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REVIEW ARTICLE

Overview of ADNI MRI

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Abstract

The magnetic resonance imaging (MRI) Core has been operating since Alzheimer's Disease Neuroimaging Initiative's (ADNI) inception, providing 20 years of data including reliable, multi-platform standardized protocols, carefully curated image data, and quantitative measures provided by expert investigators. The overarching purposes of the MRI Core include: (1) optimizing and standardizing MRI acquisition methods, which have been adopted by many multicenter studies and trials worldwide and (2) providing curated images and numeric summary values from relevant MRI sequences/contrasts to the scientific community. Over time, ADNI MRI has become increasingly complex. To remain technically current, the ADNI MRI protocol has changed substantially over the past two decades. The ADNI 4 protocol contains nine different imaging types (e.g., three dimensional [3D] T1-weighted and fluid-attenuated inversion recovery [FLAIR]). Our view is that the ADNI MRI data are a greatly underutilized resource. The purpose

of this paper is to educate the scientific community on ADNI MRI methods and content to promote greater awareness, accessibility, and use.

KEYWORDS
ADNI, Alzheimer's disease imaging, Alzheimer's disease MRI, magnetic resonance imaging

Highlights

- The MRI Core provides multi-platform standardized protocols, carefully curated image data, and quantitative analysis by expert groups.
- The ADNI MRI protocol has undergone major changes over the past two decades to remain technically current.
- As of April 25, 2024, the following numbers of image series are available: 17,141 3D T1w; 6877 FLAIR; 3140 T2/PD; 6623 GRE; 3237 dMRI; 2846 ASL; 2968 TF-fMRI; and 2861 HighResHippo (see Table 1 for abbreviations).
- As of April 25, 2024, the following numbers of quantitative analyses are available: FreeSurfer 10,997; BSI 6120; tensor based morphometry (TBM) and TBM-SYN 12,019; WMH 9944; dMRI 1913; ASL 925; TF-fMRI NFQ 2992; and medial temporal subregion volumes 2726 (see Table 4 for abbreviations).
- ADNI MRI is an underutilized resource that could be more useful to the research community.

1 | BACKGROUND

The overarching goals of the Alzheimer's Disease Neuroimaging Initiative (ADNI) magnetic resonance imaging (MRI) Core are to standardize MRI acquisitions at ADNI sites and to provide curated images and numeric summary values from relevant MRI contrast mechanisms. The images themselves and numeric analyses are made available to the scientific community to facilitate MRI in clinical trials and to provide data for observational research. MRI is frequently employed in AD clinical trials for inclusion/exclusion and safety monitoring.[1–5] The rate of change on structural MRI (sMRI) has been employed as a secondary outcome measure of efficacy in many trials. In addition to informing the design of clinical trials, ADNI data have been used extensively for observational research in normal brain aging and dementia to examine correlations between MRI, clinical, genetic, positron emission tomography (PET), and biofluid measures. ADNI MRI methods have been employed in many multicenter studies and trials including the Dominantly Inherited Alzheimer's Network (DIAN), Atherosclerotic Risk in Communities (ARIC), Standardized Centralized Alzheimer's and Related Dementias Neuroimaging (SCAN), Jackson Heart Study, Alzheimer's Clinical Trials Consortium clinical trials, Alzheimer Biomarker Consortium–Down Syndrome (ABC-DS), Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on RecoverY (DISCOVERY), Longitudinal Early-Onset Alzheimer's Disease Study (LEADS), Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER), North American Prodromal Synucleinopathy Consortium 2 (NAPS2), ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD), and others. This article provides an overview of the ADNI MRI core for the special issue of the journal highlighting 20 years of the ADNI study. We do not review the results of publications using ADNI MRI data in this article because a comprehensive review of studies using ADNI data, including MRI, was recently published.[6]

2 | STRUCTURE AND FUNCTIONALITY OF THE ADNI MRI CORE

The ADNI MRI Core has two functional components. First, the central lab at the Mayo Clinic (the Aging and Dementia Imaging Research [ADIR] lab) is responsible for site qualification, protocol distribution, data acquisition and image quality control (QC), and identification of medical findings on participant MRI exams. Second, numeric analyses that are relevant to the field are provided by experts in the MRI Core. ADNI users can access the images themselves, as well as QC information, clinically relevant findings, and numeric analyses.

3 | THE ADNI MRI PROTOCOL

Ideally, variation in quantitative MRI measures across participants and within-person over time should be a result of biological effects, not

due to inconsistent or unreliable imaging methods. To achieve the goal of standardized acquisitions across all scanners and across time, protocols are developed that are compatible with hardware/software configurations within each of the three major MRI vendors' product lines. This has resulted in a large infrastructure of standardized MRI scanners at the 60 ADNI enrollment sites. Vendor- and version-specific protocols are posted publicly ADNI | MRI Scanner Protocols (usc.edu), which has resulted in the wide use of ADNI MRI protocols both by the pharmaceutical industry and academic entities.

We note the distinction between an MRI exam and MRI series/sequence; an exam is composed of a set of series/sequences. To remain contemporary in a field like MRI that undergoes constant technical innovation, the ADNI protocol is updated every new grant cycle (and occasionally within a grant cycle). The current ADNI 4 exam consists of nine different series types (e.g., three-dimensional [3D] T1, fluid-attenuated inversion recovery [FLAIR], etc.) (Table 1). The MRI Core devotes considerable time and effort to selecting the sequences that constitute the ADNI MRI protocol for each grant cycle. Several overarching principles govern decisions about the content of the protocol.

First, the content must serve the twin aims of ADNI, which are to provide standardized methods and analysis data that may be useful in clinical trials and to provide images and numeric data for observational research.

Second, the duration of the acquisition protocol cannot exceed 1 hour. This includes time for participant positioning and pre-scanning; therefore, the total gradient time (i.e., the time during which images are being acquired) cannot exceed 45 minutes. The ADNI MRI Core receives pressure to add many different series types, but a hard time limit must be maintained in order to not overburden participants. In addition, ADNI participants are typically scanned on MRI systems that carry heavy clinical scanning loads and the fixed time allotted per imaging exam at clinical enrollment centers must be respected.

Third, the ADNI protocol must employ only product acquisition series. A manufacturer-available acquisition series (sometimes called a "product" pulse sequence) is one that is provided as part of the stock software loaded on a commercial scanner, or, alternatively, is offered by the MRI vendor as a purchasable option. Product sequences have received regulatory approval for use in clinical scanning. In distinction, a "work-in-progress" (WIP) or "research pulse sequence" is not routinely available from the vendor. A WIP pulse sequence may have been created by the vendor for pre-production beta-testing purposes, or it may be a sequence created by an academic MRI physicist for a special application. WIPs have not received regulatory approval for clinical scanning. Product pulse sequences do not require a formal research agreement between the MRI vendor and the MRI site, whereas, by contrast, WIPs do. Restricting ADNI to product sequences also complies with the ADNI mandate to facilitate clinical trials on the assumption that sequences not approved by regulatory agencies would not be used in pivotal clinical trials. This provision also aids acceptance by local institutional review boards (IRBs), since only sequences that have received regulatory approval are used. It also reinforces the general utility of ADNI protocols because one-off custom protocols would not be generally available.

Below we briefly describe the evolution of the ADNI MRI protocol over each grant cycle dating back to ADNI 1.

RESEARCH IN CONTEXT

1. **Systematic review**: Prior to this, the most recent overview of the ADNI MRI Core was published in 2015. Major changes have occurred in the interim both in the content of the ADNI MRI protocol and in the methods of quantitative analysis.
2. **Interpretation**: ADNI MRI methods are widely used in clinical trials and have been adopted by many observational studies.
3. **Future directions**: In addition to an updated MRI protocol and analytic methods, ADNI 4 will examine the feasibility of ultra-fast acquisitions in a multi-site setting and will also examine methods for post-acquisition data harmonization. Ideally, this and other papers from the MRI Core in this special issue will increase visibility of ADNI MRI data, resulting in greater use by the scientific community.

3.1 | ADNI 1

The ADNI 1 grant cycle ran from 2004 to 2009. ADNI 1 MRI was performed at 1.5T at all sites, because that was standard of care for clinical brain imaging at that time (≈2004). Because the major emphasis in ADNI 1 was on the standardization of methods for clinical trials, a simple protocol was devised that mirrored what was believed to be useful for clinical trials at that time. Only two series types were acquired: 3D T1 and a proton density/T2 weighted dual fast spin echo sequence (PD/T2). These series enabled quantitative measurements of brain volume (or cortical thickness) and white matter hyperintensity (WMH) volume, respectively. The 3D T1 was repeated (i.e., back-to-back acquisitions were performed) to determine if signal averaging improvements in signal-to-noise ratio (SNR) were beneficial for brain morphometric measurements in a clinical trial enviornment. In addition, an experimental substudy was performed in ≈25% of the ADNI 1 cohort to evaluate imaging at 3T; this enabled direct comparison of 1.5T versus 3T acquired close in time to each other. At the beginning of ADNI, the expectation was that therapeutic intervention should slow the rate of brain atrophy; therefore, change in brain volume over time was believed to be an important outcome measure for AD clinical trials. Enthusiasm for this has waned over the years[7] as more rapid whole brain volume loss has become recognized as a feature of therapeutic amyloid beta (Aβ) removal.[8,7]

TABLE 1 MRI series descriptions and abbreviations.

Series or sequence type	Abbreviations	Applications in ADNI
3DT1 weighted (3D T1w)	Magnetization Prepared Rapid Gradient Echo (MPRAGE) or Inversion recovery fast spoiled gradient echo (IR-FSPGR)	Morphometric measures—e.g., FreeSurfer cortical volume/thickness and boundary shift integral
Compressed sense accelerated 3D T1w	CS-MPRAGE (for Philips) or Hypersence-MPRAGE (for General Electric)	T1w structural analysis, testing impact of higher image acceleration on measurement accuracy.
Fluid-attenuated inversion recovery	FLAIR	White matter hyperintensity volume and pathology detection
T2*gradient echo	T2*GRE or MEGRE (multi echo gradient echo)	Detection of cerebral microbleeds or superficial siderosis, quantitative susceptibilty (QSM) maps
3D T2 weighted (3DT2w) – sagittal whole brain	T2w (vendor names: SPACE, VISTA, CUBE)	Quantification of dilated perivascular spaces (PVS)
Diffusion magnetic resonance imaging	dMRI	The direction and magnitude of the diffusion of water molecules generates the contrast in dMRI images to indicate microstructural tissue integrity
Cerebral blood flow	ASL (arterial spin labeling) PASL (pulsed ASL) pCASL (pseudo-continuous ASL)	Magnetically labeled arterial blood water protons are used as an endogenous tracer to indicate local cerebral blood flow
Resting-state or task-free functional MRI	TF-fMRI	Measuring blood oxygenation level (BOLD)–dependent changes in MRI signal over time to identify functional connectivity networks
2D T2w coronal temporal lobe coverage	2D T2w (HighResHippo)	Measuring volumes of hippocampal and medial temporal subregions

At the beginning of ADNI 1, 3D correction for geometric warping, correction of gradient instability over time, and corrections for signal intensity inhomogeneity were not available on most MRI vendor products. Consequently, post-acquisition artifact correction methods constituted a major effort by the ADNI MRI Core activities. The ADNI phantom[9] was designed at the beginning of ADNI 1 to address the then unmet need for a high-resolution 3D geometric phantom for quantitative structural MRI. The ADNI phantom was designed to enable correction of linear scaling instability and geometric warping. The ADNI 1 scanning protocol included scanning the ADNI phantom at the end of each participant exam. In addition to geometric corrections, the phantom scans were used for scanner qualification and ongoing scanner QC. The ADNI phantom was later adopted for assessing scanner performance by other multisite studies (for example, the Systolic Blood Pressure Intervention Trial: Memory and Cognition in Decreased Hypertension (SPRINT-MIND), Atherosclerosis Risk in Communities (or ARIC), Dominantly Inherited Alzheimer Network (or DIAN), and AddNeuroMed.[10] The success of the ADNI phantom raised awareness in the MRI community about the need for a high-resolution 3D geometric phantom for quantitative structural MRI. This led the International Society of Magnetic Resonance in Medicine (ISMRM) Committee on Quantitative MRI along with the National Institute of Technology Standards (NIST) to design the NIST-ISMRM MRI System Phantom.[11] The NIST-ISMRM system phantom [11] employs the ADNI phantom design for geometric fidelity but also incorporates additional elements.

3.2 | ADNI 2/GO

The ADNI 2/GO grant cycle extended from 2009 to 2016, and ADNI 2 and ADNI GO were identical from an MRI perspective. (GO stands for Grand Opportunity, the name given to a type of National Institutes of Health [NIH] funding.) ADNI 2/GO incorporated several major changes in the protocol in comparison to ADNI 1. By the start of the ADNI 2/GO grant cycle, MRI vendors had made significant advances to engineering at 3T, and 3T had become the standard field strength in neuro-MRI academic settings. Therefore, the ADNI 2/GO protocol was moved to 3T for all newly enrolled participants. Participants who had been scanned at 1.5T in ADNI 1 and rolled over to ADNI 2/GO were maintained on the 1.5T scanner that they had been scanned on previously. Other major changes to the protocol were: (1) we added a 2D gradient echo (GRE) sequence for detection of microbleeds and superficial siderosis, because by this time amyloid-related imaging abnormalities (ARIA) had become recognized as an important complication of anti-Aβ immunotherapy[12]; (2) to reflect the changing technical landscape in neuro-MRI, we replaced the dual-echo fast spin echo proton density/T2 sequence (PD/T2) that was used for vascular pathology detection in ADNI 1 with a T2-weighted 2D FLAIR, which was accelerated 2 times using parallel imaging; and (3) both a standard and a 2x accelerated 3D T1 (MPRAGE for Siemens and Philips and IR-FSPGR for General Electric, see Table 1 for abbreviations) were acquired in each exam. This allowed head-to-head comparison of morphometric

measures using standard versus accelerated 3D T1.[13] At the time, it was unknown if accelerated sequences would be equivalent to longer standard 3D T1 sequences for morphometric measures. These three series types—3D T1, FLAIR, and 2D GRE—were "core" series types acquired on all newly enrolled participants in ADNI 2/GO.

At that time, interest was growing in more advanced imaging series types that were not mainstream but could have potential for clinical trials, clinical care, and observational research. Therefore, what was termed "experimental sequences" were added to the ADNI 2/GO protocol in a vendor specific manner. Resting-state, also called task-free, functional MRI (TF-fMRI) or blood oxygenation dependent (BOLD) imaging, was added to the core set of series on Philips systems. Diffusion MR imaging (dMRI) was added to the core set on GE systems. Cerebral blood flow imaging (perfusion-weighted, arterial spin labeling [or ASL]) was added to the core sequences on Siemens systems. Unfortunately, the only ASL product available by any vendor at the time was a 2D pulsed acquisition scheme, which was eventually shown to have poor quality, and this 2D ASL data turned out to have questionable utility. The vendor-specific assignment of experimental sequences was based on the availability of product sequences from the different vendors at the time. These experimental sequences are SNR starved relative to the more standard series types but had become feasible when MRI was moved to 3T, which has twice the SNR compared to 1.5T. Our thinking was that functional measures might be more sensitive than anatomic measures to early disease-related effects. A fourth experimental sequence was added after ADNI 2 had begun–a high-resolution coronal T2 fast-spin-echo aligned with and covering the medial temporal lobes for the purpose of measuring hippocampal and medial temporal subregion volumes ("HighResHippo").

Over time, the geometric warping artifacts the ADNI phantom was designed to address (in addition to image intensity non-uniformity) were addressed by improved vendor products that were applied during the scan. Furthermore, ADNI showed that correcting scaling changes over time could be accomplished more simply with image coregistration rather than independent phantom measures.[14] Consequently, by the end of ADNI 2, a separate phantom scan was no longer acquired with each patient exam.[15]

3.3 | ADNI 3

The ADNI 3 grant cycle extended from 2016 to 2023. The ADNI 3 protocol was performed entirely at 3T and included seven different imaging sequences: 3D T1-weighted; FLAIR; T2*GRE; dMRI; TF-fMRI; ASL; and HighResHippo. However, in contrast to ADNI 2/GO, all series types (to the extent possible) were acquired in every participant with each scanner manufacturer. This was made possible by the expansion of MRI vendor product lines by the time ADNI 3 began. This change greatly increased the sample size for these experimental sequences. Second, the dMRI and TF-fMRI protocols in ADNI 3 were implemented as either standard or advanced forms—that is, two tiers. The advanced dMRI and TF-fMRI acquisitions resembled those performed in the Human Connectome Project (HCP),[16] but these could be performed only on MRI systems that supported multi-band acquisition technology. This was not widely available at that time and still is available only on more modern MRI systems. For dMRI at sites without multi-band capability, a single $b = 1000$ shell suited to basic measures (DTI and basic HARDI tractography) was acquired. At sites with multi-band capability, a three-shell dMRI protocol was acquired, which additionally enabled diffusion kurtosis measures, better tractography, and more sophisticated analyses such as neurite orientation dispersion and density imaging (NODDI) and mean apparent propagator-MRI.[17] Voxel size was kept constant between the two protocol types, and the vector sets overlapped (i.e., the $b = 1000$ s/mm^2 shell of the multi-shell scan matched that of the single-shell scan). For TF-fMRI, the advanced sequence employed multi-band acceleration to achieve acquisition rates near 1.7 frames/sec, whereas the basic TF-fMRI sequence used the 3 s frame rate possible on standard MRI systems. Voxel size was kept constant between the two TF-fMRI acquisition types. The acquisition time for TF-fMRI in ADNI 3 was 10 minutes for both the advanced and basic protocols.

3.4 | ADNI 4

The ADNI 4 grant cycle began in 2023. The ADNI 4 MRI protocol is described in detail in a separate article in this issue (Arani et al., Design and Validation of the ADNI MRI Protocol) and will be reviewed only briefly here. As in ADNI 3, the same set of sequences is performed at 3T in every participant at every time point in ADNI 4. The protocol includes nine sequences.

1. Sagittal 3D T1-w. A compressed-sensing ultra fast sagittal 3D T1w series will be added in addition to the standard 3D T1w at sites that have the appropriate technology.
2. 3D FLAIR. A compressed-sensing ultra fast FLAIR will be added in addition to the standard FLAIR at sites that have the appropriate technology.
3. T2*GRE. We take a two-tiered approach to GRE imaging in ADNI 4. A multi-echo (MEGRE) sequence is performed at sites that can effectively output complex data (real and imaginary channels, or phase and magnitude images) in standard "clinical operating mode," whereas a traditional 2D T2*GRE is acquired at sites that cannot).
4. Sagittal 3D T2 whole brain high-resolution sequence. This is an ultrafast acquisition on systems where this is possible and was newly added in ADNI 4.
5. dMRI. As in ADNI 3,[18] a two-tiered single or multi-shell dMRI approach is taken based on multi-band (slice acceleration) capability. A change from ADNI 3 is that one vendor (General Electric) has added multi-slice acceleration to their newer scanners, in a pulse sequence that includes built-in phase encoding direction flipping for correction of EPI distortion during image reconstruction. For Philips and Siemens scanners, ADNI 4 adds a short dMRI series with polarity flipped read out as an option to correct echo planar imaging

distortion without needing nonlinear registration to an undistorted image (e.g., T1-w).
6. Cerebral blood flow imaging is performed only at sites that can acquire 3D ASL—either 3D pCASL or 3D PASL, but preferably the former. 2D ASL is not being acquired in ADNI 4. In addition, the 3D ASL acquisition will employ four or five post-label delay times, which will enable calculation of arterial transit time and more accurate blood flow maps.
7. High-resolution temporal lobe coronal T2 will continue to be acquired for hippocampal and medial temporal subregion measures.
8. TF-fMRI will be included using the same two-tiered approach as in ADNI 3, but the duration will be shortened to 5 minutes from ADNI 3 to accommodate addition of the sagittal whole-brain 3D T2 sequence.

4 | CENTRAL LAB FUNCTION: PROTOCOL DISTRIBUTION, SITE QUALIFICATION, AND QUALITY CONTROL

These functions are managed by the central lab at Mayo Clinic (the ADIR lab). MRI protocol distribution and site certification entail several sequential steps:

1. An updated/modernized generic AD protocol is created for each ADNI grant cycle.
2. A platform-specific protocol is then created for each vendor/scanner model. These are made publicly available at ADNI | MRI Scanner Protocols (usc.edu). ADNI protocols have been adopted by many brain-imaging studies worldwide.
3. We distribute the current ADNI protocol to each scanner. This entails piloting the protocol on every MRI platform prior to site distribution. An essential part of QC is the distribution of scanner-specific protocols electronically (rather than entering parameters manually at each site). This ensures accurate reproduction of the standardized protocol for each ADNI MRI exam.
4. We certify each scanner at baseline and after hardware upgrades or major operating system upgrades (which are inevitable). Currently, 60 3T scanners are certified for ADNI.

QC is performed at the series level (each exam includes eight or nine different series, depending on vendor and platform) and involves the following:

1. The series type (see Table 1) is assigned to each incoming series by an automated "sorting" algorithm. The program is based on a trained ensemble of machine and deep learning methods that examine the scan parameters in the DICOM metadata. The series description tag is used only as a last resort because it is subject to arbitrary edits by technologists, but it is needed for some classification.
2. A detailed automated check of each series is then done to check for protocol adherence. This automated protocol check program created at the Mayo ADIR lab compares many tens of imaging parameters in each series against the protocol standard (which is specific for vendor/scanner model/software version). Any errors detected by the automated protocol checker are reviewed manually by trained analysts.
3. Trained analysts visually inspect each series in each incoming MRI exam throughout the study for artifacts (e.g., patient motion, excessive susceptibility artifact, patient mispositioning in field of view, artifact from malfunctioning receiver coil, etc.) and evaluate overall image quality. Each series is assigned a pass/fail QC grade. The proportion of series that passed QC by series type is found in Table 2 for ADNI 1–3. ADNI 4 is not included in Table 2 because too few exams have been completed at this point. The visual quality ratings for the exams, listed in Table 2, illustrate that a high proportion of most series pass visual QC; however, ASL has higher fail rates than the other series types.
4. MR QC results are linked with the image data in the central ADNI database. These are used by the MRI analysis groups to exclude analyses of QC-failed images and QC results are made available to the research community for incorporation in their own analysis decisions.

5 | CENTRAL LAB FUNCTION: CLINICALLY RELEVANT FINDINGS

An underappreciated role of the MRI Core that is managed by the ADIR lab at Mayo Clinic is ascertainment of clinically relevant findings on MRI.[19] Each exam is inspected by trained analysts for clinically relevant findings. If identified, these are verified by a Mayo Clinic neuroradiologist on the research team. Clinically relevant findings on MRI exams are part of the inclusion/exclusion criteria for ADNI. Medical findings assessment is also part of due diligence. Medical researchers have a responsibility to participants to identify and notify clinicians at the enrollment site (via the data entry system) if any abnormalities are identified that could be clinically relevant. Although experts at Mayo Clinic review every MRI exam, local reads of all MRI exams are still required to accommodate multisite medicolegal considerations and to ensure that appropriate patient care is provided locally in a timely manner if an emergent finding is seen. MRI medical findings are linked with the image data in the central ADNI database and made publicly available.

Clinically relevant findings include microbleeds and superficial siderosis. The x, y, and z coordinates of each micro bleed and siderosis in participant space are entered into the database along with anatomic location from the automated anatomical labeling atlas, as described in Kantarci et al.[20] The number of participants with various clinically relevant findings over the ADNI 1–3 grant cycles is shown in Table 3. ADNI 4 is not included in Table 3 because too few exams have been completed at this point.

TABLE 2 Numbers of series passing QC by series type for the ADNI 1, ADNI 2/GO, and ADNI 3 cycles.

Sequence type	ADNI 1	ADNI 2/GO	ADNI 3	Total passed QC
3DT1w	6053/6245 (97%)	8415/8551 (98%)	2673/2729 (98%)	17141/17525 (98%)
PD/T2	3140/3269 (96%)	X	X	3140/3269 (96%)
FLAIR	X	4301/4407 (98%)	2377/2470 (96%)	6678/6877 (97%)
T2*GRE	X	4208/4302 (98%)	2415/2450 (99%)	6623/6752 (98%)
dMRI	X	1023/1093 (94%)	2214/2376 (93%)	3237/3469 (93%)
ASL	X	1385/1566 (88%)	1461/1837 (80%)	2846/3403 (84%)
HighResHippo	X	556/815 (68%)	2412/2518 (96%)	2968/3333 (89%)
TF-fMRI	X	805/861 (93%)	2056/2353 (87%)	2861/3214 (89%)

Note: Each cell shows the number of that series type in that ADNI cycle that passed QC/total number received (%). 3D T1s in ADNI 1 were at 1.5T and were at 3T for ADNI 2/GO and ADNI 3. Dual echo proton density/T2 (PD/T2) were acquired only in ADNI 1. FLAIR and GRE were not acquired in ADNI 1. dMRI, ASL, TF-fMRI, and the high-resolution hippocampal imaging series (HighResHipp) were each acquired on only one MR vendor in ADNI 2/GO but on all vendors in ADNI 3.

TABLE 3 Clinically relevant MR findings in ADNI 1–3.

Findings	Number of participants with various clinically relevant findings
Cerebral microbleed (CMB) – one or more CMB	641 (56%)
Infarction	361 (31%)
Superficial siderosis	57 (5%)
Developmental veinous anomaly	46 (4%)
Benign tumor	26 (2%)
Cavernous angioma	11 (1%)
Brain hemosiderin deposition	7 (1%)

Note: A total of 1149 individual findings appear in the table. The values in the table indicate the number of participants with different findings with the % of the total (1149) in parentheses. The number of infarctions is less than one might expect because cortical infarctions were exclusionary for the ADNI –3 cycles to mirror inclusion criteria for typical AD clinical trials. GRE images were not acquired in ADNI 1 and, therefore, CMB, superficial siderosis, developmental veinous anomaly (veinous angioma), cavernous angioma, and hemosiderin deposition numbers reflect only ADNI 2 and ADNI 3 counts.

6 | CENTRAL LAB FUNCTION: DE-FACING

In response to increased awareness that MR facial image identification could compromise participant privacy,[21] the decision was made that relevant series types should undergo face de-identification ("de-facing") prior to being released to the public in ADNI 4. After extensive comparison and validation, ADNI decided to use *mri_reface*, a leading, state-of-the-art approach that "re-faces" images (where a generic synthetic face is used to replace the participant's face and ears rather than only removing it), to reduce effects on subsequent image analyses.[22] The sequences that pose a privacy risk will be de-faced, and only de-faced images will be released publicly for these series types. A detailed description of ADNI's rationale, validation, and implementation of this de-facing can be found in a separate manuscript in this issue [Schwarz et al., Implementation and Validation of Face De-Identification (de-facing) in ADNI-4]. De-facing and QC of the de-facing process are performed by the ADIR lab at Mayo.

7 | CEREBROVASCULAR MEASURES IN ADNI 4

A major shift in emphasis in ADNI 4 is toward a recruitment strategy designed to achieve greater racial/ethnic diversity. We anticipate that ADNI 4 will include a higher prevalence of cerebrovascular disease (CVD), which had been an exclusion in prior grant cycles. To accommodate this change, the ADNI 4 MRI Core includes six CVD-related MRI measures including identification of infarctions, WMH volume, and ASL cerebral blood flow. dMRI is also widely regarded as an important measure of microvascular brain injury within the CVD research community.[23] In addition to traditional measures of fractional anisotropy (FA) and mean diffusivity (MD), more advanced measures will be included in ADNI 4 for exams that include multi-shell dMRI. For example, the Isotropic Volume Fraction (ISOVF) is a free water fraction measure from neurite orientation dispersion and density imaging (or NODDI) that is considered a sensitive indicator of small vessel brain injury.[24]

A new measure in ADNI 4 will be quantification of dilated perivascular spaces (PVS), which is a promising anatomic marker of cerebral vessel injury. This metric has emerged recently as a component of a comprehensive research-grade evaluation for small vessel brain injury.[23] Dilated PVS may also be an indicator of impaired amyloid efflux and thus may provide a mechanistic bridge linking small vessel disease to AD.[25] This new measure in ADNI 4 required the addition of a new imaging sequence to the ADNI protocol—the 3D T2-w.

Cerebral micro bleeds (CMBs) are an indicator of vascular injury that can be either amyloid mediated or mediated by systemic vascular disease. CMBs should be included in a comprehensive contemporary research-grade evaluation of CVD.[23] Like dilated PVS, CMBs and siderosis (ARIA-H) may function as a bridge measure between AD and CVD. Ascertainment of ARIA-H is required for baseline

inclusion/exclusion screening and for longitudinal safety monitoring in anti-amyloid immunotherapy trials.[1,12] With the U.S. Food and Drug Administration (FDA) approval of lecanemab and donanemab,[26] ascertainment of ARIA-H has also become an important issue in clinical care and forms part of appropriate use recommendations.[27] Because standardized assessment criteria across sites is mandatory, the accepted standard acquisition used for CMB detection in clinical trials is 2D T2*-weighted gradient recalled echo (GRE), which can be executed on all MR manufacturer platforms. Although susceptibility-weighted imaging (SWI) is more sensitive to CMBs than traditional T2* GRE, it is not implemented in a uniform manner by different MR vendors and thus is not typically used in clinical trials. To address the possible use of SWI in clinical trials or clinical care, however, ADNI 4 will acquire a multi-echo GRE (MEGRE) sequence on those systems that are capable of effectively exporting phase and magnitude (real and imaginary) images. ADNI will construct both SWI images and traditional T2* GRE (from the ≈20 ms echo) from MEGRE sequences. An objective in ADNI 4 will be to assess relative sensitivity of SWI versus GRE images for CMB.

Another new measure in ADNI 4 is quantitative susceptibility mapping (QSM).[28] QSM has gained attention recently in the MR research community. In the context of neurodegenerative brain disease research, it serves as a voxel-wise measure of tissue mineral deposition (mainly iron). QSM may be useful as an indicator of striatonigral degeneration in neuronal synuclein disease,[29] even prior to onset of cognitive symptoms.[30] QSM images are derived from the MEGRE, as described earlier, and because the MEGRE sequence will be acquired anyway for SWI evaluation, the addition of QSM to ADNI 4 requires no additional imaging time.

8 | QUANTITATIVE ANALYSES

Numeric analyses are performed by highly respected research groups that, in addition to the central ADIR lab at Mayo, constitute the ADNI MRI Core (Table 4). These quantitative measures are returned to the ADNI central database and, along with the MR images themselves and associated QC information, are available to ADNI users. Investigators that produce quantitative outputs for ADNI have written separate manuscripts describing their methods; therefore, these methods will be mentioned only briefly here.

Measures of cortical thickness and volume are performed by the Tosun group using FreeSurfer.[31] This has been the most widely downloaded numeric analysis output from the MRI Core by ADNI users. To ensure optimal processing, the most current version of FreeSurfer available is employed at the commencement of each ADNI cycle. Specifically, we used FreeSurfer version 4.3 for ADNI 1 1.5T MRI data, version 5.1 for the ADNI GO/2 and ADNI 1 3T MRI data, version 6.0 for ADNI 3 3T MRI data, and the latest version 7.4 for ADNI 4. Notably, for the 3T MRI data, we utilized FreeSurfer's optimized framework designed specifically for 3T MRI data processing, ensuring the most accurate and reliable morphometric measurements.

Longitudinal measures for brain, ventricle, and hippocampal volume change between scans with the boundary shift integral (BSI) and template-based regional measures are performed by the Fox group.[32,33] Corresponding cross sectional volumes are generated and provided.[34–36]

WMH volume measures are provided by the DeCarli group,[37,38] and the current method has been tested rigorously for precision and reliability across scanner types.[39] In addition, the presence, number, size, and location of cortical and subcortical infarctions are manually recorded. A detailed description can be found in a separate manuscript in this issue (Maillard, Fletcher, Seiler, and DeCarli, Cerebrovascular Markers of WMH and Infarcts in ADNI: A historical perspective).

Quantitative susceptibility maps are provided by the Mayo group.[40] The STI suite[41] is used to process the 3D-MEGRE data and generate QSM maps.

Dilated PVS measures are provided by the Mayo group using an automated algorithm developed by Jeffrey Gunter, PhD, Mayo Clinic. Parameters from simultaneous probabilistic segmentation of T1w, FLAIR, and T2w images are combined with image-specific 3D spatial priors to detect dilated PVS volume in the centrum semiovale and the basal ganglia.

Diffusion measures are provided by the Thompson group.[17,18,42–47] Detailed descriptions can be found in a separate article in this issue (Feng et al., Microstructural Mapping of Neural Pathways in Alzheimer's Disease using Macrostructure-Informed Normative Tractometry).

The Tosun group provides ASL measures, and a detailed description of ASL in ADNI can be found in a separate article in this issue (Thropp et al., Arterial Spin Labeling Perfusion MRI in ADNI: Past, Present, and Future).

Hippocampal and medial temporal lobe subregion measures are provided by the UPenn PICSL group.[48,49] A detailed description can be found in a separate article in this issue (Yushkevich et al., Morphometry of Medial Temporal Lobe Subregions using High-Resolution T2-Weighted MRI in ADNI3: Why, How, and What's Next?).

TF-fMRI measures are provided by the Mayo group. Connectivity within and between the four default mode network (DMN) subsystems (ventral DMN, posterior DMN, anterior-ventral DMN, and anterior-dorsal DMN) is used to create a single summary metric of network failure termed the Network Failure Quotient (NFQ), which is described in Wiepert et al.[50]

Finally, one class of analytic output measures, tensor based morphometry (TBM) and a related measure TBM-SYN, was discontinued in ADNI 4. This is a precise longitudinal morphometric measure that was included in ADNI 2/GO and ADNI 3. However, it was not highly used by the ADNI user base, which has overwhelmingly preferred the FreeSurfer output for morphometric analyses.

9 | FUTURE DIRECTIONS

Despite ADNI's best efforts toward standardization of MR data acquisition across vendor platforms, heterogeneity will still be present. Users should adjust for these nuisance factors and be aware of

TABLE 4 Analytic MR measures available in ADNI 4.

Modality	Measurement methods and abbreviations	Investigator group responsible
Morphometry	FreeSurfer regional cortical volume and thickness	Tosun
Morphometry and change over time	Boundary shift integral (BSI), brain and ventricle change	Fox
Small vessel cerebral vascular disease assessment	White matter hyperintensity (WMH) volume and infarctions	DeCarli
White matter microstructural integrity, anatomic connectivity	Regional measures from dMRI	Thompson
Focal brain iron deposits	Visual ascertainment of cerebral micro bleeds, superficial siderosis, and parenchymal brain hemosiderin	Mayo
Magnetic susceptibility, largely due to regional variation in brain iron content	Quantitative susceptibility mapping (QSM)	Mayo
Small vessel cerebral vascular disease assessment	Dilated perivascular space (PVS) quantification	Mayo
Cerebral blood flow	Arterial spin labeling (ASL) quantification	Tosun
Functional connectivity	NFQ – network failure quotient	Mayo
Fine medial temporal anatomic measures	Medial temporal subregion volumes	Yushkevich

their influence when interpreting research findings. This often-misunderstood fact is true of any MR data set from a longitudinal multi-site cohort study and is not a feature limited to ADNI. However, one of the aims in ADNI 4 will focus on post-acquisition harmonization methods to further reduce data heterogeneity. An example of this is illustrated in a separate article in this issue by Feng et al., "Microstructural Mapping of Neural Pathways in Alzheimer's Disease using Macrostructure-Informed Normative Tractometry." Harmonization is an active area of research and there is no clear consensus about which methods are "best." The "best" post-acquisition harmonization method could involve: (1) changing input images, (2) changing numeric output, (3) both, or (4) concluding that no data harmonization approach seems to improve over raw image analyses and so none is indicated. The "best" harmonization method may be different for different MR measures. MRI Core members have been active in the harmonization field, developing and comparing image harmonization methods for 3D T1w and dMRI based on (1) deep learning, including generative adversarial networks such as VAE-GANs and StyleGANs[51–53] and (2) ComBat and its variants.[53–55] Each funded MRI Core lab may produce two streams of data: (1) raw output from their pipeline and (2) a harmonized data stream.

A second significant area that will be investigated in ADNI 4 is application of ultrafast MR acquisition methods. Acquisitions that require 7–8 minutes or longer using standard methods can be accomplished in ≈2 minutes without a noticeable drop off in image quality using state-of-the-art ultra-fast methods. These methods are just now appearing as vendor products and will not be widely available for some time. In ADNI 4 we will investigate these ultra-fast techniques for 3D T1w, FLAIR, and GRE imaging. These are the main series types (along with dMRI) needed for safety assessment in patients being treated with anti-Aβ immunotherapy. The numbers of patients requiring baseline and serial safety MRI has the potential to strain the capacity of many radiology departments to accommodate the clinical throughput needed as Aβ immunotherapy increasingly enters clinical practice. Demonstration that ultra-fast versions of these series types are non-inferior to longer standard acquisitions could prove valuable in clinical trials and in clinical practice.

10 | CONCLUSION

ADNI provides standardized carefully curated MR images that represent the most widely used MR image types in modern observational research and clinical trials for AD and related disorders. ADNI MRI methods have been used extensively in clinical trials and have been adopted by many observational studies. Numeric summary data using state of the art analysis methods are provided for a range of outputs that are relevant to the field https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=14&subCategoryId=54. Note, the user must be logged into LONI/ADNI to use this link. This is an under-utilized resource, particularly the advanced imaging sequences and corresponding numeric data (e.g., dMRI, ASL, fMRI), and we encourage investigators to take greater advantage of these data.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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