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Update on the Magnetic Resonance Imaging core of the Alzheimer's Disease Neuroimaging Initiative

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Abstract Functions of the Alzheimer's Disease Neuroimaging Initiative (ADNI) magnetic resonance imaging (MRI) core fall into three categories: (1) those of the central MRI core laboratory 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 the previously enrolled ''ADNI-1'' subjects who are followed up 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 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 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 multicenter (but single vendor) setting for these three emerging MRI applications.

Keywords: Alzheimer's disease; Magnetic resonance imaging; ADNI

1. Introduction

The major purpose of this article is to describe past, present, and future activities of the Alzheimer's Disease Neuroimaging Initiative (ADNI) magnetic resonance imaging (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 article 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

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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 laboratory 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. Alzheimer's Disease Neuroimaging Initiative-1

The primary objective of ADNI-1 was to improve methods for clinical trials. In addition, however, the data generated by ADNI-1 have improved the understanding of relationships between imaging and chemical biomarkers of Alzheimer's disease (AD) and clinical manifestations. 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 magnetization prepared gradient-echo (MPRAGE). The MPRAGE sequence was repeated back-to-back in ADNI-1 to increase the likelihood of acquiring at least one good quality MPRAGE scan (hence, decrease the need to repeat examinations) and also to permit signal averaging if desired. In addition, a dual fast spin-echo (proton density/T2-weighted) sequence was acquired at each time point to evaluate the presence or state of vascular disease and general pathology detection. All subjects received a 1.5T protocol examination 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 laboratory at the Mayo Clinic

Functions primarily managed by the central ADNI MRI laboratory 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 nonuniformity, warping because of gradient nonlinearity, and changes in global scaling of length over time as a result of 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 as follows:

Nick Fox—rates of brain atrophy: brain and ventricular boundary shift integral [1];

Paul Thompson—tensor-based morphometry [2];

Norbert Schuff—hippocampal volume [3];

Charles DeCarli—assessment of cerebrovascular disease [4];

Colin Studholme—tensor-based morphometry

Anders Dale—FreeSurfer with improved sub-regional change analysis [5–7];

Gene Alexander—voxel-based morphometry [8].

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 in the following paragraph.

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 [2,5,9–11] Fig. 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 [2,5,10–12].

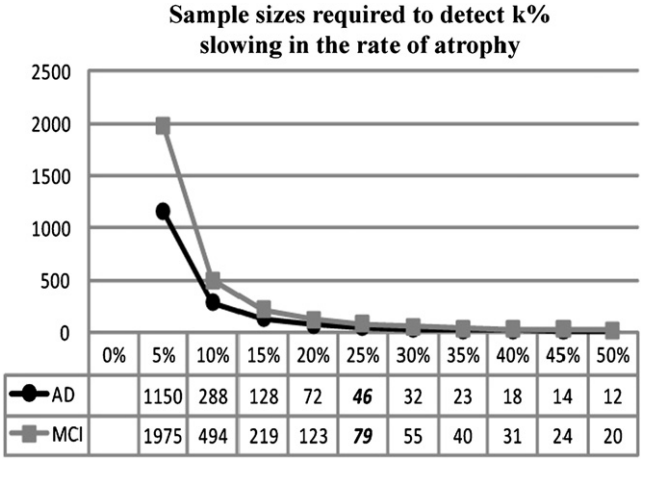

Fig. 1. Power estimates for different scan intervals (adapted from Hua et al.) [2].

3. It is 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 [13].
4. Demonstrated that MRI rates of change in cognitively normal subjects are greater in *APOE* ε4 carriers than in noncarriers [3,14,15].
5. It showed that lower CSF $A\beta_{42}$ and higher CSF tau concentrations were associated with a variety of structural brain alterations. Specifically, lower CSF $A\beta_{42}$ was associated with a thinner cortex in cognitive healthy controls (Fig. 2) [16]. In addition, lower CSF $A\beta_{42}$ and higher CSF tau were associated with higher regional brain atrophy rates across the clinical groups (Fig. 3) [16].
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 (Fig. 4) [5].
7. Baseline MRI is generally a better predictor of clinical and cognitive change than either FDG PET or CSF biomarkers [17].
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 al [18] 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 methods [12]. Note that virtually any longitudinal AD study involving imaging would be expected to include an MR component anyway, so as to rule out a clinical condition (eg, 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 $A\beta_{42}$ [17,19,20].
10. Low baseline levels of CSF $A\beta_{42}$ were associated with more rapid cortical atrophy in healthy controls [20].
11. MRI has better prediction of risk of conversion from MCI to AD than CSF tau or $A\beta_{42}$ [21].
12. It 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 [21,22]. It 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 measure [23].
13. It demonstrated no superiority for 3T vs. 1.5T in group-wise discrimination or sample sizes needed to power trials [9].
14. It confirmed previous reports that hippocampal atrophy rates in MCI and AD accelerate [3] and, further, that disease stage is associated with accelerated atrophy rates of widespread cortical areas [24].
15. It demonstrated greater white matter hyperintensity load in AD and MCI than in control subjects who would be typically enrolled in therapeutic trials [4].
16. It 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-cog [4].
17. It found associations between levels of atrophy and genetic differences in the glutamate receptor [25], the FTO obesity gene [26], and several other candidate genes [25,27–29] (Fig. 5).
18. It found gender and age differences in rates of atrophy in all diagnostic groups [30] and between atrophy and obesity [26,30].

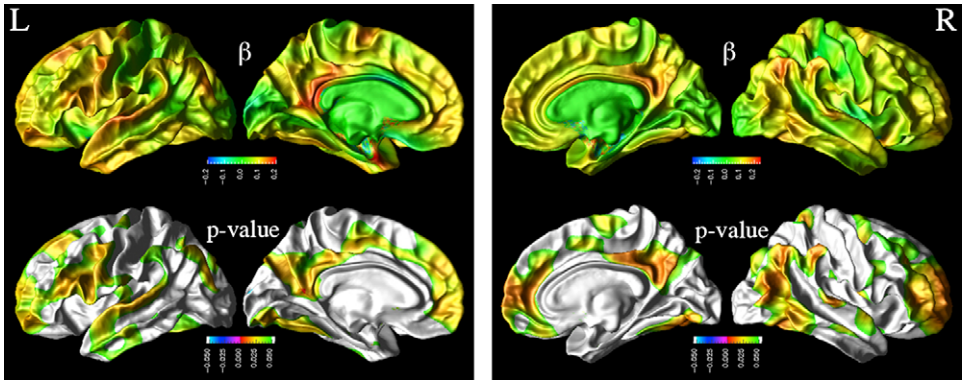

Fig. 2. Association between low baseline CSF $A\beta_{1\text{-}42}$ concentrations and cortical thickness in cognitive normal elderly. *Top row:* cortical maps of estimated cortical thinning per unit CSF $A\beta_{42}$ reduction; *bottom row:* Significance maps (adapted from Tosun) [16].

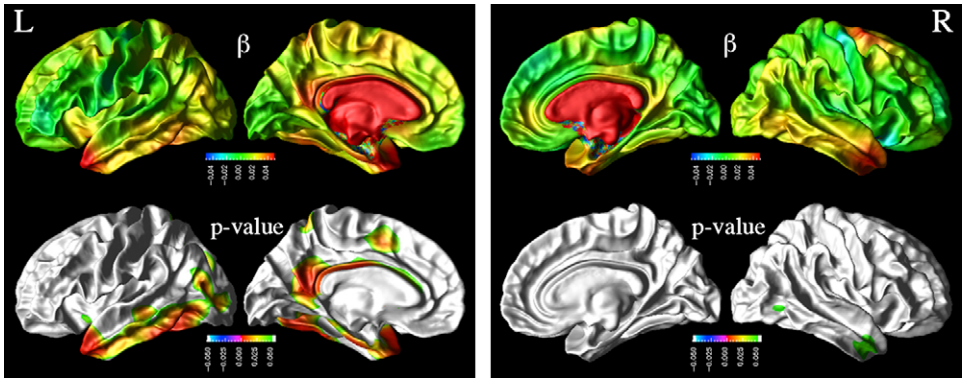

Fig. 3. Association between low baseline CSF $A\beta_{1-42}$ concentrations and increased rates of cortical atrophy in MCI. *Top row:* Maps of estimated cortical atrophy rates per unit CSF $A\beta_{42}$ reduction; *bottom row:* Significance maps (adapted from Tosun) [16].

19. It mapped 3D profiles of caudate atrophy and ventricular expansion and their pathological and clinical correlates [31,32].
20. It 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.
21. It 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 by the International Society for Magnetic Resonance in Medicine (ISMRM) Quantitative MRI sub-committee.
22. It 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.
23. It demonstrated value of scanner monitoring with the ADNI phantom. We estimate that 20% of all ADNI-1 scans would have been affected by errors of various types had each scanner not been monitored. 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].
24. It demonstrated that longitudinal consistency is improved with correction of scaling [34], gradient non-linearity [33], and 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 multisite study. The excellent measurement precision of MRI in a multisite environment points to MRI as a useful 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 underscore 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 to evaluate biomarkers in AD and its prodromal and preclinical stages. ADNI-GO and ADNI-2 will follow 3 cohorts of subjects. (1) Cognitively normal and late MCI subjects carried forward from ADNI-1 (followed at 1.5T); (2) early MCI enrolled in GO and carried forward into ADNI-2 (scanned at 3T); and (3) cognitively normal, late MCI, 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, and 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

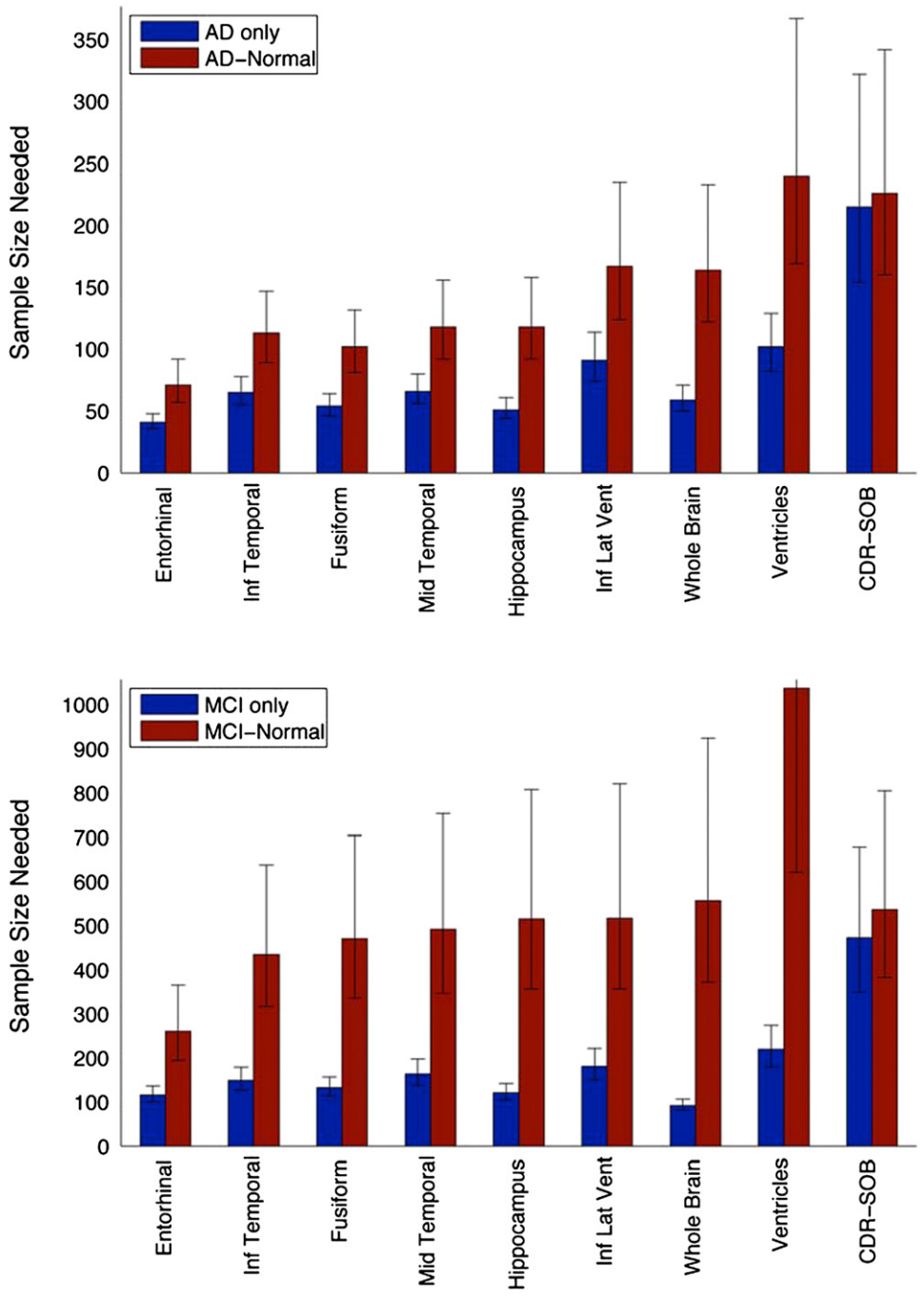

Fig. 4. Estimated sample sizes (with approximate 95% confidence intervals) needed to detect a 25% reduction in absolute (blue bars) or relative (red bars) rate of change, at $P < .05$ level, with 80% power, based on a mixed effects general linear model (updated from Holland et al.) [5].

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, whereas 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 MRI platforms, reliability of

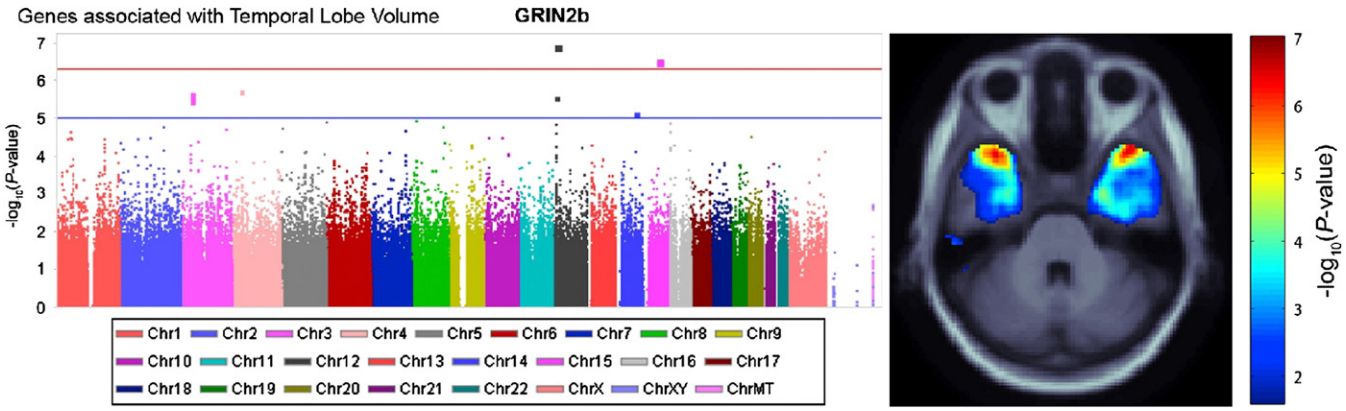

Fig. 5. Genome-wide association study of temporal lobe structure (adapted from Stein et al.) [29].

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. 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 images [37].

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

1. Scanning will be performed exclusively at 3T.
2. Duration of the examination 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 used.
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 used 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 Fig. 6.
6. In ADNI-1, we acquired dedicated B1-correction calibration series on GE and Siemens scanners, whereas 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 1.5T [38], provided that further correction such as "N3m" (a customized method for intensity correction [38]) 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 nonaccelerated 3D T1-weighted sequence will be acquired in each examination. Some inter-vendor variation remains in the implementation of parallel imaging, for example, on the Siemens scanners the GRAPPA algorithm is used, whereas Philips and GE use SENSE. The inclusion of the accelerated T1-weighted volumetric sequence, however, should generally allow us to test further [39] 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 because of the use of parallel imaging. If so, this result could be of great practical value to future designers of multicenter 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,

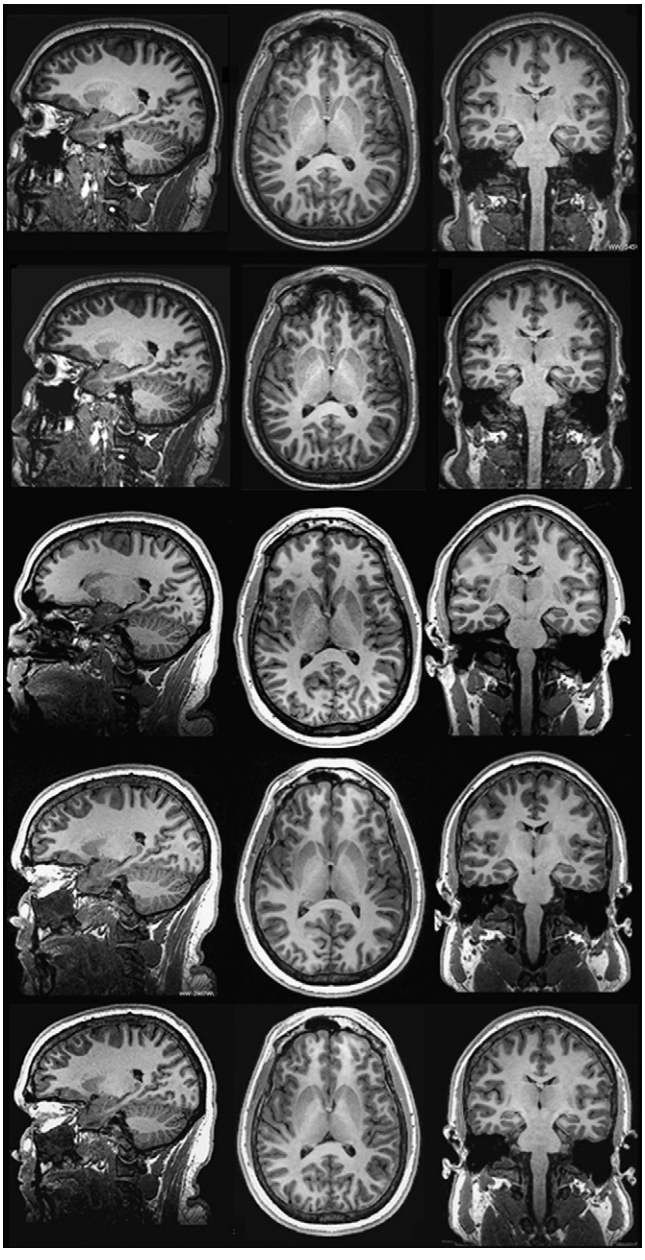

Fig. 6. Comparison of 3D T1-weighted image sets acquired on a healthy 35-year-old male volunteer subject. *First row*: Philips MPRAGE 1.0 × 1.0 × 1.2 mm spatial resolution, acquired in 9:06. *Second row*: Philips accelerated MPRAGE: 1.1 × 1.1 × 1.2 mm, 5:35. *Third row*: GE MPRAGE (as used in ADNI-1) 1.0 × 1.0 × 1.0 mm, 9:17. *Fourth row*: GE IR-FSPGR 1.0 × 1.0 × 1.2 mm, 9:41. *Bottom row*: GE accelerated IR-FSPGR 1.1 × 1.1 ×1.2 mm, 5:34. Siemens accelerated and non-accelerated MPRAGE images, although not available on this subject, are also of high quality.

diffusion, or connectivity, and the need to keep the protocol to an acceptable time for patient acceptance purposes. Perhaps most importantly, we note that because of 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 to pilot these approaches for potential use in multicenter 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 (approximately, 30 minutes) for patients (who will undergo MRI examinations at four time points in the first 12 months of ADNI-GO) to limit motion artifact, patient discomfort, and attrition. 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-weighted volumetric acquisition, which to restore lost SNR employs a slight increase in voxel size compared to its non-accelerated counterpart (see Fig. 6).

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 multitrack 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 examination will contain both an accelerated and a non-accelerated 3D T1-weighted acquisition.

b. *Experimental sub-studies:* In addition to the core protocol described earlier, 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) because of the longer lifetime of spin labels and RSFC from stronger BOLD contrast.

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