk for development of cognitive decline and dementia. Presently, no treatments have been convincingly demonstrated to slow the progression of AD pathology.

The historical background to Alzheimer's Disease Neuroimaging Initiative (ADNI) is a long and complex story, best summarized in Reference [4]. Because AD is a disorder which affects cognition (especially memory) and leads to dementia, for many years a major focus was the behavioral characterization of the disorder including the development of standardized methods for assessment, diagnosis, and monitoring of progression of clinical symptoms and impairments. The recognition that AD dementia slowly develops as part of a spectrum from normal aging to MCI sprang out of the clinical and behavioral context. At the same time, for the past 20-30 years, a number of biological methods have been increasingly used to obtain quantitative information concerning changes in the brain and in biological fluids which occur in AD. Most notably, the development of FDG PET and MRI in the 1970s has led to an increasingly large body of knowledge about the changes in AD. Furthermore, changes in cerebrospinal fluid (CSF) proteins, notably abeta and tau, have also been studied for many years. One important highlight in the use of biomarkers was an National Institutes of Health (NIH) conference in 2000, organized by Dr Neil Buckholz, concerning the use of Biomarkers in AD. Shortly thereafter, the Alzheimer's Imaging Consortium was established as a forum for discussion and exchange of ideas and information concerning using MRI and PET to study AD. In summary, during the 1980s and particularly the 1990s, there was increasing research activity using a wide variety of biomarkers, especially MRI, FDG PET, and measurements of CSF to study this disorder. Many investigators were reporting studies using different methods on different cohorts of subjects. Thus, it was somewhat difficult to compare the value of all these different methods. The need to develop a large cohort, in which the methods could be compared, became increasingly obvious to all in the field.

The original impetus for the ADNI began around 2000, when it was observed that many academic investigators, pharmaceutical companies, and biotech companies were beginning to develop treatments aimed at slowing the progression of AD. Measurements of cognition or conversion from MCI (generally accepted as a precursor to dementia) to dementia could not in themselves demonstrate that the treatments were slowing disease progression, because impaired cognition in AD and MCI can be improved with symptomatic treatments such as acetylcholinesterase inhibitors. Additionally, in 2000, there were insufficient standards for obtaining or measuring imaging and/or biomarkers for AD for the numerous investigators who were studying disease progression by measuring various imaging and CSF/blood biomarkers. Also lacking at the time was sufficient data to determine the relative value of biomarker measures to detect progression of AD in treatment trials. A comprehensive understanding of the sequence of pathophysiological events that cause AD and lead to dementia at the molecular, cellular, brain, and clinical levels was clearly needed. In addition, measurements that identify the various elements and the factors that influence AD pathology in living human subjects needed to be developed for use in early diagnosis and as risk factors and/or predictors for cognitive decline or dementia. Such measurements could eventually have utility in clinical trials and practice and thus support the ultimate goal of AD research to develop treatments that can slow the progression of AD and ultimately prevent the development of AD (either secondary, prevention, or primary prevention).

# 1.2. Disease model

ADNI research is based on a model (Fig. 1) positing that AD begins with A $\beta$  accumulation in the brain, which ultimately leads to synaptic dysfunction, neurodegeneration, and cognitive or functional decline. This predicts that the earliest detectable changes (measured in the ADNI project) are those related to A $\beta$  (detected in CSF and by PET amyloid imaging). Subsequently, neurodegeneration is detected by a rise of CSF tau species, synaptic dysfunction (measured by FDG-PET), and neuron loss indicated by atrophy, most notably in



Fig. 1. Overall model of changes in the progression from normal aging to MCI to AD.

medial temporal lobe (measured with MRI). The temporal sequence of changes in A $\beta$  deposition, CSF tau species, and imaging using FDG-PET and MRI remains to be determined. These changes ultimately lead to memory loss, general cognitive decline, and eventually dementia. Expression of each element of AD pathology (e.g., A $\beta$  and tau deposits, atrophy) is influenced by many modifying factors including age, *APOE* genotype, and cerebrovascular disease (white matter lesions detected by fluid attenuated recovery [FLAIR MRI]) and microbleeds (detected by T2\* MRI), and there are expected to be wide differences among individuals.

Although this simple model does not convey the complexities of the relationships among aging, tau phosphorylation and conformational change, amyloid peptide accumulation and conformational change, synaptic dysfunction and neuronal loss, we believe it is useful for the interpretation of biomarker, cognitive and clinical data from ADNI and other studies, and in the incorporation of biomarker measures into trial designs.

The ADNI project, however, is not built around, and does not depend on, the amyloid hypothesis. Despite the evidence in favor of this hypothesis [5], other evidence does not necessarily support all aspects of it. For example, the early Braak stage consists of tau tangles and synapse loss in the entorhinal cortex and hippocampus without amyloid accumulation [6-8]. In addition, there is poor correlation between brain amyloid level and cognitive impairment. A follow-up study of subjects in the Wyeth Elan 1792 vaccine trial showed amyloid removal (at pathology) in some subjects, while they continued to decline cognitively [9]. One possibility is that subjects with dementia have such severe brain damage that amyloid removal does not slow progression of symptoms. However, the failure of anti-amyloid clinical trials could be due to many reasons, including the possibility that the treatments did not sufficiently reduce brain amyloid. In possible support of this model, it has been recently reported (in one subject) that CSF amyloid falls before development of C-11 Pittsburgh compound B (PIB) positivity, which precedes cognitive impairment [10]. Replication and extension of this sequence of events in a multisite study with large sample size will provide critical information concerning the neuroscience of AD.

An important point to emphasize is that we have limited information concerning the pathophysiological sequence of events of AD in human beings from autopsy studies and from studies measuring only cognition. Our model suggests that different imaging modalities, measurements, and different biochemical markers will usefully serve as predictors (measurements which predict future change) and outcomes (measurements that detect change) at different stages in the transition from normal aging, to MCI, to dementia. Furthermore, the model suggests that the measurements most likely to predict decline in normal subjects will be the detection of A $\beta$  in CSF, using PET perhaps in combination with measurements of CSF tau species, the use of brain imaging by FDG-PET, and MRI. Although amyloid biomarkers may be useful predictors of decline in early MCI (EMCI), CSF tau measurements, FDG-PET, and MRI measures of regional atrophy, which likely change after amyloid markers change, may be more predictive. In late MCI (LMCI) and AD, we hypothesize that the most effective biomarkers for prediction of further decline will be FDG-PET, MRI, and cognition. Biomarkers that are most likely to correlate with, and augment the utility of, cognitive and clinical measures as outcomes in clinical trials are FDG-PET, possibly MRI measures of volume (especially of hippocampus and temporal cortex) at early stages, and atrophy throughout the brain at later stages. However, it is recognized that the performance of the various imaging and CSF/blood measurements depends both on the biological sequence of events as well as the sensitivity, accuracy, and precision of the various measurements. Thus, for example, a test which best predicts future cognitive decline in normal subjects may not necessarily represent the earliest biological change, but rather the earliest change that is detected by a sensitive and robust test.

#### 1.3. Goals of ADNI

The overarching goals of ADNI, therefore, were to determine the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of AD as the pathology evolves from normal aging through very mild symptoms, to MCI, to dementia, and to establish standardized methods for imaging/biomarker collection and analysis for ultimate use in clinical trials.

Initially, ADNI primarily aimed to ascertain the relative value of various imaging, and CSF/blood biomarkers as outcome measures in trials of AD and MCI subjects. Specific goals to this end included the validation of MRI and PET imaging, and of blood and CSF biomarker measures by examining their relationships with cognitive and functional measures, the identification of the most effective measures for monitoring treatment effects in different stages in the progression of normal aging, through MCI to AD, and the development of statistical models of cross-sectional and longitudinal clinical, imaging, and biomarker data, which could be used for future hypothesis generation and testing. Other goals of ADNI were to develop improved standardized methods for performing AD trials by creating uniform standards for MRI and PET acquisition, to develop improved methods of acquiring and processing multisite longitudinal data that would increase costeffectiveness and power of future treatment trials, and to develop statistical models of cross-sectional and longitudinal clinical, imaging, and biomarker data that could be used for future hypothesis generation and testing. Finally, ADNI aimed to create a data repository for academics and industry for a multiplicity of purposes. This repository would provide further information regarding longitudinal changes in brain structure, function, cognition, blood, urine, and CSF biomarkers that occur in normal aging, MCI, and AD as well as transitions from one of these states to another. Data generated by ADNI would be available to qualified scientists worldwide without embargo.

In the 5 years since the funding of ADNI in 2004, there has been increased interest in the use of imaging and CSF/blood biomarkers to identify AD pathology in subjects before dementia, and to develop diagnostic criteria that use these measurements [11]. Data from ADNI have proved to be a valuable resource to address these issues, and thus the development of imaging and CSF/blood biomarkers as predictors has become an important goal of ADNI.

#### 1.4. Identification of outcomes and predictors

Different biomarkers will be effective *predictors* of cognitive decline or dementia or *outcomes* (measures of change) at different stages across the continuum from normal cognition to AD dementia. Understanding the sequential change of biomarkers and their relative value as predictors and outcomes at the presymptomatic, mild symptoms or MCIs, and dementia stages of the disease is crucial to understanding the neuroscience of AD, and may lead to improved diagnostic tests and facilitate design and power calculations of clinical trials for disease-modifying agents.

Measures of rates of change serve as *outcomes* in clinical trials. A problem with AD clinical trials is the length of time and large sample sizes required because of the high variability of clinical and cognitive measures. Numerous reports suggested that changes in brain structure (detected by MRI) or brain glucose metabolism (detected by FDG-PET) had higher statistical power to detect change than clinical or cognitive measures because of their low variability. Interest in biomarkers was further increased because measures of function and cognition are affected by many things (e.g., depression, other illnesses) in addition to features of AD, are potentially affected by drugs such as cognitive enhancers, have low statistical power to determine effects of disease-modifying treatments, and only indirectly reflect disease progression.

Furthermore, biomarkers that directly or indirectly measure AD pathology may be used as predictors of cognitive decline or dementia. Such predictors will assist in the enrichment and selection of subjects with mild impairment and in normal elderly subjects for treatment trials and even prevention trials. It is generally accepted that AD pathology (amyloid plaques, tau tangles, synapse loss, gross neuron loss, and brain shrinkage) begins many years before dementia and often exists with no evidence of cognitive impairment. The cognitive impairment caused by AD pathology is thought to occur within the context of the cognitive changes which occur in normal aging, and is characterized initially by problems with memory functioning. This progresses to deficits in other cognitive domains, functional abilities, and frank dementia. Evidence exists that the pathological and cognitive changes are nonlinear in that there is a gradual acceleration of pathological and cognitive changes. There is a compelling need to identify measurements that identify the presence and extent of AD pathology in the living brain, thus characterizing the stage of disease. Because of the nonlinear nature of the process, knowledge of the stage of progression could potentially be used to predict the future rate of cognitive decline and the future occurrence of dementia (the more advanced the progression, the greater the rate of future change). As amyloid plaques develop, considerable evidence suggests that CSF Aβ amyloid decreases [12,13]. Thus, CSF A $\beta$  is a putative measure of brain amyloid deposition. Brain amyloid is directly detected by PET amyloid ligands. CSF tau increases in the progression of controls to MCI to AD [12,13], and is a putative measure of the deposition of tau tangles and neurodegeneration. No direct measures of brain synaptic density exist in human beings, but brain activity is reduced as synaptic density falls, and FDG-PET is a quantitative measure of brain activity that appears to identify early AD. Structural MRI detects brain atrophy, and hippocampal volume shrinkage has been correlated with neuronal loss [14] and neurofibrillary tangles . Thus, each of these measures has predictive value, but their relative values at the different stages across the continuum have not been established. Several investigators have proposed that imaging and CSF biomarkers could be used to identify AD pathology in subjects who are not demented, and could thus be used for diagnosis of AD [11]. Several pharmaceutical companies and the Alzheimer's Disease Cooperative Study (ADCS) have proposed performing AD treatment studies using subjects with early AD, meaning nondemented subjects with cognitive impairments who have imaging/CSF biomarker evidence of AD pathology (especially low CSF Aβ and/or C-11 PIB positivity), but the value of this approach has not been established. Genetics may also be considered a predictor in AD. ADNI included analysis of the APOE ɛ4 gene during enrolment to balance the frequency of this gene in the PET and CSF substudies. Subsequently, a genome-wide association analysis was performed on the DNA of all ADNI subjects.

#### 2. Methods

#### 2.1. ADNI structure and organization

ADNI is structured as eight cores under the auspices of the Administrative Core, directed by Dr Weiner, the principle Investigator. ADNI is a U01 cooperative agreement grant, and the NIA requires that this project be governed by a Steering Committee consisting of Dr Weiner and all funded Core leaders, all Site Principal Investigators, representatives from the NIH and US Food and Drug Administration (FDA), and representatives from each of the contributing companies as observers only. The day to day decisions are made by the ADNI Executive Committee (Excom) which includes the Principal Investigator, the Core leaders, a representative of the NIA (Dr Buckholtz), the current, past, and future Chairs of the Industry Scientific Advisory Board (ISAB; as observers), and David Lee of the Foundation for the NIH (as an observer). The governance and organization of ADNI are depicted in Fig. 2.



Fig. 2. Patient recruitment sites in ADNI (provided by Sarah Walter at ADCS).

The original cooperative agreement (U01) grant, termed ADNI1, was funded as a public/private partnership with \$40 million from NIA and \$20 million from 13 companies in the pharmaceutical industry and two Foundations, for a total of \$60 million. Since then, additional companies have joined, bringing the total to 22. An additional \$7 million has been provided in the form of supplements for (1) the C-11 PIB sub-study; (2) the lumbar puncture extension (beyond the original 1 year of funding); and (3) the genome-wide association analysis of the DNA of all ADNI subjects. All funds from industry are provided to the Foundation for NIH which then provides the combined funds to NIA who awards funds in the form of a UO1 grant to ADNI. (Table 1).

All sites are managed by the ADNI Clinical Core at the ADCS, University of California, San Diego (Paul Aisen, PI). The Data and Publications Committee (DPC) vets all publications using ADNI data (see description in the supplemental references, online only). The ISAB is composed of representatives from all companies which provide funds to ADNI and is managed by the Foundation for NIH. The ISAB is chaired on a rotating basis. Chairs have included William Potter (Merck 2005, 2006), Eric Siemers (Lilly, 2007), Patricia Cole (Eisai, 2008), Holly Soares (Pfizer, 2009), and in 2010 Mark Schmidt (Novartis).

The Scientific Advisory Board is Chaired by Zaven Khachaturian, meets annually, and has consisted of many prominent physicians and scientists including Lewis Kuller, Dennis Choi, Gregory Sorensen, Peter Snyder, William Thies, Howard Fillit, William Friedewald, Richard Frank, Richard Frakowiack, and Thomas Budinger.

All requests for specimens (blood, plasma, CSF, DNA, immortalized cell lines) go directly to the Resource Allocation Review Committee (RARC), consisting of members independent of ADNI, approved by the NIA, and chaired by Dr Tom Montine at the University of Washington, Seattle, Washington. After approval by the RARC, the NIA must approve release of all specimens.

#### 2.1.1. Administrative core

The Administrative Core is located at the San Francisco VA Medical Center/University of California, San Francisco/NCIRE. It consists of the Principal Investigator of ADNI (M.W. Weiner), his administrative staff, statistical support, and the DPC administered by Robert Green at Boston University. Dr Weiner has responsibility for all administrative, financial, and scientific aspects of ADNI. In addition to the highly complex administration of grant finances, some image analysis of ADNI data, using FreeSurfer (from Massachusetts General Hospital, Bruce Fischl,

Table 1
ADNI site table

Site	City	State	Site PI	Study coordinator
Oregon Health and Science University	Portland	OR	Kaye, Jeffrey	Dolen, Sara
University of Southern California	Los Angeles	CA	Schneider, Lon	Becerra, Mauricio
University of California, San Diego	La Jolla	CA	Brewer, James	Vanderswag, Helen
University of Michigan, Ann Arbor	Ann Arbor	MI	Heidebrink, Judith	Lord, Joanne
Mayo Clinic, Rochester	Rochester	MN	Petersen, Ronald	Johnson, Kris
Baylor College of Medicine	Houston	TX	Doody, Rachelle	Chowdhury, Munir
Columbia University	New York	NY	Stern, Yaakov	Yeung, Philip
Washington University, St. Louis	St. Louis	MO	Morris, John	Oliver, Angela
University of Alabama, Birmingham	Birmingham	AL	Marson, Daniel	Ledlow, Denise
Mount Sinai School of Medicine	New York	NY	Grossman, Hillel	Marzloff, George
Rush University Medical Center	Chicago	IL	deToledo-Morrell, Leyla	Samuels, Patricia
Wien Center for Clinical Research	Miami Beach	FL	Duara, Ranjan	Roberts, Peggy
Johns Hopkins University	Baltimore	MD	Albert, Marilyn	Shao, Shuai
New York University Medical Center	New York	NY	Rusinek, Henry	Glodzik-Sobanska, Lidia
Duke University Medical Center	Durham	NC	Doraiswamy, P. Murali	Aiello, Marilyn
University of Pennsylvania	Philadelphia	PA	Arnold, Steven	Nunez-Lopez, Jessica
University of Kentucky	Lexington	KY	Smith, Charles	Martin, Barbara
University of Pittsburgh	Pittsburgh	PA	Lopez, Oscar	Oakley, MaryAnn
University of Rochester Medical Center	Rochester	NY	Ismail, M. Saleem	Brand, Connie
University of California, Irvine	Irvine	CA	Mulnard, Ruth	McAdams-Ortiz, Catherine
University of Texas, Southwestern MC	Dallas	TX	Womack, Kyle	Martin-Cook
Emory University	Atlanta	GA	Levey, Allan	Cellar, Janet
University of Kansas	Kansas City	KS	Burns, Jeffrey	Laubinger, Pat
University of California, Los Angeles	Los Angeles	CA	Apostolova, Liana	Eastman, Jennifer
Mayo Clinic, Jacksonville	Jacksonville	FL	Graff-Radford, Neill	Jonnson, Heatner
	Indianapolis	IN	Farlow, Martin	Herring, Scott
Y ale University School of Medicine	New Haven		Van Dyck, Christopher	Benincasa, Amanda
Sumawharak Haalth Saianaga Cantar	Toronto	QC	Cherikow, Howard	Hosein, Chris
Sunnybrook Healin Sciences Centre	1 oronto Venecuwer		Black, Sandra	Lawrence, Joanne Mudgo, Popito
St. Joseph's Health Center Cognitive Neurology	London	ON	Finger Elizabeth	Mudge, Berlina Morlog, Derlyno
St. Joseph S Health Center-Cognitive Neurology	Chicago	UN II	Wu John (Chuang Kuo)	Lipowski Kristine
Medical University of South Carolina	North Charleston	IL SC	Mintzer Jacobo	Williams Arthur
Premiere Research Institute	West Palm Beach	FL	Sadowsky Carl	Villena Teresa
University of California San Francisco	San Francisco	CA	Rosen Howard	Urbano Marissa
Georgetown University	Washington	DC	Reynolds Brigid	Behan Kelly
Brigham and Women's Hospital	Boston	MA	Sperling, Reisa	Frey, Meghan
Stanford / PAIRE	Palo Alto	CA	Yesavage, Jerome	
Banner Sun Health Research Institute	Sun City	AZ	Sabbagh, Marwan	Sirrel, Sherve
Boston University	Boston	MA	Killiany, Ron	Wulff, Megan
Howard University	Washington	DC	Obisesan, Thomas	Wolday, Saba
Case Western Reserve University	Beachwood	OH	Lemer, Alan	Hudson, Jr., Leon
University of California, Davis	Martinez	CA	Olichney, John	Vieira, Katharine
Neurological Care of CNY	Syracuse	NY	Kittur, Smita	Cowley, Charity
Dent Neurologic Institute	Amherst	NY	Bates, Vernice	Rainka, Michelle
Parkwood Hospital	London	Ontario	Borrie, Michael	Best, Sarah
University of Wisconsin	Madison	WI	Johnson, Sterling	Harding, Sandra
University of California, Irvine (BIC)	Irvine	CA	Potkin, Steven	Ceballos III, Edward
Banner Alzheimer's Institute	Phoenix	AZ	Fleisher, Adam	Reeder, Stephanie
Ohio State University	Columbus	OH	Scharre, Douglas	Knick, Jennifer
Albany Medical College	Albany	NY	Zimmerman, Earl	Cowan, John
Thomas Jefferson University	Philadelphia	PA	Marenberg, Marjorie	Maloney, Eileen
Olin Neuropsychiatry Research Center	Hartford	СТ	Pearlson, Godfrey	Anderson, Karen
Dartmouth Medical Center	Lebanon	NH	Saykin, Andrew	Englert, Jessica
Wake Forest University Health Sciences	Winston Salem	NC	Williamson, Jeff	Gordineer, Leslie
Rhode Island Hospital	Providence	KI	Ott, Brian	Oden, Esther
Cleveland Clinic Lou Ruvo Center for Brain Health	Las Vegas	NV DI	Bernick, Charles	Sholar, Michelle
butter nospital memory and Aging Program	riovidence	KI	Sanoway, Stephen	i irpaeck, Lincoln



Fig. 3. Governance and organization of ADNI.

PI) is performed at the San Francisco, VA, overseen by Dr Schuff. This work is part of the MRI Core (Fig. 3).

# 2.1.2. Data and publications committee (DPC: PI Robert Green)

The DPC performs three tasks: (1) It develops and proposes policy to the Executive and Steering Committees regarding data access and publication; (2) It screens all applications for access to ADNI data; and (3) It reviews all publications for adherence to ADNI publication policy guidelines. The DPC helped develop policies for open data access such that virtually all requests for data access are granted. Persons requesting access to the data fill out a brief online application form in which they indicate their academic affiliation and reason for requesting access, or a statement about the project area they are interested in. Each of these applications is individually reviewed by the DPC Chair. A table of individuals with access to the data and the projects they are pursuing is publically available so that data users can be aware of the interests of others and reach out to other data users to form collaborations if they wish. The DPC Administrator reviews manuscripts and requires all scientists who are developing manuscripts using ADNI data to adhere to ADNI publication guidelines. These guidelines request that authorship be stated in the "modified corporate authorship" format, in which the particular writing team is named, and the authorship list is followed by the words, "for the ADNI Study\*"; the asterisk here refers to a web page where the ADNI leadership and individual site directors and co-investigators at each ADNI site are named. In this manner, the ADNI leadership and ADNI site investigators can obtain group authorship credit that provides at least modest academic credit for the work they are doing toward all ADNI publications.

A member of the DPC also reviews each manuscript for any that may have egregiously poor quality, but importantly, does not attempt to review manuscripts for scientific quality or for duplication. It has been our conscious policy to avoid practices that would inhibit or slow the utilization of ADNI data by the worldwide scientific community. Therefore, we have decided that scientific review should occur at the level of publication review, and that we will tolerate, and even encourage, multiple examinations of ADNI data by multiple investigators. Although this philosophy raises the possibility that two papers could present conflicting analyses or interpretations, we have elected to let such potential conflicts play out in the marketplace of ideas.

#### 2.1.3. Other cores

Briefly, the eight cores for which the administrative core is responsible are as follows: (1) Clinical Core, based at the University of California, San Diego, and the Mayo Clinic, and is responsible for the recruitment of subjects, the development of an electronic data capture system at each site, and of protocols and procedures for ADNI; (2) MRI Core, based at the Mayo Clinic, and responsible for all MRI procedures and for developing standardized imaging methods; (3) PET Core, based at the University of California, Berkeley, and responsible for all PET procedures and for developing standardized imaging methods; (4) Biomarker Core, based at the University of Pennsylvannia, and responsible for the collection and analysis of biomarkers in biofluids, and for the establishment of an archive of biofluids; (5) Genetics Core, based at Indiana University and responsible for genotyping participants; (6) Neuropathology Core, based at Washington University, and responsible for the establishment of protocols to facilitate brain autopsies of ADNI patients who die; (7) Biostatistics Core, based at the University of California, Davis, and responsible for the statistical analysis of data generated from the other Cores; (8) Informatics Core, based at the University of California, Los Angeles, and responsible for the establishment of a website to facilitate data-sharing of data generated by ADNI projects.

Detailed summaries of the results of the ADNI Cores are provided in the accompanying articles of this special issue.

# 3. Limitations of ADNI

One limitation of ADNI is that our population represents a clinical trial population and not an epidemiologically selected real life population. Our subjects do not include those with cortical strokes, cancer, heart failure, substance abuse, etc. Therefore, the extent to which the results from ADNI can be generalized to the entire population remains to be determined. Future population-based studies will be required to determine whether the information derived from ADNI is relevant to the greater population. One approach has been for ADNI investigators to develop collaborations with investigators who are conducting population-based studies, so that ADNI methods can be used in such studies. A second limitation is that ADNI only studies subjects aged 55-90 years, and there is considerable evidence that AD pathology may begin to occur in the human brain well before this age. Autopsy studies and amyloid imaging have suggested that a substantial fraction of cognitively normal subjects in their 70s have AD pathology. A full understanding of the pathophysiological sequence of events that occur in AD will require longitudinal studies of subjects beginning at a young age. A third limitation of ADNI is the type of data that are not being collected including computerized neuropsychological testing, electroencephalogram, magnetoencephalography, magnetic resonance spectroscopy, metabolic and inflammatory markers, and lifestyle information. The decision concerning which measures to include was reached by consensus among the Site Principal Investigators (PIs), Core leaders, and the NIA. Although many of these measures might provide useful information, they are not included because of the following reasons: (1) The measures have not yet been demonstrated to have high value as either predictors or outcomes, and are not currently being incorporated into clinical trials; (2) The subject burden of ADNI is already quite great (clinical/cognitive battery, MRI, FDG/amyloid PET, lumbar puncture) and there are concerns that adding additional tests will impair enrollment and increase dropout; (3) The additional cost of these measures is not supported by evidence for inclusion. One final limitation of ADNI has been that not all measurements (like FDG-PET and lumbar puncture) were obtained on all subjects, limiting the ability to compare methods. This is being overcome in the current study in which all subjects will have (at least) baseline lumbar puncture and AV-45 amyloid imaging as well as the other measurements.

#### 4. Results

# 4.1. Overall ADNI impact

The effect of ADNI thus far falls into three main areas. First, the establishment of standardized methods for imaging/biomarker collection and analysis has been a key step forward, and these methods are starting to be used in clinical trials. For instance, ADNI results on LMCI subjects replicated rates of conversion in a similar group of MCI subjects enrolled using the Petersen criteria in the ADCS Vitamin E/Donepezil trial, and the standardized neuropsychological battery used by ADNI is now being used by industry and ADCS trials. The MRI core developed a structural MRI protocol, identical across vendors, with an MRI phantom for calibration which has since been used in numerous phase 2 and 3 treatment trials. The PET core established methods for multisite FDG-PET, and the first multisite C-11 PIB study. The biomarker core established standardized methods for measurements of CSF A $\beta$  amyloid and species of tau. The importance of these standardization efforts should not be underemphasized because the ADNI methods have now been adopted for other ADNI-like studies outside of the U.S. and this will facilitate comparisons of results among countries, cultures, and ethnicities, and provide an infrastructure for worldwide clinical trials by the pharmaceutical industry. Second, ADNI has resulted in the provision of a large data base of images, genetic, fluid biomarker, and clinical data that are being used by many investigators and industry. Finally, ADNI has generated new results in many areas, such as the identification of outcome measures with high power to detect treatment effects, and of predictors such as CSF biomarkers which have been shown to predict future rates of brain atrophy, brain glucose metabolism, and cognition in MCI. Contributing to the knowledge of AD neuroscience is the finding that there is evidence that AD pathology in normal subjects is associated with greater rates of change of brain structure and brain glucose metabolism. Amyloid imaging and CSF A<sup>β</sup> have been found to provide similar information. An important long-term goal of our field is to identify and validate imaging/biomarkers for AD progression which can be used as surrogate markers in place of clinical/cognitive tests in clinical trials. This is a very long way off, because such surrogate markers must be validated in the treatment setting, across various types of treatments. Nevertheless, the ADNI results are providing an important first step toward this goal.

ADNI has also had a great effect in a global sense (Fig. 4). At the time when ADNI1 was funded, there were no plans for similar efforts in other countries. However, the establishment of ADNI stimulated many such efforts resulting in the following: (1) The Australian study, AIBL (PI Colin Masters) [15], is a two-site longitudinal study of 1,100 subjects with MRI (using ADNI protocol), a subset with C-11 PIB, and cognitive measures (similar to ADNI). In fact, AIBL was



Fig. 4. Map showing all ADNI and ADNI-like efforts in the world (Figure kindly provided by Maria Carillo of the Alzheimer's Association).

conceived of before and began independent of U.S. ADNI; (2) Japanese ADNI (PI Takeshi Iwatsubo) [16], which studies 220 subjects using methods identical to ADNI in all respects except for language; (3) European ADNI (PI Giovanni Frisoni), which is enrolling 150 subjects. There are also several large longitudinal projects beginning in China using imaging/ CSF biomarkers and a Korean ADNI is being planned. The Alzheimer's Association has organized a quarterly teleconference of all worldwide ADNI PIs, is working to fund more data-sharing efforts among the projects, and Dr Iwatsubo hosted the first worldwide ADNI meeting in Sendai, Japan, in November, 2009.

Thus, the effect of ADNI and these numerous projects around the world on AD research is huge, as is the value of the information gained to academic scientists and to the pharmaceutical industry as a result of the sharing of all data. To our knowledge, ADNI is the only neuroscience project in the world that is having such a worldwide effect in the AD field. To date, there have been more than 60 publications arising from AD, both directly, or indirectly through shared data (Appendix list, online only).

# 4.2. Grand opportunities grant

A Grand Opportunities (GO) grant (American Recovery Act funds, i.e., stimulus funds) was recently awarded to the identical team of investigators overseeing ADNI. Dr Weiner is also PI of the GO grant, which closely relates to ADNI and is separately administered with its own account/fund and separate subcontracts. This grant will provide an additional \$24 million of funding over 2 years to enroll 200 EMCI subjects, some of whom will have early biomarker signals of AD pathology. This category of subjects has not been enrolled in ADNI thus far, and so it will bridge the gap between normal elderly and LMCI subjects who are more amnestic than EMCI subjects. These GO subjects will have clinical/cognitive, blood/CSF/genetic, FDG and amyloid PET, and MRI measurements during the 2-year period of the GO grant. This grant will also fund F18 amyloid PET imaging on all existing normal control and LMCI subjects, and newly enrolled EMCI subjects, which will allow correlation and comparison of this modality with all of the other clinical/cognitive, neuroimaging, genetic, and biomarker data collected in the project. The GO grant will extend the follow-up of LMCI and normal subjects who were enrolled in ADNI1 and are being carried forward in GO, and will allow analysis of all of the ADNI data that was not able to be done in the initial grant (since it was a data collection grant, and few funds were provided for analysis) as well as analysis of the data from this GO project, to test hypotheses and perform data explorations.

#### 4.3. Future directions of ADNI

Funding for ADNI1 ends October 1, 2010. The future of ADNI will depend on a successful competitive renewal (termed ADNI2). ADNI2 will be focused on predictors, outcomes, and clinical trial design, but fulfillment of these aims will add considerably to what is known about the pathophysiological sequence of changes in the brain that occur across the continuum from normal aging to MCI to AD dementia. Now the major goals of ADNI, therefore, are as follows: (1) To identify and validate imaging and blood/CSF biomarker predictors of cognitive decline/dementia for early detection of AD; (2) To identify and validate imaging and blood/CSF biomarker outcomes that reflect progression of AD pathology; and (3) To develop information leading to improved clinical trials of treatments to slow disease progression, ultimately contributing to the prevention of AD dementia.

#### 5. Summary

Taken together, ADNI is the only multisite longitudinal observational clinical/imaging/biomarker study being performed in the U.S. ADNI data are widely available to all scientists throughout the world without embargo through the UCLA/LONI/ADNI website. ADNI has already demonstrated its high value by providing a great deal of scientific information, and providing information for development of clinical trial protocols that are being used in several current phase 3 studies. ADNI also serves as a model of ADNI-like efforts in other countries. The continuation of this study, through the GO and, hopefully, ADNI2 grant will contribute considerably to the development of new diagnostic approaches, improved clinical trials, and to the identification of effective treatments that slow the progression of AD pathology in demented and nondemented subjects. Ultimately, the results from ADNI will contribute considerably to the development of AD treatment trials and to effective measures that prevent the development of AD.

# Acknowledgments

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. Complete listing of ADNI investigators is available at www.loni.ucla. edu/ADNI/Collaboration/ADNI\_Manuscript\_Citations.pdf.

#### References

- 2009 Alzheimer's disease facts and figures. Alzheimers Dement 2009; 5:234–70.
- [2] Katzman R, Fox P. The world-wide impact of dementia. Projections of prevalence and costs. In: Mayeaux R, Christen Y, eds. Epidemiology of Alzheimer's Disease: From Gene to Prevention. Berlin, Germany: Springer-Verlag; 1999. p. 1–17.
- [3] Acosta D, Wortmann M. Alzheimer's Disease International World Alzheimer Report 2009. In: Prince M, Jackson J, eds. London, UK: Alzheimer's Disease International; 2009. p. 1–92.
- [4] Khachaturian ZS. Diagnosis of Alzheimer's disease: two-decades of progress. J Alzheimers Dis 2006;9:409–15.
- [5] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002; 297:353–6.
- [6] Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–7.
- [7] Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002;58:1791–800.
- [8] Thal DR, Rub U, Schultz C, Sassin I, Ghebremedhin E, Del Tredici K, et al. Sequence of Abeta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 2000;59:733–48.
- [9] Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, et al. Long-term effects of Abeta<sub>42</sub> immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet 2008;372:216–23.
- [10] Cairns NJ, Ikonomovic MD, Benzinger T, Storandt M, Fagan AM, Shah AR, et al. PiB-PET detection of cerebral abeta may lag clinical, cognitive, and CSF markers of Alzheimer's disease: a case report. Arch Neurol (in press).
- [11] Gauthier S, Dubois B, Feldman H, Scheltens P. Revised research diagnostic criteria for Alzheimer's disease. Lancet Neurol 2008; 7:668–70.
- [12] Visser PJ, Verhey F, Knol DL, Scheltens P, Wahlund LO, Freund-Levi Y, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. Lancet Neurol 2009;8:619–27.
- [13] Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment. JAMA 2009;302:385–93.
- [14] Bobinski M, de Leon MJ, Wegiel J, Desanti S, Convit A, Saint Louis LA, et al. The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. Neuroscience 2000;95:721–5.
- [15] Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, et al. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. Int Psychogeriatr 2009; 21:672–87.
- [16] Arai H. Alzheimer's disease neuroimaging initiative and mild cognitive impairment. Rinsho Shinkeigaku 2007;47:905–7.

# **Appendix: End notes**

<sup>A1</sup>The Tables below show the schedule of events and scope of work performed for ADNI1, and the proposed work for the funded GO grant and ADNI2 which was under submission at the time of writing this manuscript. Table A1 shows the years for ADNI1, GO, and ADNI2 and how Year 1of the GO grant overlaps with Year 6 of ADNI1, and how Year 2 of the GO grant overlaps with Year 1 of ADNI2.

<sup>A2</sup>Table A2 shows the schedule of events for ADNI1. Year 1 was the preparatory phase with little enrolment. Year 6 just began, and thus the actual number of subjects or scans is not known.

<sup>A3</sup>Table A3 shows the subjects enrolled in the GO grant study, including existing subjects from ADNI1 and newly enrolled subjects.

<sup>A4</sup>Table A4 shows the schedule of events for the proposed ADNI2, which, if funded, would begin on September 1, 2010.

Table A1 Work flow for ADNI1, GO grant and ADNI2 for each year of activity

ADNI1	2004–2005 Yr 1	2005–2006 Yr 2	2006–2007 Yr 3	2007–2008 Yr 4	2008–2009 Yr 5	2009–2010 Yr 6	2010–2011	2011-2012	2012–2013	2013–2014	2014–2015
GO ADNI2						Yr 1*	Yr 2 Yr 1*	Yr 2	Yr 3	Yr 4	Yr 5

\*Overlapping years.

Table A2	
ADNI1 scope of work	

	Total subjects	ojects 2005-2006					2006–2007					2007–2008 Yr 4						2008–2009							
	enrolled		Yr 2						Yr 3									Yr 5							
		N	CL	MRI	FDG	LP	PIB	N	CL	MRI	FDG	LP	PIB	N	CL	FDG	LP	MRI	PIB	N	CL	FDG	MRI	LP	PIB
Normals	229	139	364	235	85	75	0	205	505	480	166	109	8	187	397	81	40	252	18	187	361	79	189	31	16
MCI	402	155	478	287	106	98	0	308	916	831	329	178	21	261	655	328	91	722	63	216	537	155	302	49	40
AD	188	73	220	134	45	49	0	138	422	363	151	89	8	115	288	87	36	200	17	88	99	31	68	15	8
Total	819	367	1,062	656	236	222	0	651	1,843	1,674	646	376	37	563	1,340	496	167	1,174	98	491	997	265	559	95	64

Abbreviations: N, sample; CL, clinical visit; AMY, F18 amyloid PET scan; LP, limb puncture.

NOTE. ADNI1 recruited 819 subjects divided as follows: 229 Normals, 402 MCI and 188 AD subjects. After enrollment subjects had a baseline visit that included a clinical visit, an MRI, a PET scan in about half of the subjects and an LP in about 20% of the subjects. Subjects had follow-up visits at 6, 12, 18, 24, 30, and 36 months. AD subjects, however, were only followed up for 24 months. The follow-up visits essentially included a clinical visit, an MRI, an FDG PET scan in about 50% of the subjects and an LP in 20% of the subjects.

Table A3 GO grant

	2009-2	2010				2010–2011											
	Yr 1					Yr 2											
	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	AMY	FDG	LP					
Normals																	
From ADNI1	211	105	0	105	105	0	200	200	200	100	100	110					
MCI																	
EMCI newly enrolled	200	300	300	200	200	120	200	300	300	0	200	120					
LMCI from ADNI1	319	160	0	160	160	0	306	306	306	153	153	152					
Total	730	565	300	465	465	120	706	806	806	253	453	382					

NOTE. The estimated number of the current ADNI1 subjects that will be followed up in the GO Grant is 211 normal and 319 LMCI subjects, a total of 530 subjects. In year 2 we anticipate small attrition, resulting on 200 normal subjects and 306 MCI subjects for a total of 506. The enrollment of new subjects will be 200 EMCI subjects all in year 1. EMCI subjects will have an MRI visit 6 months after recruitment, that will make a total of 200 limited visits, 100 in the first year and 100 in the second year. The following tests will be done for the 530 subjects currently in ADNI: MRI scans on the second year (506). All current ADNI subjects are already scanned in year 1 under ADNI protocol. F18 amyloid scans for 265 subjects in year 1 and 253 in year 2 for a total of 518. All subjects who are having F18 amyloid PET scans will also be scanned with FDG PET. In year 2, the half of the group of subjects that did not have an FDG and part of the GO, will be scanned with FDG PET. LP on 262 subjects in year 2. The following tests will be done for all subjects. Limited FU visits at the 6 month time point for all newly recruited subjects. MRI scan at baseline for all subjects and another one at the 1 year point. In addition at the 6 month period, subjects will have one additional scan, the total on the 200 EMCI will be 100 in the first year for the GO subjects recruited in the first year and 100 in year 2 for the rest of the subjects that will be recruited in the second half of the first year. FDG scans for all new subjects at baseline and in year 2. F18 amyloid scans on all new subjects at baseline. LP on 60% of subjects at baseline and at the 1 year follow-up period.

Table A4	
ADNI2 schedule of activities	per year and type of subject

	2010-	-201	1				2011–2012 7 Yr 2					2012–2013						2013-2014			2014–2015				
	Yr 1											Yr 3						Yr 4			Yr 5				
	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	АМУ	' FDG	N	CL	MRI	AMY	FDG	LP	N	CL	MRI	Ν	CL	MRI	LP	
Normals																									
From ADNI1	202						190	190	190	95	95	179	179	179	90	90	107	168	168	168	158	158	158	95	
Newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	125	125	125	118	118	118	118	
MCI																									
EMCI from GO grant	200						188	188	188	188	188	177	177	177	0	0	177	166	166	166	156	156	156	156	
EMCI newly enrolled	100	100	300	100	100	100	94	94	94	0	0	88	88	88	88	88	88	83	83	83	78	78	78	78	
LMCI from ADNI1	274						258	258	258	129	129	243	243	243	122	122	146	228	228	228	214	214	214	128	
LMCI newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	125	125	125	118	118	118	118	
AD																									
Newly enrolled	150	150	450	150	150	150	141	141	141	0	0	133	133	133	133	133	133	0	0	0	0	0	0	0	
Total	1,226	550	1,650	550	550	550	1,153	1,153	1,153	412	412	1,086	1,086	1,086	699	699	917	895	895	895	842	842	842	693	

#### List of all publications based on ADNI data

- Trojanowski JQ. Searching for the biomarkers of Alzheimer's. Pract Neurol 2004;3:30–4.
- [2] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, Trojanowski JQ, Toga AW, Beckett L. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement 2005; 1:55–66.
- [3] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L. The Alzheimer's Disease Neuroimaging Initiative. Neuroimaging Clin N Am 2005; 15:869–77.
- [4] Fukuyama H. Neuroimaging in mild cognitive impairment. Rinsho Shinkeigaku 2006;46:791–4.
- [5] Iwatsubo T. Beta-and gamma-secretases. Rinsho Shinkeigaku 2006; 46:925–6.
- [6] Leow AD, Klunder AD, Jack CR Jr, Toga AW, Dale AM, Bernstein MA, et al. ADNI preparatory phase study: longitudinal stability of MRI for mapping brain change using tensor-based morphometry. Neuroimage 2006;31:627–40.
- [7] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett LA. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative. Cognition and Dement 2006;5:56–62.
- [8] Arai H. Alzheimer's Disease Neuroimaging Initiative and mild cognitive impairment. Rinsho Shinkeigaku 2007;47:905–7.
- [9] Fletcher PT, Powell S, Foster NL, Joshi SC. Quantifying metabolic asymmetry modulo structure in Alzheimer's disease. Inf Process Med Imaging 2007;20:446–57.
- [10] Ihara Y. Overview on Alzheimer's disease. Rinsho Shinkeigaku 2007; 47:902–4.
- [11] Murayam S, Saito Y. Neuropathology of mild cognitive impairment Alzheimer's disease. Rinsho Shinkeigaku 2007;47:912–4.
- [12] Haschke M, Zhang YL, Kahle C, Klawitter J, Korecka M, Shaw LM, Christians U. HPLC-atmospheric pressure chemical ionization MS/ MS for quantification of 15-F2t-isoprostane in human urine and plasma. Clin Chem 2007;53:489–97.
- [13] Shaw LM, Korecka M, Clark CM, Lee VM-Y, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. Nat Rev Drug Discov 2007;6:295–303.
- [14] Fan Y, Batmanghelich N, Clark CM, Davatzikos C, the Alzheimer's Disease Neuroimaging Initiative. Spatial patterns of brain atrophy in MCI Patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline. Neuroimage 2008;39:1731–43.
- [15] Hampel H, Burger K, Teipel SJ, Bokde ALW, Zetterberg H, Blennow K. Core candidate neurochemical and imaging biomarkers of Alzheimer's Disease. Alzheimers Dement 2008;4:38–48.
- [16] Nestor SM, Rupsingh R, Borrie M, Smith M, Accomazzi V, Wells JL, Fogarty J, Bartha R, the Alzheimer's Disease Neuroimaging Initiative. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's Disease Neuroimaging Initiative database. Brain 2008;131(Pt. 9):2443–54.
- [17] Shaw LM. PENN biomarker core of the Alzheimer's Disease Neuroimaging Initiative. Neurosignals 2008;16:19–23.
- [18] Visser PJ, Verhey FRJ, Boada M, Bullock R, De Deyn PP, Frisoni GB, et al., DESCRIPA study group. Development of screening guidelines and clinical criteria for predementia Alzheimer's Disease. Neuroepidemiology 2008;30:254–65.
- [19] Boyes RG, Gunter JL, Frost C, Janke AL, Yeatman T, Hill DL, et al., for the ADNI study. Intensity non-uniformity corrections using N3 on 3-T scanners with multichannel phased array coils. Neuroimage 2008; 39:1752–62.
- [20] Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al., ADNI Study. The Alzheimer's disease neuroimaging

initiative (ADNI): MRI methods. J Magn Reson Imaging 2008; 27:685-91.

- [21] Hua X, Leow AD, Lee S, Klunder AD, Toga A, Lepore N, et al., the Alzheimer's Disease Neuroimaging Initiative. 3D characterization of brain atrophy in Alzheimer's disease and mild cognitive impairment using tensor-based morphometry. Neuroimage 2008;41:19–34.
- [22] Frisoni GB, Henneman WJP, Weiner MW, Scheltens P, Vellas B, Reynish E, et al., the Alzheimer's Disease Neuroimaging Initiative. The pilot European Alzheimer's Disease Neuroimaging Initiative of the European Alzheimer's Disease Consortium. Alzheimers Dement 2008;4:255–64.
- [23] Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, et al., the Alzheimer's Disease Neuroimaging Initiative. Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease mild cognitive impairment, and elderly controls. Neuroimage 2008;43:59–68.
- [24] Hua X, Leow AD, Parikshak N, Lee S, Chiang MC, Toga AW, Jack CR Jr, Weiner MW, Thompson PM, the Alzheimer's Disease Neuroimaging Initiative. Tensor-based morphometry as a neuroimaging biomarker for Alzheimer's disease: an MRI study of 676 AD, MCI, and normal subjects. Neuroimage 2008;43:458–69.
- [25] Becker RE, Greig NH. Alzheimer's disease drug development: old problems require new priorities. CNS Neurol Disord Drug Targets 2008;7:499–511.
- [26] Walhovd KB, Fjell AM, Dale AM, McEvoy LK, Brewer J, Karow DS, Salmon DP, Fennema-Notestine C. the Alzheimer's Disease Neuroimaging Initiative. Multi-modal imaging predicts memory performance in normal aging and cognitive decline. Neurobiol Aging (in press).
- [27] Clark CM, Davatzikos C, Borthakur A, Newberg A, Leight S, Lee VM-Y, Trojanowski JQ. Biomarkers for early detection of Alzheimer pathology. NeuroSignals 2008;16:11–8.
- [28] Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, et al., the Alzheimer's Disease Neuroimaging Initiative. Episodic memory loss is related to hippocampal-mediated betaamyloid deposition in elderly subjects. Brain 2009;132(Pt. 5):1310.
- [29] Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, et al., the Alzheimer's Disease Neuroimaging Initiative. Automated mapping of hippocampal atrophy in 1-year repeat MRI data from 490 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Neuroimage 2009;45(Suppl 1):S3–15.
- [30] Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al., the Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. Ann Neurol 2009;65:403–413.
- [31] Morra J, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, et al. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Human Brain Mapping 2009; 30:2766–2788.
- [32] Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. Neuroimage 2009; 44:1415–1422.
- [33] Leow AD, Yanovsky I, Parikshak N, Hua X, Lee S, Toga AW, et al., the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative: a one-year follow-up study using tensor-based morphometry correlating degenerative rates, biomarkers and cognition. Neuroimage 2009;45:645–655.
- [34] Langbaum JBS, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, et al., the Alzheimer's Disease Neuroimaging Initiative. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 2009;45:1107–1116.
- [35] Weiner MW. Imaging and biomarkers will be used for detection and monitoring progression of early Alzheimer's Disease [Editorial]. J Nutr Health Aging 2009;13:332.

- [36] Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, Thompson PM, Jack CR Jr, Weiner MW, the Alzheimer's Disease Neuroimaging Initiative. MRI of hippocampal volume loss in early Alzheimer's Disease in relation to ApoE genotype and biomarkers. Brain 2009;132(Pt. 4):1067–1077.
- [37] McEvoy LK, Fennema-Notestine C, Cooper JC, Hagler D Jr, Holland D, Karow DS, Pung CJ, Brewer JB, Dale AM, for the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease: quantitative structural neuroimaging for detection and prediction clinical and structural changes in mild cognitive impairment. Radiology 2009;251:195–205.
- [38] Chupin M, Gerardin E, Cuingnet R, Boutet C, Lemieux L, Lehericy S, Benali H, Garnero L, Colliot O. Fully automatic hippocampus segmentation and classification in Alzheimer's disease and mild cognitive impairment applied on data from ADNI. Hippocampus 2009; 19:579–587.
- [39] Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al., the Alzheimer's Disease Neuroimaging Initiative. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain 2009;132(Pt. 5):1355–1365.
- [40] Potkin SG, Guffanti G, Lakatos A, Turner JA, Kruggel F, Fallon JH, et al. Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. PLoS ONE 2009;4:e6501–15.
- [41] Chou YY, Leporé N, Avedissian C, Madsen SK, Parikshak N, Hua X, et al., the Alzheimer's Disease Neuroimaging Initiative. Mapping correlations between ventricular expansion and CSF amyloid and tau biomarkers in 240 Subjects with Alzheimer's disease, mild cognitive impairment and elderly controls. Neuroimage 2009;46:394–410.
- [42] Kovacevic S, Rafii MS, Brewer BJ, the Alzheimer's Disease Neuroimaging Initiative. High-throughput, fully-automated volumetry for prediction of MMSE and CDR decline in mild cognitive impairment. Alzheimer Dis Assoc Disord 2009;23:139–45.
- [43] Clarkson MJ, Ourselin S, Neilsen C, Leung KK, Barnes J, Whitwell JL, et al. Comparison of phantom and registration scaling corrections using the ADNI cohort. Neuroimage 2009;47:1506–13.
- [44] Hua X, Lee S, Yanovsky I, Leow AD, Chou YY, Ho AJ, et al., the Alzheimer's Disease Neuroimaging Initiative. Optimizing power to track brain degeneration in Alzheimer's disease and mild cognitive impairment with tensor-based morphometry: an ADNI study of 515 subjects. Neuroimage 2009;48:668–81.
- [45] Hinrichs C, Singh V, Mukherjee L, Xu G, Chung MK, Johnson SC, the Alzheimer's Disease Neuroimaging Initiative. Spatially augmented LPboosting for AD classification with evaluations on the ADNI dataset. Neuroimage 2009;48:138–49.
- [46] Gunter JL, Bernstein MA, Borowski BJ, Ward CP, Britson PJ, Felmlee JP, Schuff N, Weiner M, Jack CR. Measurement of MRI scanner performance with the ADNI phantom. Med Phys 2009; 36:2193–205.
- [47] King RD, George AT, Jeon T, Hynan LS, Youn TS, Kennedy DN, Dickerson B, the Alzheimer's Disease Neuroimaging Initiative. Characterization of atrophic changes in the cerebral cortex using fractal dimensional analysis. Brain Imag Behav 2009;3:154–66.
- [48] Petersen RC, Trojanowski JQ. Use of Alzheimer's disease biomarkers: potentially yes for clinical trials, but not yet for clinical practice. JAMA 2009;302:436–7.
- [49] Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner M, Knopman DS, Petersen RC, Jack CR Jr, the Alzheimer's Disease Neuroimaging Initiative. MRI and CSF biomarkers in normal, MCI, AD: diagnostic discrimination and cognitive correlations. Neurol 2009;73:287–93.
- [50] Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner M, Knopman DS, Petersen RC, Jack CR Jr, the Alzheimer's Disease Neuroimaging Initiative. MRI and CSF biomarkers in normal, MCI, AD: predicting future clinical change. Neurology 2009; 73:294–301.

- [51] McDonald CR, McEvoy LK, Gharapetian L, Fennema-Notestine C, Hagler DJ Jr, Holland D, Koyama A, Brewer JB, Dale AM, the Alzheimer's Disease Neuroimaging Initiative. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. Neurology 2009;73:457–65.
- [52] Querbes O, Aubry F, Pariente J, Lotterie JA, Demonet JF, Duret V, et al., the Alzheimer's Disease Neuroimaging Initiative. Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. Brain 2009;132:2036–47.
- [53] Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC, the Alzheimer's Disease Neuroimaging Initiative (ADNI). Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res 2009;6:347–61.
- [54] Jagust WJ, Landau SM, Shaw LM, Trojanowski JQ, Koeppe RA, Reiman EM, et al., the Alzheimer's Disease Neuroimaging Initiative. Relationships between biomarkers in aging and dementia. Neurology 2009;73:1193–9.
- [55] Petersen RC. Commentary on "A roadmap for the prevention of dementia II: Leon Thal Symposium 2008. a national registry on aging. Alzheimers Dement 2009;5:105–7.
- [56] Petersen RC. Early diagnosis of Alzheimer's disease: is MCI too late? Curr Alzheimer Res 2009;6:324–30.
- [57] Petersen RC, Jack CR Jr. Imaging and biomarkers in early Alzheimer's disease and mild cognitive impairment. Clin Pharmacol Ther 2009;86:438–41.
- [58] Huang A, Abugharbieh R, Tam R, the Alzheimer's Disease Neuroimaging Initiative. A hybrid geometric-statistical deformable model for automated 3-D segmentation in brain MRI. IEEE Trans Biomed Eng 2009;56:1838–48.
- [59] Langbaum JB, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, et al., the Alzheimer's Disease Neuroimaging Initiative. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 2009;45. 11078–16.
- [60] Hirschman C. Alzheimer's Disease Neuroimaging Initiative (ADNI) Generates Promising Early Findings. Connections: News from the Alzheimer's Disease Education and Referral (ADEAR) Center, National Institute on Aging, Fall 2009. Available at: http://www.nia. nih.gov/Alzheimers/ResearchInformation/Newsletter/Fall2009/ feature01.htm.
- [61] Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM. One-year brain atrophy evident in healthy aging. J Neurosci 2009;29:15223–31.
- [62] Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, Weiner MW, Jagust WJ. the Alzheimer's Disease Neuroimaging Initiative. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol Aging (in press).
- [63] Fennema-Notestine C, Hagler DJ Jr, McEvoy LK, Fleisher AS, Wu EH, Karow DS, Dale AM. the Alzheimer's Disease Neuroimaging Initiative. Structural MRI biomarkers for preclinical and mild Alzheimer's disease. Hum Brain Mapp (in press).
- [64] Ho AJ, Hua X, Lee S, Leow AD, Yanovsky I, Gutman B, et al. the Alzheimer's Disease Neuroimaging Initiative. Comparing 3 T and 1.5 T MRI for tracking Alzheimer's disease progression with tensor-based morphometry. Hum Brain Mapp (in press).
- [65] Chang YL, Jacobson MW, Fennema-Notestine C, Hagler DJ Jr, Jennings RG, Dale AM, McEvoy LK. the Alzheimer's Disease Neuroimaging Initiative. Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. Cereb Cortex (in press).
- [66] Haense C, Herholz K, Jagust WJ, Heiss WD. Performance of FDG PET for detection of Alzheimer's disease in two independent multicentre samples (NEST-DD and ADNI). Dement Geriatr Cogn Disord 2009;28:259–66.

- [67] Hampel H, Shen Y, Walsh DM, Aisen P, Shaw LM, Zetterberg H, Trojanowski JQ, Blennow K. Biological markers of β-amyloid related mechanisms in Alzheimer's disease. Exper Neurol (in press).
- [68] Petersen RC, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Roberts RO, Jack CR Jr. Mild cognitive impairment ten years later. Arch Neurol 2009;66:1447–55.
- [69] Fleisher AS, Donohue M, Chen K, Brewer JB, Aisen PS, the Alzheimer's Disease Neuroimaging Initiative. Applications of neuroimaging to disease-modification trials in Alzheimer's disease. Behav Neurol 2009;21:129–36.
- [70] Holland D, Brewer JB, Hagler DJ, Fenema-Notestine C, Dale AM, the Alzheimer's Disease Neuroimaging Initiative. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. Proc Natl Acad Sci U S A 2009;106:20954–9.
- [71] Cruchaga C, Kauwe JS, Bertelsen S, Nowotny P, Shah AR, et al. SNPs in the regulatory subunit of calcineurin are associated with CSF tau protein levels, brain mRNA levels. Alzheimers Dement 2009; 5:471–2.
- [72] Joyner AH, Roddey CJ, Bloss CS, Bakken TE, Rimol LM, Melle I, et al. A common MECP2 haplotype associates with reduced cortical surface area in two independent populations. Proc Natl Acad Sci USA 2009;106:15483–8.
- [73] Ito K, Ahadleh S, Corrigan B, French J, Fullerton T, Tensfeldt T, the Alzheimer's Disease Neuroimaging Initiative. Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement 2009;6:39–53.
- [74] Petersen RC, Aisen PS, Beckett LA, Donahue MJ, Gamst AC, Harvey DJ, et al., the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurol 2010;74:201–9.
- [75] Fjell AM, Amlien IK, Westlye LT, Stenset V, Fladby T, Skinningsrud A, Eilsertsen DE, Bjørnerud A, Walhovd KB. CSF biomarker pathology correlates with a medial temporo-parietal network affected by very mild to moderate Alzheimer's disease but not a fronto-striatal network affected by healthy aging. Neuroimage 2010;49:1820–30.
- [76] Rimol LM, Agartz I, Djurovic S, Brown AA, Roddey JC, Kähler AK, et al., the Alzheimer's Disease Neuroimaging Initiative. Sexdependent association of common variants of microcephaly genes with brain structure. Proc Natl Acad Sci U S A 2010;107:384–8.
- [77] Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Petersen RC, Weiner MW, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.
- [78] Wolz R, Aljabar P, Hajnal JV, Hammers A, Rueckert D, the Alzheimer's Disease Neuroimaging Initiative. LEAP: learning embeddings for atlas propagation. Neuroimage 2010;49:1316–25.
- [79] Kruggel F, Turner J, Muftuler LT, the Alzheimer's Disease Neuroimaging Initiative. Impact of scanner hardware and imaging protocol on image quality and compartment volume precision in the ADNI cohort. Neuroimage 2010;49:2123–33.
- [80] Lötjönen JM, Wolz R, Koikkalainen JR, Thurfjell L, Waldemar G, Soininen H, Rueckert D, the Alzheimer's Disease Neuroimaging Initiative. Fast and robust multi-atlas segmentation of brain magnetic resonance images. Neuroimage 2010;49:2352–65.
- [81] Leung KK, Clarkson MJ, Bartlett JW, Clegg S, Jack CR Jr, Weiner MW, Fox NC, Ourselin S, the Alzheimer's Disease Neuroimaging Initiative. Robust atrophy rate measurement in Alzheimer's disease using multi-site serial MRI: tissue-specific intensity normalization and parameter selection. Neuroimage 2010;50:516–23.
- [82] Yushkevich PA, Avants BB, Das SR, Pluta J, Altinay M, Craige C, the Alzheimer's Disease Neuroimaging Initiative. Bias in estimation of hippocampal atrophy using deformation-based morphometry arises from asymmetric global normalization: an illustration in ADNI 3 T MRI data. Neuroimage 2010;50:434–45.
- [83] Walhovd KB, Fjell AM, Brewer J, McEvoy LK, Fennema-Notestine C, Hagler DJ Jr, Jennings RG, Karow D, Dale AM,

the Alzheimer's Disease Neuroimaging Initiative. Combining MR imaging, Positron-Emission Tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer'sdisease. AJNR Am J Neuroradiol 2010;31:347–54.

- [84] Cronk BB, Johnson DK, Burns JM. the Alzheimer 's Disease Neuroimaging Initiative. Body mass index and cognitive decline in mild cognitive impairment. Alzheimer Dis Assoc Disord (in press).
- [85] Kauwe JS, Bertelsen S, Mayo K, Cruchaga C, Abraham R, Hollingworth P, et al. the Alzheimer's Disease Neuroimaging Initiative. Suggestivesynergy between genetic variants in TF and HFE as risk factors for Alzheimer's disease. Am J Med Genet B Neuropsychiatr Genet (in press).
- [86] Chang YL, Bondi MW, Fennema-Notestine C, McEvoy LK, Hagler DJ Jr, Jacobson MW, Dale AM. the Alzheimer's Disease Neuroimaging Initiative. Brain substrates of learning and retention in mild cognitive impairment diagnosis and progression to Alzheimer's disease. Neuropsychologia (in press).
- [87] Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Blennow K, Brewer JB, Dale AM. the Alzheimer's Disease Neuroimaging Initiative. Brain atrophy in healthy aging is related to CSF levels of A{beta}1-42. Cereb Cortex (in press).
- [88] Franke K, Ziegler G, Klöppel S, Gaser C, the Alzheimer's Disease Neuroimaging Initiative. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. Neuroimage 2010;50:883–92.
- [89] Shen L, Kim S, Risacher SL, Nho K, Swaminathan S, West JD, et al. the Alzheimer's Disease Neuroimaging Initiative. Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: a study of the ADNI cohort. Neuroimage (in press).
- [90] Okonkwo OC, Alosco ML, Griffith HR, Mielke MM, Shaw LM, Trojanowski JQ, Tremont G. the Alzheimer's Disease Neuroimaging Initiative. CSF abnormalities and rate of decline in everyday function. Arch Neurol (in press).
- [91] De Meyer G, Shapiro F, Vanderstichele H, Vanmechelen E, Engleborghs B, De Deyn P-P, et al. the Alzheimer's Disease Neuroimaging Initiative. Diagnosis-independent Alzheimer's disease biomarker signature in cognitively normal elderly people. Arch Neurol (in press).
- [92] McEvoy LK, et al. Enrichment strategies for secondary prevention trials in Alzheimer's disease. Alzheimer's Dis Assoc Diss (in press).
- [93] Ott B, et al. Complex relationships between ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. J Alzheimers Dis (in press).
- [94] Thompson P, Hua X, Lee S, Hibar DP, Yanovsky I, Leow AD, et al. the Alzheimer's Disease Neuroimaging Initiative. Mapping Alzheimer's disease progression in 1309 MRI scans: power estimates for different inter scan intervals. Neuroimage (in press).
- [95] Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, et al. the Alzheimer's Disease Neuroimaging Initiative. Effect of APOE on biomarkes of amyloid load and neuronal pathology in Alzheimer's disease. Ann Neurol (in press).
- [96] De Meyer G, Shapiro F, Vanderstichele H, Vanmechelen E, Engleborghs B, De Deyn P-P, et al., the Alzheimer's Disease Neuroimaging Initiative. A mixture modeling approach to biomarker assessment reveals an Alzheimer's disease signature in more than a third of cognitively normal elderly people. Arch Neurol 2010 (in press).
- [97] Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack CR Jr, et al., the Alzheimer's Disease Neuroimaging Initiative (ADNI). Multi-modal biological marker based signature and diagnosis of early Alzheimer's disease. Neurobiol Aging 2010 (in press).
- [98] Ewers M, Faluyi YO, Bennett D, Trojanowski JQ, Shaw LM, Petersen R, et al., the Alzheimer's Disease Neuroimaging Initiative (ADNI). Body mass index associated with biological CSF markers of core brain pathology in mild cognitive impairment and Alzheimer's disease. Neurology 2010 (in press).

- [99] Korecka M, Clark CM, Lee VM-Y, Trojanowski JQ, Shaw LM. Simultaneous HPLC-MS-MS quantification of 8-iso-PGF<sub>2a</sub> and 8,12iso-iPF<sub>2a</sub> in CSF and brain tissue samples with on-line cleanup and 2 dimensional chromatography. J Chromatography B 2010 (in press).
- [100] Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM, for the Alzheimer's Disease Neuroimaging Initiative. CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease. J Neurosci 2010;30:2088–101.
- [101] Evans MC, Barnes J, Nielsen C, Kim LG, Clegg SL, Blair M, et al., the Alzheimer's Disease Neuroimaging Initiative. Volume changes in Alzheimer's disease and mild cognitive impairment: cognitive associations. Eur Radiol 2010;20:674–82.
- [102] Kauwe JS, Bertelsen S, Mayo K, Cruchaga C, Abraham R, Hollingworth P, et al., the Alzheimer's Disease Neuroimaging Initiative. Replication of synergy between genetic variants in TF and HFE as risk factors for Alzheimer's disease. Alzheimer's Disease Cooperative Study. Avialable at http://www.adcs.org/Admin/publication.aspx. Submitted, 2009.
- [103] Bossa M, Zacur E, Olmos S. Alzheimer's Disease Neuroimaging Initiative. Tensor-based morphometry with stationary velocity field diffeomorphic registration: application to ADNI. Neuroimage 2010 (in press).
- [104] Okonkwo OC, Alosco ML, Griffith HR, Mielke MM, Shaw LM, Trojanowski JQ, et al., the Alzheimer's Disease Neuroimaging Initiative. Association between cerebrospinal fluid abnormalities and rate of decline in everyday function across dementia spectrum: normal aging, mild cognitive impairment, and Alzheimer's disease. Arch Neurol 2010 (in press).
- [105] Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, et al., the Alzheimer's Disease Neuroimaging Initiative. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in healthy elderly. Proc Nat Acad Sci 2010 (in press).
- [106] Stein JL, Hua X, Lee S, Ho AJ, Leow AD, et al., the Alzheimer's Disease Neuroimaging Initiative. Voxelwise genome-wide association study (vGWAS). Neuroimage 2010 (in press).
- [107] Fjell AM, Westlye LT, Espeseth T, Reinvang I, Dale AM, Holland D, et al. Cortical gray matter atrophy in healthy aging can not be explained by undetected incipient cognitive disorders: a comment on Burgmans et al. (2009). Neuropsychology 2010;24:258–63.
- [108] Chen K, Langbaum JB, Fleisher AS, Ayutyanont N, Reschke C, Lee W, et al., the Alzheimer's Disease Neuroimaging Initiative. Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment using an empirically pre-

defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. Neuroimage 2010 (in press).

- [109] Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, et al., the Alzheimer's Disease Neuroimaging Initiative. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010 (in press).
- [110] Leung KK, Barnes J, Ridgway GR, Bartlett JW, Clarkson MJ, Mecdonald K, et al., the Alzheimer's Disease Neuroimaging Initiative. Automated cross-sectional and longitudinal hippocampal volume measurement in mild cognitive impairment and Alzheimer's disease. Neuroimage 2010 (in press).
- [111] Stonnington CM, Chu C, Kloppel S, Jack CR Jr, Ashburner J, Frackowiak RS, the Alzheimer's Disease Neuroimaging Initiative. Predicting clinical scores from magnetic resonance scans in Alzheimer's disease. Neuroimage 2010 (in press).
- [112] Wolz R, Heckemann RA, Aljabar P, Hajnal JV, Hammers A, Lotjonen J, et al., the Alzheimer's Disease Neuroimaging Initiative. Measurement of hippocampal atrophy using 4D graph cut segmentation: application to ADNI. Neuroimage 2010 (in press).
- [113] Schneider LS, Insel PS, Weiner MW, the Alzheimer's Disease Neuroimaging Initiative. Cholinesterase inhibitors and memantine use by patients in the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol 2010 (in press).
- [114] Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvery D, Beckett L, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol 2010 (in press).
- [115] Thompson P, Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, et al. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol Aging 2010 (in press).
- [116] Trojanowski JQ, Vandeerstichele H, Korecka M, Clark CM, Aisen PS, Petersen RC, et al., the Alzheimer's Disease Neuroimaging Initiative. Update on the biomarker core of Alzheimer's Disease Neuroimaging Inititative subjects. Alzheimers Dement 2010;5:230–8.
- [117] Tosun D, Schuff N, Truran-Sacrey D, Shaw LM, Trojanowski JQ, Aisen P, et al., the Alzheimer's Disease Neuroimaging Initiative. Relations between brain tissue loss, CSF biomarkers and the ApoE genetic profile: a longitudinal MRI study. Neurobiol Aging 2010 (in press).
- [118] Beckett LA, Harvey DJ, Gamst A, Donohue M, Kornak J, Zhang H, et al., the Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Neuroimaging Initiative: annual change in biomarkers and clinical outcomes. Alzheimers Dement 2010; 5:257–64.