Published in final edited form as:

Alzheimers Dement. 2010 May ; 6(3): 212–220. doi:10.1016/j.jalz.2010.03.004.

Update on the MRI Core of the Alzheimer's Disease Neuroimaging Initiative

Clifford R Jack Jr^{*,A1}, Matt A Bernstein^{A2}, Bret J Borowski^{A1}, Jeffrey L Gunter^{A1}, Nick C Fox^B, Paul M Thompson^C, Norbert Schuff^D, Gunnar Krueger^E, Ronald J Killiany^F, Charles S DeCarli^G, Anders M Dale^H, Michael W Weiner^I, and the Alzheimer's Disease Neuroimaging Initiative

^{A1}Department of Radiology Mayo Clinic, Rochester, MN, USA 55905

^{A2}Department of Radiologic Physics, Mayo Clinic, Rochester, MN, USA 55905

^BDementia Research Centre, UCL Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

^CDepartment of Neurology and Laboratory of Neuro Imaging, David Geffen School of Medicine, UCLA, CA, USA 90095

^DCenter for Imaging of Neurodegenerative Diseases, Veterans Affairs Medical Center, Department of Radiology and Biomedical Imaging, University of California, San Francisco, USA 94121

^ESiemens AG, Department of MREA, Karl-Schall-Str. 6, Erlangen, 91052 Germany

^FCenter for Biomedical Imaging, Department of Anatomy and Neurobiology, Boston University School of Medicine, Department of Environmental Health, Boston University School of Public Health, Boston, MA 02118

^GDepartment of Neurology and Center for Neuroscience, UC Davis, Davis, CA

^HDepartments of Neurosciences and Radiology, University of California at San Diego, La Jolla CA 92093

^IVeterans Affairs and University of California, San Francisco, CA, USA

Abstract

Functions of the ADNI MRI core fall into three categories: (1) those of the central MRI core lab at Mayo Clinic, Rochester, Minnesota, needed to generate high quality MRI data in all subjects at each time point; (2) those of the funded ADNI MRI core imaging analysis groups responsible for analyzing the MRI data, and (3) the joint function of the entire MRI core in designing and problem solving MR image acquisition, pre-processing and analyses methods. The primary objective of ADNI was and continues to be improving methods for clinical trials in Alzheimer's disease. Our approach to the present ("ADNI-GO") and future ("ADNI-2", if funded) MRI protocol will be to maintain MRI methodological consistency in previously enrolled "ADNI-1" subjects who are followed longitudinally in ADNI-GO and ADNI-2. We will modernize and expand the MRI protocol for all newly enrolled ADNI-GO and ADNI-2 subjects. All newly enrolled subjects will be scanned at 3T

Corresponding Author: Clifford R. Jack, Jr., 200 1st Street SW, Rochester MN USA 55905, 507-284-7096 (phone), 507.284.9778 (fax), jack.clifford@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with a core set of three sequence types: 3D T1-weighted volume, FLAIR, and a long TE gradient echo volumetric acquisition for micro hemorrhage detection. In addition to this core ADNI-GO and ADNI-2 protocol, we will perform vendor specific pilot sub-studies of arterial spin labeling perfusion, resting state functional connectivity and diffusion tensor imaging. One each of these sequences will be added to the core protocol on systems from each MRI vendor. These experimental sub-studies are designed to demonstrate the feasibility of acquiring useful data in a multi-center (but single vendor) setting for these three emerging MRI applications.

1. Introduction

The major purpose of this paper is to describe past, present, and future activities of the ADNI MRI core. In doing so, we hope that the ADNI MRI database (available at www.loni.ucla.edu/ADNI) will become more transparent and more easily accessible to potential users. This paper is divided into two main sections: 1) a description of MRI activities during the first 5 years of ADNI funding, approximately from 2005 – 2010, referred to as “ADNI-1”; 2) plans for the second 5 years of ADNI running through 2015. “ADNI-GO” is the currently active extension of ADNI (GO stands for “Grand Opportunity”, a type of stimulus grant from the NIH). “ADNI-2” is the 5 year competitive renewal of ADNI, which if funded, will be active from late 2010 through 2015.

MRI core activities fall into three categories: (1) service activities of the central MRI lab at Mayo Clinic, Rochester, MN, needed to generate high quality MRI data in all subjects at each time point; (2) the funded ADNI MRI core imaging analysis groups responsible for analyzing the MRI data using state-of-the-art methods and making numeric summary data publicly available, and (3) the joint function of the entire MRI core in designing and problem solving MR image acquisition, pre-processing and analyses methods. Although separated geographically, the MRI core communicates regularly and operates in a consensus-driven manner on all major decisions relating to operations and future planning.

2. ADNI-1

The primary objective of ADNI-1 was to improve methods for clinical trials. In addition, however, the data generated by ADNI-1 has improved understanding of relationships between imaging and chemical biomarkers of Alzheimer's disease (AD) and clinical manifestations of the disease. The main focus of the ADNI-1 MRI acquisition protocol was on structural MRI of the brain, and the imaging sequence selected for this purpose was a 3D T1-weighted sequence known as MPRAGE (Magnetization Prepared Gradient Echo). The MPRAGE sequence was repeated back-to-back in ADNI-1 to increase the likelihood of acquiring at least one good quality MPRAGE scan (and hence decrease the need to repeat exams) and also to permit signal averaging if desired. In addition, a dual fast spin echo (proton density/T2) sequence was acquired at each time point to evaluate the presence/state of vascular disease and general pathology detection. All subjects received a 1.5T protocol exam at multiple time points which varied by baseline clinical diagnosis: MCI at 0, 6, 12, 24 and 36 months; AD at 0, 6, 12 and 24 months; and controls at 0, 6, 12, 24 and 36 months. A sub-set of participants (approximately 25%) were enrolled in a 3T arm which involved MRI scanning at both 1.5T and 3T at each scheduled time point.

2.1 Central MRI lab at the Mayo Clinic

Functions primarily managed by the central ADNI MRI lab at the Mayo Clinic included the following:

1. implementing methods for standardizing MRI acquisition across sites and over time, including the electronic distribution, loading, and checking of the MRI pulse sequence parameters
2. quality control of all images acquired
3. correcting common image artifacts - intensity non-uniformity, warping due to gradient non-linearity, and changes in global scaling of length over time due to variation in gradient amplitude
4. monitoring technical performance of each scanner in the study.

2.2 Funded image analysis groups

Seven different research groups were funded to perform analysis of ADNI-1 MRI data at 0, 6 and 12 month time points. The principal investigators and the analyses performed were:

Nick Fox – rates of brain atrophy: brain and ventricular boundary shift integral ⁵

Paul Thompson – tensor-based morphometry ³

Norbert Schuff – hippocampal volume ⁶

Charles DeCarli – assessment of cerebrovascular disease ⁷

Colin Studholme – tensor-based morphometry

Anders Dale – FreeSurfer with improved sub-regional change analysis ^{1, 8, 9}

Gene Alexander – voxel-based morphometry ¹⁰

2.3. Results and conclusions

ADNI MRI core activities led to meaningful conclusions in areas ranging from MRI technology to the biology of AD. Some are briefly described below.

1. MRI has much better longitudinal power to detect change than clinical measures, resulting in substantially smaller sample sizes for clinical trials in both MCI and AD patients ^{1, 3, 11-13} Figure 1.
2. Some MRI analysis methods have greater power to detect change-over-time than others. The best performing measures (defined as smallest sample sizes needed to detect a 25% absolute rate reduction in AD and MCI subjects) were boundary shift integral, FreeSurfer hippocampal volume and entorhinal cortex volume change, and tensor-based morphometry measures of selected voxels in the temporal lobe ^{1, 3, 12-14}.
3. Confirmed that rates of MRI atrophy differ by clinical group and appropriately track clinical and psychological measures of cognitive decline, thus demonstrating relevance of these measures as disease biomarkers ¹⁵.
4. Demonstrated that MRI rates of change in cognitively normal subjects are greater in APOE e4 carriers than non-carriers ^{6, 16, 17}.
5. Showed that lower CSF A β ₄₂ and higher CSF tau concentrations were associated with a variety of structural brain alterations. Specifically, lower CSF A β ₄₂ was associated with a thinner cortex in cognitive healthy controls Figure 2 ². In addition, lower CSF A β ₄₂ and higher CSF tau were associated with higher regional brain atrophy rates across the clinical groups Figure 3 ².
6. The choice of treatable effect model strongly influences the power of different MRI outcome measures. Power calculations using disease-specific change (defined as

change in patients relative to change in healthy controls, as opposed to absolute change in AD) favored sub-regional cortical measures over the more global whole-brain, ventricle, and hippocampal measures Figure 4¹.

7. Baseline MRI is generally a better predictor of clinical and cognitive change than either FDG PET or CSF biomarkers¹⁸.
8. When MRI methods for measuring longitudinal change were compared with FDG PET methods for measuring longitudinal change, the MRI methods typically had greater power to detect longitudinal change. The exception to this were the results generated by Chen et al¹⁹ who used a statistically driven voxel based method for identifying regions of interest. With this method FDG PET had similar power to detect change as MRI methods¹⁴. Note that virtually any longitudinal AD study involving imaging would be expected to include an MR component anyway, in order to rule out a clinical condition (e.g., stroke) that a subject could develop over the course of the study.
9. MRI has better correlation with clinical group membership and with cognitive tests than CSF tau or A β ₄₂^{18, 20, 21}.
10. Low baseline levels of CSF A β ₄₂ were associated with more rapid cortical atrophy in healthy controls²¹.
11. MRI has better prediction of risk of conversion from MCI to AD than CSF tau or A β ₄₂²².
12. Supported the idea that baseline MRI measures can be used to identify a pattern of atrophy characteristic of mild AD and demonstrated that the presence of this pattern in MCI patients is predictive of more rapid clinical decline^{22, 23}. Further showed that enrichment of an MCI clinical trial using this regional atrophy pattern would allow for much smaller sample sizes (reduction in sample size of 43-60% dependent on outcome measure²⁴.
13. Demonstrated no superiority for 3T vs. 1.5T in group-wise discrimination or sample sizes needed to power trials¹¹.
14. Confirmed previous reports that hippocampal atrophy rates in MCI and AD accelerate⁶ and, further, that disease stage is associated with accelerated atrophy rates of widespread cortical areas²⁵.
15. Demonstrated greater white matter hyperintensity load in AD and MCI than in control subjects who would be typically enrolled in therapeutic trials⁷. Confirmed previous associations between white matter hyperintensity volume measures and baseline cognition as well as baseline measures of white matter hyperintensity and longitudinal change in ADAS-Cog⁷.
16. Found associations between levels of atrophy and genetic differences in the glutamate receptor²⁶, the FTO obesity gene²⁶, and several other candidate genes²⁷⁻²⁹ Figure 5.
17. Found sex and age differences in rates of atrophy in all diagnostic groups³⁰ and between atrophy and obesity^{26, 30}.
18. Mapped 3D profiles of caudate atrophy and ventricular expansion and their pathological and clinical correlates^{31, 32}.
19. Achieved consistent acquisition methods across 89 MRI scanners at 59 sites. A total of 38 different vendor and platform specific ADNI-1 protocols were created and distributed to sites, and posted publically in PDF format on the ADNI-LONI web site.

20. Designed and distributed to all enrollment sites a quantitative MRI phantom known as the ADNI phantom. This phantom was later adopted as the starting point for design of a phantom that will be endorsed by the International Society for Magnetic Resonance in Medicine (ISMRM) Quantitative MRI subcommittee.
21. Designed software for analysis of the ADNI phantom data. The source code for ADNI phantom analysis was made freely available on the ADNI-LONI web site.
22. Demonstrated value of scanner monitoring with the ADNI phantom. We estimate that 20% of all ADNI-1 scans would have been affected by the errors of various types. Monitoring scanner performance with the ADNI phantom is a relatively inexpensive way to ensure that scanner errors are discovered and appropriate corrective action is taken ³³.
23. Demonstrated that longitudinal consistency is improved with correction of scaling ³⁴, gradient non-linearity ³³, and with intensity non-uniformity correction ^{35, 36}.

In summary, ADNI-1 has shown that with proper implementation methods, high quality MRI acquisition can be achieved in a large multi-site study. The excellent measurement precision of MRI in a multi-site environment points to MRI as an attractive endpoint for clinical trials. MRI measures, both global and regional, are sensitive to longitudinal and cross-sectional associations with cognition and other biological indicators which underscores the validity of MRI as a biomarker for clinical trials. Vascular brain injury is common even in carefully selected clinical trial designs and independently influences common cognitive outcome measures,

3. Present and future: ADNI-GO and plans for ADNI-2

The objectives of ADNI-GO and ADNI-2 (if funded) for the MRI core will include steps to further evaluate methodological improvements for clinical trials and evaluate biomarkers in AD and its prodromal and preclinical stages. ADNI-GO and ADNI-2 will follow 3 cohorts of subjects. 1) Cognitively Normal (CN) and late MCI (LMCI) subjects carried forward from ADNI-1 (followed at 1.5T); 2) EMCI (early MCI) enrolled in GO and carried forward into ADNI-2 (scanned at 3T); 3) CN, LMCI, and Alzheimer's Disease (AD) subjects newly enrolled in ADNI- 2 (scanned at 3T).

Next, we describe the rationale that led to the selection of the MRI protocol for ADNI-GO and ADNI-2. Our approach to the ADNI-GO and ADNI-2 MRI protocol will be to maintain MRI methodological consistency to the greatest extent possible in previously enrolled ADNI-1 subjects, to maximize the value of the longitudinal MRI data in these subjects. However, for newly enrolled subjects in GO (and ADNI-2 if funded), we will modernize and expand the MRI protocol to remain technically current, within the constraints imposed by having to operate in a reasonably consistent manner across many individual scanner models representing the three largest MRI vendors. Given the sensitivity of MRI as a biological marker demonstrated in ADNI-1, ADNI-GO and ADNI-2 are designed to further assess usefulness among individuals who are cognitively normal or have even more subtle cognitive impairment. This approach will serve to address two important objectives: how well does MRI identify the earliest change in brain pathology and what is the particular pattern of regional brain change?

3.1. Rationale for selection of core sequences for the ADNI-GO and ADNI-2 protocol

The ADNI-GO and ADNI-2 protocol is divided into a core set of sequences that will be performed on all scanners in all subjects, and a series of more experimental vendor specific sub-studies. This approach was arrived at after extensive discussion within the ADNI MRI core, aligned external investigators, the ADNI Steering committee, and the industry scientific advisory board (ISAB).

A 3D T1-weighted volume and a 2D FLAIR sequence were considered the minimum requirements for the protocol. The 3D T1-weighted volume is the primary sequence for structural MRI analysis, while FLAIR is the sequence most widely used in clinical neuroradiology for general pathology detection – including cerebrovascular disease. We then considered adding one or two additional sequences to this minimum core from the following: long-TE (i.e., 20 ms) gradient echo (GRE) micro hemorrhage imaging, resting-state functional connectivity (RSFC), Arterial Spin Labeling Perfusion imaging (ASL), and diffusion tensor imaging (DTI). Criteria for selecting additional sequences to include in the core protocol were: relevance to clinical trials, availability among the major MR vendors, ability to standardize across various models and platforms from a single vendor, reliability of quantitative measurements, evidence of test-retest precision of longitudinal measures, availability of data (cross-sectional and longitudinal) indicating evidence of diagnostic efficacy, and interest on the part of the ISAB and associated ADNI scientific investigators. All three emerging MRI applications (ASL, DTI and RSFC) selected for inclusion in ADNI-2 are generally considered to be “signal-starved”; that is, they all benefit from the increased SNR at 3T compared to 1.5T even more than the typical MR application. This benefit of 3T also applies to the accelerated version of the T1-volumetric acquisition. We elected to include GRE imaging as part of the core protocol on all systems. GRE imaging has become a routine component of the MRI protocol for all anti-amyloid clinical trials. Up to 20% of all AD subjects enrolled in anti-amyloid clinical trials have an abnormality detectable on GRE images³⁷.

Features of the ADNI-GO and ADNI-2 protocol for newly enrolled subjects are:

1. Scanning will be performed exclusively at 3T.
2. Duration of the exam should not exceed approximately 30 minutes.
3. The ADNI-GO and the ADNI-2 protocols will be identical.
4. Only manufacturer-available pulse sequences will be employed.
5. The manufacturer-available pulse sequence limitation dictates that we will use MPRAGE for the structural T1-weighted sequence for Siemens and Philips systems and a closely-related manufacturer-available pulse sequence, 3D IR-FSPGR, on GE systems. ADNI-1 utilized a works-in-progress (WIPS) version of MPRAGE on the GE scanners. This maximized inter-vendor standardization, but it had several drawbacks; most notably, it made it difficult for other studies to precisely replicate ADNI-1 methods on GE scanners. A comparison of images obtained with MPRAGE versus IR-FSPGR protocols at 3T is provided in Figure 6.
6. In ADNI-1, we acquired dedicated B1-correction calibration series on GE and Siemens scanners, while the manufacturer-available feature “CLEAR” was used on Philips scanners. A lesson learned was that site compliance to acquire these dedicated calibration series was poor because the acquisitions require the switching between the head and body RF coils. Fortunately, testing during ADNI-1 showed that these calibration data were not essential at 1.5T³⁸ provided that further correction such as “N3m” (a customized method for intensity correction³⁸) processing is used. In ADNI-GO and ADNI-2, only manufacturer-available B1-calibration and correction will be used. On the Siemens scanners, “prescan normalize” will be used, on Phillips “CLEAR” will be used, and on GE scanners, the correction will be omitted as their “PURE” feature is not yet commercially available for 3T.
7. Both an accelerated and a non-accelerated 3D T1-weighted sequence will be acquired in each exam. Some inter-vendor variation remains in the implementation of parallel imaging, e.g., on the Siemens scanners the GRAPPA algorithm is used, while Philips and GE use SENSE. The inclusion of the accelerated T1-weighted volumetric

sequence, however, should generally allow us to further test³⁹ whether at 3T the reduced acquisition time (roughly halved) and resulting reduced likelihood of patient-motion artifacts compensates for increased image artifacts and image noise due to the use of parallel imaging. If so, this result could be of great practical value to future designers of multi-center studies.

8. The dual echo fast spin echo sequence that was used for vascular pathology detection in ADNI-1 will be replaced by a FLAIR, accelerated two-fold using parallel imaging on systems where this is a manufacturer-available option.
9. A long TE (i.e., TE = 20 ms) gradient echo (GRE) sequence will be included for micro hemorrhage detection.

3.2. Rationale for selection of experimental sub-study sequences for ADNI-GO and ADNI-2

We elected not to include ASL, RSFC or DTI in the core protocol for all sites for several reasons. These include; general uncertainty about long-term test-retest precision, minimal evidence of diagnostic efficacy in AD, questionable relevance to clinical trials in the near term, absence of widely available phantoms to calibrate measurements of perfusion, diffusion, or connectivity, and the need to keep the protocol to an acceptable time for patient acceptance purposes. Perhaps most importantly, we note that due to rapidly developing technology and differing design choices among vendors it is not currently practical to standardize DTI and especially ASL across vendors using manufacturer-available sequences. A key guideline for ADNI-GO and ADNI-2 is that only manufacturer-available sequences will be used. We believe that placing fundamentally incompatible across-vendor MRI data into the public domain would not be helpful to the scientific community. At the same time, we did think that it was important to consider including each of these important and emerging sequence types in ADNI-GO and ADNI-2 in order to pilot these approaches for potential use in multi-center clinical trials. These considerations led us to conclude that a viable approach would be to add a different one of each of the three experimental sequence types to the core protocol of each of the three major MRI vendors – creating vendor-specific protocols, while retaining the vendor independent three “core” pulse sequences. Including only one experimental sequence per vendor protocol will keep the duration of the protocol to an acceptable time (~30 minutes) for patients (who will undergo MRI exams at four time points in the first 12 months of ADNI-GO) to limit motion artifact, patient discomfort, and attrition.

In summary, present and future plans for ADNI MRI acquisition were dictated by many considerations. Chief among these were improving methods for clinical trials in AD, modernizing the acquisition from ADNI-1, patient comfort and acceptance, and incorporating lessons learned from ADNI-1. These principles point to a multi-track MRI acquisition approach with the following features:

1. ADNI-1 subjects: Continue to follow existing ADNI-1 subjects with serial MRI studies on the same 1.5T scanner on which they have been scanned, using the ADNI-1 1.5T protocol.
2. Newly enrolled ADNI-GO and ADNI-2 subjects:
 - a. Core protocol: Scan newly enrolled subjects at 3T with a core set of three types of sequences - 3D T1-weighted volume, FLAIR, and a long TE GRE. Each MRI exam will contain both an accelerated and a non-accelerated 3D T1-weighted acquisition.
 - b. Experimental sub-studies: In addition to the core protocol described above, we will perform pilot sub-studies of ASL perfusion, RSFC, and DTI. Where local software licensing permits, one of these sequences will be added to the

core protocol on each of the systems belonging to a single MRI vendor. Each of these three experimental sequences will benefit from the improved SNR at higher magnetic field strength used in ADNI-GO and ADNI-2. ASL will also realize benefits at 3T (vs. 1.5T) due to the longer lifetime of spin labels and RSFC from stronger BOLD contrast.

Acknowledgments

NIH Alzheimer's Disease Neuroimaging Initiative (AG24904); NIH Identifying Mechanisms of Dementia – Role for MRI (AG11378); NIH Construction Grant (NIH C06 RR018898); Denise Reyes

References

- Holland D, Brewer JB, Hagler DJ, Fenema-Notestine C, Dale AM, Weiner M, Thal L, Petersen R, Jack CR Jr, Jagust W, Trojanowki J, Toga AW, Beckett L, Green RC, Gamst A, Potter WZ, Montine T, Anders D, Bernstein M, Felmlee J, Fox N, Thompson P, Schuff N, Alexander G, Bandy D, Koeppe RA, Foster N, Reiman EM, Chen K, Shaw L, Lee VM, Korecka M, Crawford K, Neu S, Harvey D, Kornak J, Kachaturian Z, Frank R, Snyder PJ, Molchan S, Kaye J, Vorobik R, Quinn J, Schneider L, Pawluczyk S, Spann B, Fleisher AS, Vanderswag H, Heidebrink JL, Lord JL, Johnson K, Doody RS, Villanueva-Meyer J, Chowdhury M, Stern Y, Honig LS, Bell KL, Morris JC, Mintun MA, Schneider S, Marson D, Griffith R, Badger B, Grossman H, Tang C, Stern J, Detolledo-Morrell L, Shah RC, Bach J, Duara R, Isaacson R, Strauman S, Albert MS, Pedroso J, Toroney J, Rusinek H, de Leon MJ, De Santi SM, Doraiswamy PM, Petrella JR, Aiello M, Clark CM, Pham C, Nunez J, Smith CD, Given CA 2, Hardy P, Dekosky ST, Oakley M, Simpson DM, Ismail MS, Porsteinsson A, McCallum C, Cramer SC, Mulnard RA, McAdams-Ortiz C, Diaz-Arrastia R, Martin-Cook K, Devous M, Levey AI, Lah JJ, Cellar JS, Burns JM, Anderson HS, Laubinger MM, Bartzokis G, Silverman DH, Lu PH, Fletcher R, Parfitt F, Johnson H, Farlow M, Herring S, Hake AM, van Dyck CH, Macavoy MG, Bifano LA, Chertkow H, Bergman H, Hosein C, Black S, Graham S, Caldwell C, Feldman H, Assaly M, Hsiung GY, Kertesz A, Rogers J, Trost D, Bernick C, Gitelman D, Johnson N, Mesulam M, Sadowsky C, Villena T, Mesner S, Aisen PS, Johnson KB, Behan KE, Sperling RA, Rentz DM, Johnson KA, Rosen A, Tinklenberg J, Ashford W, Sabbagh M, Connor D, Obradov S, Killiany R, Norbash A, Obisesan TO, Jayam-Trouth A, Wang P, Auchus AP, Huang J, Friedland RP, Decarli C, Fletcher E, Carmichael O, Kittur S, Mirje S, Johnson SC, Borrie M, Lee TY, Asthana S, Carlsson CM, Potkin SG, Highum D, Preda A, Nguyen D, Tariot PN, Hendin BA, Scharre DW, Kataki M, Beversdorf DQ, Zimmerman EA, Celmins D, Brown AD, Gandy S, Marenberg ME, Rovner BW, Pearlson G, Blank K, Anderson K, Saykin AJ, Santulli RB, Pare N, Williamson JD, Sink KM, Potter H, Ashok Raj B, Giordano A, Ott BR, Wu CK, Cohen R, Wilks KL, Safirstein BE. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci U S A* 2009 Dec 8;106(49):20954–9. [PubMed: 19996185]
- Tosun. Relations between brain tissue loss, CSF, biomarker and ApoE genetic profile. *ISMRM*; 2010 May 1-7; Stockholm, Sweden. 2010.
- Hua X, Lee S, Hibar DP, Yanovsky I, Leow AD, Toga AW, Jack CR Jr, Bernstein MA, Reiman EM, Harvey DJ, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM. Mapping Alzheimer's disease progression in 1309 MRI scans: Power estimates for different inter-scan intervals. *Neuroimage*. Feb 6;
- Stein JL, Hua X, Morra JH, Lee S, Ho AJ, Leow AD, Toga AW, Sul J, Kang HM, Eskin E, Saykin AJ, Shen L, Foroud T, Pankratz N, Huettelman MJ, Craig DW, Gerber JD, Allen A, Corneveaux J, Stephan DA, Webster J, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW. Genome-wide association study of temporal lobe structure identifies novel quantitative trait loci for neurodegeneration in alzheimer's disease. *Neuron*. 2009 Submitted July 21 2009.
- Freeborough PA, Fox NC. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans Med Imaging* 1997 Oct;16(5):623–9. [PubMed: 9368118]
- Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, Thompson PM, Jack CR Jr, Weiner MW. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain* 2009 Apr;132(Pt 4):1067–77. [PubMed: 19251758]

7. Carmichael OT, Drucker D, Schwarz C, Fletcher E, Martinez O, Yoshita M, He J, DeCarli C. Longitudinal changes in cognition and cerebrovascular disease in the Alzheimers disease neuroimaging initiative. *Alzheimer's and Dementia* 4(4):T277–T8.
8. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999 Feb;9(2):179–94. [PubMed: 9931268]
9. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 1999 Feb;9(2):195–207. [PubMed: 9931269]
10. Ashburner J, Friston KJ. Voxel-based morphometry -- the methods. *Neuroimage* 2000 Jun;11(6 Pt 1):805–21. [PubMed: 10860804]
11. Hua X, Yanovsky I, Leow AD, Lee S, Ho AJ, Parikshak N, Toga AW, Jack CR Jr, Weiner MW, Thompson PM. Tensor based morphometry as surrogate marker for Alzheimer's disease and mild cognitive impairment: Optimizing Statistical Power. Organization for Human Brain Mapping. 2009
12. Hua X, Lee S, Yanovsky I, Leow AD, Chou YY, Ho AJ, Gutman B, Toga AW, Jack CR Jr, Bernstein MA, Reiman EM, Harvey DJ, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM. 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 Dec;48(4):668–81. [PubMed: 19615450]
13. Leung KK, Clarkson MJ, Bartlett JW, Clegg S, Jack CR Jr, Weiner MW, Fox NC, Ourselin S. Robust atrophy rate measurement in Alzheimer's disease using multi-site serial MRI: Tissue-specific intensity normalization and parameter selection. *Neuroimage* Apr 1;50(2):516–23. [PubMed: 20034579]
14. Kohannim O, Hua X, Hibar DP, Lee S, Chou YY, Toga AW Jr, J CR, Weiner MW, Thompson PM. Boosting power for clinical trials using classifiers based on multiple biomarkers. *Neurobiology of Aging*, Special Issue on ADNI. 2010 Jan;
15. Evans MC, Barnes J, Nielsen C, Kim LG, Clegg SL, Blair M, Leung KK, Douiri A, Boyes RG, Ourselin S, Fox NC. Volume changes in Alzheimer's disease and mild cognitive impairment: cognitive associations. *Eur Radiol* Mar;20(3):674–82. [PubMed: 19760240]
16. Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, Parikshak N, Hua X, Toga AW, Jack CR Jr, Schuff N, Weiner MW, Thompson PM. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Hum Brain Mapp* 2009 Sep;30(9):2766–88. [PubMed: 19172649]
17. Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Blennow K, Brewer JB, Dale AM. Brain Atrophy in Healthy Aging Is Related to CSF Levels of A{beta}1-42. *Cereb Cortex*. Jan 4;
18. Walhovd KB, Fjell AM, Brewer J, McEvoy LK, Fennema-Notestine C, Hagler DJ Jr, Jennings RG, Karow D, Dale AM. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *AJNR Am J Neuroradiol* Feb;31(2):347–54. [PubMed: 20075088]
19. Chen K, Langbaum JBS, Fleisher AS, Ayutyanont N, Reschke C, Lee W, Liu X, Bandy D, Alexander GE, Thompson PM, Foster NL, Harvey DJ, Leon MJd, Koeppe RA, Jagust WJ, Weiner MW, Reiman EM, Initiative* AsDN. Twelve-Month Metabolic Declines in Probable Alzheimer's Disease and Amnesic Mild Cognitive Impairment Assessed Using an Empirically Pre-Defined Statistical Region-of-Interest: Findings from the Alzheimer's Disease Neuroimaging Initiative. *NeuroImage*. 2010 Accepted.
20. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Petersen RC, Jack CR Jr. MRI and CSF biomarkers in normal, MCI, and AD subjects: Diagnostic discrimination and cognitive correlations. *Neurology* 2009 Jul 28;73(4):287–93. [PubMed: 19636048]
21. Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM. CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease. *J Neurosci* Feb 10;30(6):2088–101. [PubMed: 20147537]
22. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Petersen RC, Jack CR Jr. MRI and CSF biomarkers in normal, MCI, and AD subjects: Predicting future clinical change. *Neurology* 2009 Jul 28;73(4):294–301. [PubMed: 19636049]

23. McEvoy LK, Fennema-Notestine C, Roddey JC, Hagler DJ Jr, Holland D, Karow DS, Pung CJ, Brewer JB, Dale AM. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. *Radiology* 2009 Apr;251(1):195–205. [PubMed: 19201945]
24. McEvoy L, Hagler D, Holland D, Roddey J, Fennema-Notestine C, Salmon D, Koyama A, Aisen P, Brewer J, Dale A, Initiative* AsDN. Neuroimaging Enrichment Strategy for Secondary Prevention Trials in Alzheimer's. *Disease Alzheimer's Disease and Related Disorders*. In press.
25. McDonald CR, McEvoy LK, Gharapetian L, Fennema-Notestine C, Hagler DJ Jr, Holland D, Koyama A, Brewer JB, Dale AM. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. *Neurology* 2009 Aug 11;73(6):457–65. [PubMed: 19667321]
26. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Lee S, Hibar DP, Dinov ID, Stein JL Jr, J CR, Weiner MW, Toga AW, Thompson PM. Obesity and brain structure in 700 MCI and AD patients. *Neurobiology of Aging, Special Issue on ADNI*. 2010 Jan;
27. Stein JL, Hua X, Lee S, Ho AJ, Leow AD, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen A, Corneveaux J, Stephan DA, Webster J, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW, Thompson PM. Voxelwise Genome-Wide Association Study (vGWAS). *Neuroimage*. 2009 Submitted August 31, 2009.
28. Joyner AH, J CR, Bloss CS, Bakken TE, Rimol LM, Melle I, Agartz I, Djurovic S, Topol EJ, Schork NJ, Andreassen OA, Dale AM. A common MECF2 haplotype associates with reduced cortical surface area in humans in two independent populations. *Proc Natl Acad Sci U S A* 2009 Sep 8;106(36):15483–8. [PubMed: 19717458]
29. Rimol LM, Agartz I, Djurovic S, Brown AA, Roddey JC, Kahler AK, Mattingsdal M, Athanasios L, Joyner AH, Schork NJ, Halgren E, Sundet K, Melle I, Dale AM, Andreassen OA. Sex-dependent association of common variants of microcephaly genes with brain structure. *Proc Natl Acad Sci U S A* Jan 5;107(1):384–8. [PubMed: 20080800]
30. Hua X, Hibar DP, Lee S, Toga AW Jr, J CR, Weiner MW, Thompson PM. Sex and age differences in brain atrophic rates: an ADNI study with N=1368 MRI scans. *Neurobiology of Aging, Special Issue on ADNI*. 2010 Jan;
31. Chou, YY.; Leporé, N.; Madsen, SK.; Saharan, P.; Hua, X., Jr.; J, CR.; Shaw, LM.; Trojanowski, JQ.; Weiner, MW.; Toga, AW.; Thompson, PM. Ventricular Maps in 804 Subjects Correlate with Cognitive Decline, CSF Pathology, and Imminent Alzheimer's Disease. *ISBI*; April 14-17, 2010; Rotterdam, The Netherlands. 2010.
32. Chou YY, Leporé N, Saharan P, Madsen SK, Hua X Jr, J CR, Shaw LM, Trojanowski JQ, Weiner MW, Toga AW, Thompson PM, Initiative* AsDN. Ranking the Clinical and Pathological Correlates of Ventricular Expansion Mapped in 804 Alzheimer's Disease, MCI, and Normal Elderly Subjects. *Neurobiology of Aging, Special Issue on ADNI*. 2010 Jan;
33. 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 Jun;36(6):2193–205. [PubMed: 19610308]
34. Clarkson MJ, Ourselin S, Nielsen C, Leung KK, Barnes J, Whitwell JL, Gunter JL, Hill DL, Weiner MW, Jack CR Jr, Fox NC. Comparison of phantom and registration scaling corrections using the ADNI cohort. *Neuroimage* 2009 Oct 1;47(4):1506–13. [PubMed: 19477282]
35. Leow AD, Klunder AD, Jack CR Jr, Toga AW, Dale AM, Bernstein MA, Britson PJ, Gunter JL, Ward CP, Whitwell JL, Borowski BJ, Fleisher AS, Fox NC, Harvey D, Kornak J, Schuff N, Studholme C, Alexander GE, Weiner MW, Thompson PM. Longitudinal stability of MRI for mapping brain change using tensor-based morphometry. *Neuroimage* 2006 Jun;31(2):627–40. [PubMed: 16480900]
36. Boyes RG, Gunter JL, Frost C, Janke AL, Yeatman T, Hill DL, Bernstein MA, Thompson PM, Weiner MW, Schuff N, Alexander GE, Killiany RJ, DeCarli C, Jack CR, Fox NC. Intensity non-uniformity correction using N3 on 3-T scanners with multichannel phased array coils. *Neuroimage* 2008 Feb 15;39(4):1752–62. [PubMed: 18063391]
37. Bednar, M.; Zhao, Q.; Landen, JW.; Clare, B.; Billing, J.; Rohrbacher, K.; Kupiec, JW. Safety and Pharmacokinetics of the Anti-Amyloid Monoclonal Antibody PF-04360365 Following a Single Infusion in Patients with Mild-to-Moderate Alzheimer's Disease: Preliminary Results. *International Conference on Alzheimer's Disease*; 2009 July 11-16; Vienna, Austria. 2009.

38. Gunter, J.L.; Preboske, G.M.; Ward, C.P.; Vemuri, P.; Bernstein, M.; Jack, C.R., Jr. Is B1-correction for Neuroanatomy necessary?. International Society for Magnetic Resonance in Medicine; Honolulu, HI: 2009 Apr.
39. Krueger, G.; Fischer, H.; Jahns, K.; Driemel, D.; Littmann, A.; Kannengiesser, S.; Sorensen, A.; Bernstein, M.; Britson, P.; Ward, C.; Gunter, J.; Reyes, D.; Jack, C.R., Jr. Towards a 10 minute clinical Alzheimer MR imaging protocol. International Society for Magnetic Resonance in Medicine; Berlin, Germany: 2007 May.

Sample sizes required to detect k% slowing in the rate of atrophy

Figure 1.
Power estimates for different scan intervals from Hua et al ³.

Figure 2.

Association between low baseline CSF A β_{1-42} concentrations and cortical thickness in cognitive normal elderly. *Top row:* cortical maps of estimated cortical thinning per unit CSF A β_{42} reduction; *bottom row:* Significance maps from Tosun et al ².

Figure 3.

Association between low baseline CSF $A\beta_{1-42}$ concentrations and increased rates of cortical atrophy in MCI. *Top row:* Maps of estimated cortical atrophy rates per unit CSF $A\beta_{42}$ reduction; *bottom row:* Significance maps from Tosun et al ².

Figure 4.

Estimated sample sizes (with approximate 95% confidence intervals) needed to detect a 25% reduction in absolute (blue bars) or relative (red bars) rate of change, at $p < 0.05$ level, with 80% power, based on a mixed effects general linear model updated from Holland et al.¹

Figure 5.
Genome-wide association study of temporal lobe structure from Stein et al ⁴.

Figure 6.

Comparison of 3D T1-weighted image sets acquired on a healthy 35 y.o. male volunteer subject. *First row:* Philips MPRAGE $1.0 \times 1.0 \times 1.2$ mm spatial resolution, acquired in 9:06. *Second row:* Philips accelerated MPRAGE: $1.1 \times 1.1 \times 1.2$ mm, 5:35. *Third row:* GE MPRAGE (as used in ADNI-1) $1.0 \times 1.0 \times 1.0$ mm, 9:17. *Fourth row:* GE IR-FSPGR $1.0 \times 1.0 \times 1.2$ mm, 9:41. *Bottom row:* GE accelerated IR-FSPGR $1.1 \times 1.1 \times 1.2$ mm, 5:34. Siemens accelerated and non-accelerated MPRAGE images, although not available on this subject, are also of high quality.