Received: 2 May 2024 | Accepted: 25 June 2024

DOI: 10.1002/alz.14162

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Design and validation of the ADNI MR protocol

Arvin Arani[1] | Bret Borowski[1] | John Felmlee[1] | Robert I. Reid[1] | David L. Thomas[2] | Jeffrey L. Gunter[1] | Lara Stables[3] | Randy L. Buckner[4] | Youngkyoo Jung[5] | Duygu Tosun[3] | Michael Weiner[3] | Clifford R. Jack Jr.[1] | for the Alzheimer's Disease Neuroimaging Initiative

[1]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[2]Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK

[3]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California, USA

[4]Department of Psychology, Center for Brain Science, Harvard University, Cambridge, Massachusetts, USA

[5]Department of Biomedical Engineering, University of California Davis, Davis, California, USA

Correspondence
Arvin Arani, Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, 55905, USA.
Email: arani.arvin@mayo.edu

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

Funding information
National Institute on Aging; National Institutes of Health, Grant/Award Numbers: R37 AG011378, U19AG024904; Alexander family professorship, and the GHR Foundation

Abstract

Phase four of the Alzheimer's Disease Neuroimaging Initiative (ADNI4) magnetic resonance imaging (MRI) protocols aim to maintain longitudinal consistency across two decades of data acquisition, while adopting new technologies. Here we describe and justify the study's design and targeted biomarkers. The ADNI4 MRI protocol includes nine MRI sequences. Some sequences require the latest hardware and software system upgrades and are continuously rolled out as they become available at each site. The main sequence additions/changes in ADNI4 are: (1) compressed sensing (CS) T1-weighting, (2) pseudo-continuous arterial spin labeling (ASL) on all three vendors (GE, Siemens, Philips), (3) multiple-post-labeling-delay ASL, (4) 1 mm^3 isotropic 3D fluid-attenuated inversion recovery, and (5) CS 3D T2-weighted. ADNI4 aims to help the neuroimaging community extract valuable imaging biomarkers and provide a database to test the impact of advanced imaging strategies on diagnostic accuracy and disease sensitivity among individuals lying on the cognitively normal to impaired spectrum.

KEYWORDS
Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative, amyloid-related imaging abnormalities monitoring, clinical neuroimaging, magnetic resonance imaging protocols, neuroimaging, patient screening

Highlights

- A summary of MRI protocols for phase four of the Alzheimer's Disease Neuroimaging Initiative (ADNI 4).
- The design and justification for the ADNI 4 MRI protocols.
- Compressed sensing and multi-band advances have been applied to improve scan time.
- ADNI4 protocols aim to streamline safety screening and therapy monitoring.
- The ADNI4 database will be a valuable test bed for academic research.

1 | BACKGROUND

Phase four of the Alzheimer's Disease Neuroimaging Initiative (ADNI4) began in 2023. Standardized ADNI protocols have been adopted in several clinical trials and observational studies, which has motivated the adoption of new relevant sequences into the ADNI4 protocol. ADNI4 is still bound to only using product sequences to ensure study continuity and large-scale accessibility to the protocols. The start of ADNI4 corresponded to magnetic resonance imaging (MRI) vendors introducing product sequences with compressed sensing (CS), a cross-vendor adoption of pseudo-continuous arterial spin labeling (pCASL), multi-band slice excitation for some sequences, and some significant hardware improvements (head coils, increased gradient performance, etc.). These advances open up the possibility to acquire new imaging biomarkers and reduce scan times, which has resulted in significant changes from the previous ADNI3 MRI protocol.[1] The ADNI4 MRI protocol aims to maintain longitudinal consistency across two decades of data acquisition, while introducing new technologies that are highly likely to be adopted into future clinical practices. Here we describe the design and justification behind the ADNI4 protocol and list the targeted imaging biomarkers.

RESEARCH IN CONTEXT

1. **Systematic review:** To optimize each imaging sequence for the development of the magnetic resonance imaging (MRI) protocols for phase four of the Alzheimer's Disease Neuroimaging Initiative (ADNI4), the authors used a combination of internal investigation, literature reviews, and expert consensus from site scientists, academic scientists, and clinicians in the field.
2. **Interpretation:** Our investigational findings resulted in the development of several new MRI protocols that will help measure new imaging biomarkers and significantly streamline clinical and safety-screening protocols, as well as potentially fulfilling the required imaging for amyloid-related imaging abnormalities in Food and Drug Administration-approved amyloid monoclonal antibody therapies.
3. **Future directions:** The ADNI4 database will serve the fast-growing artificial intelligence and machine learning research fields by providing quality-controlled neuroimaging biomarkers and clinically identified disease states well suited for algorithm training sets and the development of new post-processing pipelines. The use of these data by the academic community will continue to significantly improve our understanding of Alzheimer's disease and related disorders.

2 | METHODS

At this current cycle, the ADNI4 MRI protocol includes nine MRI sequences: (1) T1-weighted (T1w) magnetization-prepared rapid acquisition gradient echo (MP-RAGE); (2) a CS T1w MP-RAGE; (3) 3D T2-weighted (T2w) fluid-attenuated inversion recovery (FLAIR); (4) structural isotropic 3D T2w; (5) T2*-weighted susceptibility imaging; (6) multi-post-labeling-delay (PLD) 3D arterial spin labeling (ASL); (7) 2D multi-band-multiple-shell diffusion (dMRI); (8) 2D multi-band echo-planar imaging (EPI) blood-oxygen level dependent (BOLD); and (9) high-resolution, limited field of view, coronal fast T2w imaging centered on the hippocampus. A detailed summary of each ADNI4 imaging contrast type is provided in the subsections below. When appropriate, justification and motivation behind each set of sequence parameters are also described.

2.1 | T1w MP-RAGE

T1w 1 mm isotropic images are collected to perform structural analysis in the context of Alzheimer's disease (AD) and related disorders. Three-dimensional MP-RAGE[2] has been a product sequence for Philips and Siemens for a number of years and recently became a product on GE systems. These are the three primary MR vendors in North America participating in ADNI. This adoption has facilitated the standardization of the T1w imaging protocols in ADNI4, with only minor variations specific to each vendor's implementation. For the systems that already had MP-RAGE in place during ADNI3 (Siemens and Philips), and those currently unable to acquire MP-RAGE sequences, their ADNI4 protocols remain consistent with their ADNI3 protocol. However, once MP-RAGE sequences become available at these sites, the T1w MRI protocol will be updated accordingly.

2.2 | CS T1w MP-RAGE

CS sequences,[3,4] which enable high-fidelity ultra-fast imaging with acceleration factors of approximately 5 to 8x, are now being offered as product sequences for structural imaging, by certain vendors (Philips, GE). These accelerated imaging techniques permit the acquisition of structural imaging sequences that were around 6 minutes long, to be acquired in approximately 2 to 4 minutes, while maintaining clinically acceptable image quality. Initial explorations demonstrate that ultra-fast imaging yields morphometric estimates comparable to those obtained in ADNI3.[5]

The importance of fast imaging is growing, particularly in the context of screening patients for baseline eligibility and ascertainment of treatment-related amyloid-related imaging abnormalities (ARIA) in AD-related pharmaceutical trials, including the US Food and Drug Administration (FDA)-approved disease-modifying treatments based on anti-amyloid monoclonal antibodies.[6] It can also help mitigate motion artifacts in patients who struggle to remain still for extended scan durations. In ADNI4, a 6x CS T1w MP-RAGE sequence is available

for distribution from one vendor (Philips). However, another vendor (GE) has used a combination of CS and parallel imaging to achieve a similar image quality with a 4.8x acceleration. Considering the differences in vendor implementation of CS and variations in the deployment timelines for acceleration strategies, the most advanced acceleration methods available as product from each vendor will be evaluated to determine the feasibility of significantly reducing scan times for each structural imaging sequence (T1, T2, FLAIR). The emphasis will be on achieving similar image quality with ultra-fast imaging, rather than standardizing acceleration techniques across vendors. Once these ultra-fast sequences have been thoroughly tested and agreed upon, they will be incorporated into the MRI protocols.

2.3 | 3D T2w FLAIR

White matter disease, infarctions, the identification of ARIA and other brain pathologies are commonly assessed using a FLAIR sequence. In ADNI3, a 3D volume acquisition was adopted over the traditional 2D multi-slice sequence. During the optimization of the 3D protocol parameters, significant efforts were made to standardize the contrast profiles across all three vendors and maximize the contrast between white matter hyperintensities (WMH) and healthy brain tissue. Through internal investigations, we explored the ideal echo time (TE) to maximize WMH contrast and found that the TE used in ADNI3 (effective TE = 119 ms) was similar to that reported by Kakeda et al.[7] (TE = 114 ms) for white matter to gray matter contrast at 3T.

Furthermore, we used the National Institute of Standards and Technology (NIST)/International Society for Magnetic Resonance in Medicine (ISMRM) system phantom to compare contrast profiles from different vendors. The NIST system phantom contains spheres with T1 and T2 relaxation times, providing a range within which brain tissue falls. By scanning the 3D FLAIR sequence on the same phantom for each vendor, we gained insight into how the relative contrast profiles changed with sequence parameters for each system tested. This investigation highlighted the impact that T2 preparation modules (a technique to further improve contrast between tissues of interest) alter contrast profiles. Consequently, we needed to use different vendor-specific settings to better standardize contrast in the study.

Initially, most testing was done on high-end systems with a 1 mm isotropic resolution. However, when protocols were implemented on older systems, it was observed that some images had insufficient signal-to-noise ratio (SNR). To address this, the slice thickness was increased to 1.2 mm. In ADNI4, there was a priority to standardize the voxel size to 1 mm isotropic resolution for the MP-RAGE, 3D T2w FLAIR, and structural 3D T2w image volumes. To account for the anticipated SNR loss, the TE was reduced to 104 ms instead of 119 ms. Internal testing demonstrated good agreement between the WMH maps obtained using the ADNI3 and ADNI4 FLAIR sequences.

2.4 | Structural isotropic 3D T2w

ADNI4 aims to increase the recruitment rate of participants from under-represented populations, which is expected to result in higher cerebrovascular heterogeneity. In anticipation of this change, a 3D 1 mm isotropic T2w imaging acquisition was introduced. The resolution and coverage were set to match the MP-RAGE and 3D T2w FLAIR sequences. This sequence will be used to further improve structural analysis and for the quantification of dilated perivascular space. Moreover, including T1w, T2w, and FLAIR images in a single probabilistic segmentation model opens the possibility of simultaneous (self-consistent) estimation of tissue classes including WMH as well as gray matter, white matter, and cerebrospinal fluid (CSF), which is especially important in populations with higher cerebrovascular heterogeneity.

2.5 | T2*-weighted susceptibility imaging

For ADNI, T2*-weighted imaging has historically been used for detection of microbleeds and other forms of tissue iron deposition. During the development of ADNI3 we tested the feasibility of obtaining multiple echoes within the same acquisition time to enable the generation of susceptibility-weighted images (SWI)[8] and to quantitative susceptibility mapping (QSM).[9] In ADNI4 we have implemented a four- (for some platforms) or five-echo acquisition (TE = 6.71 ms, 10.62 ms, 14.53 ms, 18.44 ms, 22.35 ms) to give better QSM estimates. Currently, QSM and SWI are only available on vendors capable of outputting complex data (real & imaginary channels, or phase & magnitude images) during standard "clinical mode" operations, and not requiring a "research mode." As more and more systems are capable of outputting this information in "clinical mode," multi-echo T2*-weighted sequences will be added to the MRI protocols.

It must also be emphasized that the parameters of this sequence prioritized clinically used voxel sizes and echo times for optimal microbleed detection, which did not allow it to be optimized solely for QSM. There are two main reasons for this: (1) microbleed detection is of paramount importance for patient treatment eligibility and patient safety monitoring in pharmaceutical clinical trials (a primary objective of ADNI) and clinical care, and (2) to maintain longitudinal continuity and consistency with previous generations of ADNI. Recently, and after the roll-out of ADNI4, a consensus paper on the implementation of QSM was published by the ISMRM,[10] which recommended the use of at least 1 mm isotropic resolution for QSM. In contrast, for microbleed detection, higher in-plane resolution is exchanged for larger ≈ 4 mm slice thickness. For these reasons, as a compromise, we maintained the same matrix size as in ADNI3 ($0.5 \times 0.5 \times 1.8\ mm^3$) for the 3D T2* imaging series, which still has finer through-plane resolution than what is typically used clinically.

2.6 | Multi-PLD 3D ASL

ASL is used to measure cerebral blood flow (CBF) and arterial transit time (ATT). Before the start of ADNI4, pCASL began to be released as a product sequence on all three vendors, although some software versions do not support this. In addition, there was active research being conducted to explore the use of multiple PLDs to improve the accuracy of quantitative CBF maps and to allow for the estimation of ATT maps. Variations in blood flow between subjects and tissue types and location result in different arrival times of the bolus of tagged blood traveling from the tagging plane in the carotid arteries to the brain parenchyma. A single post-labeling delay time makes it challenging to ensure that the blood has had enough time to reach the parenchyma for all subjects. Therefore, in ADNI4 a multiple PLD strategy was adopted.

To maintain a reasonable scan time, each PLD has a reduced number of measurement averages, instead of the five used in ADNI3. Due to the lower SNR of each individual PLD, it must be emphasized that all five PLDs are intended to be used in combination with kinetic modeling to derive single CBF and ATT maps from the collection of all PLDs. Furthermore, to ensure that more sites had access to multi-PLD ASL, no product multi-PLD single sequence will be used in ADNI4. Instead, each PLD is acquired as a separate single PLD series. There were four main reasons for this: (1) initially there was a bug in which parameters were not being saved when trying to distribute multi-PLD electronic protocols; (2) in some cases, the multi-PLD sequence required an additional license, which limited its accessibility; (3) for Hadamard/time-encoded multi-PLD schemes, as implemented on some vendors, all PLDs are acquired within the same sequence, and any abrupt motion during an acquisition corrupts all the PLD images; (4) Multi-PLD ASL sequences were not available across all vendors. By acquiring multiple single-series PLDs, more sites can adopt the sequences and better robustness to motion can be achieved.

2.7 | Diffusion MRI

Diffusion MRI images are used to assess local microstructural integrity in the brain. ADNI began acquiring dMRI in ADNI2, but only on GE scanners. The diffusion protocol had a single b = 1000 s/mm^2 shell and 2.7 mm spatial resolution, suitable for diffusion tensor imaging (DTI) and basic tractography. ADNI3 extended its diffusion acquisitions to Philips and Siemens scanners and improved the spatial resolution to 2.0 mm isotropic. The then-recent introduction of multi-band (multi-slice) acceleration in product software allowed for the acquisition of multi-shell (b = 0, 500, 1000, and 2000 s/mm^2) dMRI on capable scanners with the same scan duration (7–10 minutes) as the single-shell protocol without multi-band. This gave rise to an "Advanced" multi-shell acquisition on compatible scanners, and a "Basic" protocol for scanners without multi-band. The b = 1000 s/mm^2 shell and the spatial resolution are identical for both protocols. Therefore, it is possible to extract a basic scan from an advanced one. dMRI parameters such as spatial resolution have been standardized across scanner models; however, due to different scanner hardware limitations, there are slight variations in echo time and, in some cases, the number of acquired diffusion directions needed to be reduced to maintain reasonable scan durations.

Multi-slice acceleration has become more common across ADNI sites as scanners are upgraded or replaced, and as more vendors have made multi-band product sequences. In ADNI4 multi-shell dMRI is now available on all three vendors, although there are still scanners running the basic protocol. The acquisition of multiple shells greatly expands the number of possible dMRI analyses and becomes especially useful for resolving tissue components in voxels with multiple diffusion environments (e.g., tissue + CSF, crossing fibers). A few of the analyses supported by multi-shell dMRI are diffusion kurtosis,[11] high angular resolution diffusion imaging (HARDI) tractography,[12] neurite orientation dispersion and density imaging (NODDI),[13] and mean apparent propagator (MAP)-MRI.[14] The ADNI3 protocol[15,16] will continue to be used in ADNI4, with the addition of a short (≈ 90 seconds) scan in which the phase encoding direction is flipped from the posterior to anterior direction to the anterior to posterior direction, on Philips and Siemens scanners. The short scan will be used to improve EPI distortion correction. The Advanced GE protocol performs the correction as part of the on-scanner reconstruction, so the flipped phase encoding sequence is not needed for these systems. On GE systems without the on-scanner correction option there is also no option to change the phase encoding direction under "clinical operation mode," or to save such changes in electronic protocols. As an alternative approach, EPI distortion can be corrected for in the Basic GE dMRIs by warping the dMRI to an undistorted image such as the T1w or T2w scans (or vice versa).[17] This approach is also recommended for all ADNI3 scans for which acquiring flipped phase encoding was impractical due to either software bugs/limitations.

2.8 | 2D multi-band EPI BOLD

Resting-state or task-free functional MRI (TF-fMRI) associates synchronous signal changes in different regions of the brain to help estimate functional connectivity spatially. Recently, multi-band excitation has become a product sequence for all three vendors. However, depending on the gradient performance and the vendor implementations, variation in acceleration factors exist. This has resulted in both basic and advanced protocols with repetition time (TR) values of 1.5 seconds and 0.6 seconds, respectively, for ADNI4. The ADNI3 basic version that had a 3 second TR and did not use multi-band excitation will continue to be acquired on older systems. Due to the addition of a new 3D isotropic T2w sequence and ultra-fast structural scans in the ADNI4 protocol, the scan time for fMRI needed to be reduced to 5 minutes from the 10 minutes allotted in ADNI3. In some protocols, in which several accelerated structural imaging sequences are added, it will not be possible to do fMRI due to time restrictions. Although we believe that fMRI can give valuable insight into brain function, we needed to prioritize accelerated structural scans in the ADNI4 protocol due to their important role in patient safety screening in pharmaceutical and clinical trials.

TABLE 1 ADNI4 imaging parameters.

Series	Geometry (resolution mm^3, FOV mm^3)	Timing & params (times in ms)	Approx. time (min:sec)	Purpose	Notes
MP-RAGE	1 × 1 × 1 240 × 256 × 208	TR = 2300 TE = min full TI = 900	5:12	T1w structural analysis	2x acceleration
CS-MP-RAGE	1 × 1 × 1 240 × 256 × 208	TR = 2300 TE = min full TI = 900	1:44	T1w structural analysis, testing impact of higher image acceleration on biomarker accuracy	4.8-6x acceleration. CS is called Hypersense (HS) on GE scanners
3D T2w FLAIR	1 × 1 × 1 240 × 256 × 208	TR = 5000 Effective TE = 104 TI = vendor specific (1526 – 1700)	6:20	White matter disease, infarction, other brain pathology	Change from ADNI3: went to isotropic resolution and reduced TE
Structural 3D isotropic T2w	1 × 1 × 1 240 × 256 × 208	TR = 2500/3200 TE = 75/106	4:53/6:42	T2w structural analysis	Vendor sequence names: CUBE, VISTA, SPACE
Multi-PLD 3D ASL	Basic: 1.9 × 1.9 × 4.5 240 × 240 × 144 Advanced: 1.9 × 1.9 × 4 240 × 240 × 160	Basic: PASL, TI2s = 1000, 1500, 2000, 2500, 3000 Advanced: pCASL, PLDs = 1025, 1525, 2025, 2525, 3025.	8:20 7:31	Metabolism, including cerebral blood flow and arterial transit time	Some sequences require a separate M_0 to be calculated, which will add to these scan times
T2* weighted GRE	Basic: 2D single-echo, 0.86 × 0.86 × 4, 256 × 192 × 200 Advanced: 3D multi-echo 0.5 × 0.5 × 1.8mm^3, 200 × 200 × 158.4	Basic: TR = 650, TE = 20 Advanced: TR = 37 TEs = 6.71, 10.62, 14.53, 18.44, 22.35	4:17 5:37/8:44	Microbleed detection, SWI, QSM	QSM and SWI are only available on vendors capable of outputting complex data (real & imaginary channels, or phase & magnitude images)
Diffusion	Basic: 2 × 2 × 2 232 × 232 × 162 Advanced: 2 × 2 × 2 232 × 232 × 162	TR = 3306 TE = 70 TR = 3400 TE = 82	7:06 7:13	Multiple analysis methods	Basic (b = 1000 s/mm^2) Advanced sequences have three shells (b = 500, 1000 and 2000 s/mm^2) and a shorter reversed phase encoding direction for distortion correction
TF-EPI-BOLD	Basic: 3.4 × 3.4 × 3.4 Or 3.0 × 3.0 × 3.0 220 × 220 × 163.2 Or 217 × 217 × 153 Advanced: 2.5 × 2.5 × 2.5 220 × 220 × 160	TR = 1500 TE = 30 FA = 90° TR = 600 TE = 30 FA = 50°	5:00 5:00	Task-free functional MRI (P to A phase encoding)	Due to protocol time limitations, the scan time was reduced from ADNI3
High-resolution hippo	0.34 × 0.34 × 2 175 × 175 × 60	TR = 8020 TE = 48	4:33	Hippocampal subfield measurements	Oblique acquisition, 2D T2w fast/turbo spin echo, aligned with hippocampus

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CS, compressed sensing; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; GRE, gradient recalled echo; MP-RAGE, magnetization-prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging; PASL, pulsed arterial spin labeling; pCASL, pseudo-continuous arterial spin labeling; PLD, post-labeling delay; QSM, quantitative susceptibility mapping; SWI, susceptibility-weighted imaging; T1w, T1-weighted; T2w, T2-weighted; TE, echo time; Task-Free-EPI-BOLD, XXXXXXXX echo-planar imaging blood-oxygen level dependent; TR, repetition time.

TABLE 2 Main changes from ADNI3 to ADNI4.

Series	Changes from ADNI3 to ADNI4
MP-RAGE	Kept the same for continuity.
CS-MP-RAGE	New added sequence. Will test the diagnostic potential of an under 2-minute acquisition using advanced compressed sensing reconstructions on data with 4.8- and 6-fold acceleration.
3D T2w FLAIR	Reduced slice thickness from 1.2 to 1 mm to produce isotropic voxels that match T1w and T2w structural images. Also, reduced echo time from 119 to 104 ms to compensate for SNR loss.
Structural 3D isotropic T2w	New isotropic resolution structural T2w sequence with matched T1w and 3D T2w FLAIR coverage.
Multi-PLD 3D ASL	Went from single PLD in ADNI3 to a new multiple PLD ASL and proton density volumes to enable quantitative cerebral blood flow and arterial transit time mapping across all three vendors.
T2* weighted GRE	Went from three echoes in ADNI3 to five echoes in ADNI4 to improve QSM estimates.
Diffusion	Added multi-band slice excitation acquisition on vendors where it recently became product. Added an additional short anterior–posterior acquisition to improve distortion correction.
TF-EPI-BOLD	Used multi-band slice excitation to improve the basic acquisitions sampling rate from 3 seconds to 1.5 seconds. Due to overall protocol duration, the total acquisition time was reduced from 10 minutes to 5 minutes.
High-resolution hippo	Kept the same for continuity.

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; ASL, arterial spin labeling; CS, compressed sensing; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; MP-RAGE, magnetization-prepared rapid acquisition gradient echo; PLD, post-labeling delay; QSM, quantitative susceptibility mapping; SNR, signal-to-noise ratio; T1w, T1-weighted; T2w, T2-weighted; Task-Free-EPI-BOLD, XXXXXXXX echo-planar imaging blood-oxygen level dependent.

2.9 | High-resolution, limited field-of-view, imaging centered on the hippocampus

A high-resolution oblique-oriented, limited field of view, T2w imaging volume centered on the hippocampus is used to make hippocampal subfield volume measurements. For continuity, this sequence has not been changed in ADNI4.

3 | RESULTS

The key protocol parameters and imaging biomarkers that can be obtained from each series in the ADNI4 protocol have been summarized in Table 1. The full detailed MRI protocols for each software version and vendor type can be found at https://adni.loni.usc.edu/methods/documents/mri-protocols/. All basic structural imaging that was conducted in ADNI3 was kept consistent across imaging sites for ADNI4, except on GE systems for which T1w MP-RAGE became available. Variations in vendor-specific sequences, software upgrades, and hardware performance capabilities, resulted in variations in advanced imaging strategies. Table 2 highlights the advanced sequences introduced in ADNI4 and their variations from ADNI3. Advanced sequences will gradually be implemented into protocols as the required upgrades and licenses are obtained at each site.

The main sequence changes in ADNI4 from ADNI 3 are (1) CS for T1w images, (2) pCASL being implemented on all three vendors (GE, Siemens, Philips); (3) multi-PLD ASL, which allows for the generation of quantitative maps of CBF and ATTs; (4) isotropic $1mm^3$ resolution 3D FLAIR; (5) 3D CS T2w. When ADNI4 began, product sequences that used artificial intelligence (AI) were not widely available and could not be adequately tested before the start date of the study. However, as more acceleration methods become available for each vendor, new ultra-fast structural imaging sequences (T1w, FLAIR, 3D isotropic T2w) will be added to the protocols. If AI-based reconstruction methods improve the SNR of these ultra-fast sequences, they too will be later incorporated into the advanced protocols. In all cases, the original structural imaging sequences will continue to be acquired to enable cross-comparison with the ultra-fast sequences.

4 | DISCUSSION

The ADNI4 MRI database will continue to help the neuroimaging community, not only to extract valuable imaging biomarkers, but to provide the data necessary to test the impact of advanced imaging strategies on diagnostic accuracy and disease sensitivity. An additional goal of testing ultra-fast acceleration strategies is to help with the development of short clinically available MRI screening protocols to enable the widespread use of safety screening methods for pharmaceutical imaging trials and clinical practice, as well as the required imaging for ARIA in FDA-approved amyloid monoclonal antibody therapies. Last, we hope that these data will serve the fast-growing AI and machine learning research fields by providing quality-controlled neuroimaging biomarkers and clinically identified disease states well suited for algorithm training sets and the development of new post-processing pipelines. The use of these data by the academic community will continue to significantly improve our understanding of AD and related disorders.

ACKNOWLEDGMENTS

We would like to thank all the volunteers who give their valuable time to participate in ADNI, as well as the study coordinators, MRI

technologists, the quality control analysts, the lab managers, and all the database and support staff across all the ADNI sites who consistently work to acquire the MRI data. Without their dedication, none of this would be possible. This work was supported by NIH grant U19AG024904 funded by the National Institute on Aging to Dr. Michael Weiner. This funding source had no involvement in the writing of this review. Dr. Jack receives grant funding from the National Institutes of Health (R37 AG011378), the Alexander family professorship, and the GHR Foundation.

CONFLICT OF INTEREST STATEMENT

Dr. Arani, Mr. Borowski, Mr. Felmlee, Dr. Reid, Dr. Thomas, Dr. Gunter, Dr. Stables, Dr. Buckner, Dr. Jung, Dr. Tosun, and Dr. Jack have no conflicts to declare. Dr. Jack, Dr. Arani, Mr. Borowski, Mr. Felmlee, Dr. Reid, and Dr. Gunter are employed by Mayo Clinic. Within the past 36 months, Dr. Jack has served on a DSMB for Roche pro bono; no payments to the individual or institution were involved. He has received funding from the Alzheimer's Association for travel. In addition, he holds index funds. Dr. Thomas is supported by the UCLH NIHR Biomedical Research Centre. Dr. Weiner serves on editorial boards for *Alzheimer's & Dementia*, *MRI*, and *TMRI*. He has served on advisory boards for Acumen Pharmaceutical, ADNI, Alzheon, Inc., Biogen, Brain Health Registry, Cerecin, Dolby Family Ventures, Eli Lilly, Merck Sharp & Dohme Corp., National Institute on Aging(NIA),Nestle/Nestec, PCORI/PPRN, Roche, University of Southern California (USC), and NervGen. He has provided consulting to Baird Equity Capital, BioClinica, Cerecin, Inc., Cytox, Dolby Family Ventures, Duke University, Eisai, FUJIFILM-Toyama Chemical (Japan), Garfield Weston, Genentech, Guide point Global, Indiana University, Japanese Organization for Medical Device Development, Inc. (JOMDD), Medscape, Nestle/Nestec, NIH, Peerview Internal Medicine, Roche, T3D Therapeutics, University of Southern California (USC), and Vida Ventures. He has acted as a speaker/lecturer to The Buck Institute for Research on Aging, China Association for Alzheimer's Disease (CAAD), Japan Society for Dementia Research, and Korean Dementia Society. He holds stock options with Alzheon, Inc., Alzeca, and Anven. The following entities have provided funding for academic travel: University of Southern California (USC), NervGen, ASFNR, and CTAD Congress. Author disclosures are available in the supporting information.

ORCID

Arvin Arani https://orcid.org/0000-0001-6607-8781

REFERENCES

1. Gunter J, Thostenson K, Borowski B, et al. ADNI-3 MRI protocol. *Alzheimer's Dementia*. 2017;13:P104-P105.
2. Mugler JP III, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magnet Reson Med*. 1990;15:152-157.
3. Lustig M, Donoho D, Pauly JM. Sparse MRI: the application of compressed sensing for rapid MR imaging. *Magn Reson Med*. 2007;58:1182-1195.
4. Donoho DL. Compressed sensing. *Ieee T Inform Theory*. 2006;52:1289-1306.
5. Elliott ML, Hanford LC, Hamadeh A, et al. Brain morphometry in older adults with and without dementia using extremely rapid structural scans. *Neuroimage*. 2023;276:120173.
6. Dyck CHv, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9-21.
7. Kakeda S, Korogi Y, Hiai Y, Ohnari N, Sato T, Hirai T. Pitfalls of 3D FLAIR brain imaging: a prospective comparison with 2D FLAIR. *Acad Radiol*. 2012;19:1225-1232.
8. Haacke EM, Xu Y, Cheng Y-CN, Reichenbach JR. Susceptibility weighted imaging (SWI). *Magnet Reson Med*. 2004;52:612-618.
9. Wang Y, Liu T. Quantitative susceptibility mapping (QSM): decoding MRI data for a tissue magnetic biomarker. *Magnet Reson Med*. 2015;73:82-101.
10. Committee QCO, Bilgic B, Costagli M, et al. Recommended implementation of quantitative susceptibility mapping for clinical research in the brain: a consensus of the ISMRM electro-magnetic tissue properties study group. *Magnet Reson Med*. 2024;91:1834-1862.
11. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magnet Reson Med*. 2005;53:1432-1440.
12. Frank LR. Characterization of anisotropy in high angular resolution diffusion-weighted MRI. *Magnet Reson Med*. 2002;47:1083-1099.
13. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage*. 2012;61:1000-1016.
14. Özarslan E, Koay CG, Shepherd TM, et al. Mean apparent propagator (MAP) MRI: a novel diffusion imaging method for mapping tissue microstructure. *Neuroimage*. 2013;78:16-32.
15. Reid RI, Borowski BJ, Thostenson K, et al. [P3–327]: tHE ADNI3 DIFFUSION MRI PROTOCOL: bASIC + ADVANCED. *Alzheimer Dement*. 2017;13:P1075-P1076.
16. Zavaliangos-Petropulu A, Nir TM, Thomopoulos SI, et al. Diffusion MRI indices and their relation to cognitive impairment in brain aging: the updated multi-protocol approach in ADNI3. *Front Neuroinform*. 2019;13:2.
17. Schilling KG, Blaber J, Huo Y, et al. Synthesized b0 for diffusion distortion correction (Synb0-DisCo). *Magn Reson Imaging*. 2019;64:62-70.

SUPPORTING INFORMATION

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

How to cite this article: Arani A, Borowski B, Felmlee J, et al. Design and validation of the ADNI MR protocol. *Alzheimer's Dement*. 2024;20:6615–6621.
https://doi.org/10.1002/alz.14162