Alzheimer's Disease Neuro Imaging III (ADNI3)
MRI Analysis User Document

MRI Analysis Processing Pipeline Suggestions and Tips

Contents

1. CONTACT INFORMATION FOR THE ADNI3 STUDY

If you have any questions or concerns regarding MRI imaging, please contact the Mayo Clinic Aging and Dementia Imaging Research (ADIR) Laboratory:

ADNIMRI@mayo.edu

If you have any questions regarding the scan uploading or downloading, please contact LONI:

dba@loni.usc.edu

2. BACKGROUND AND SIGNIFICANCE OF THE ADNI3 STUDY

Since its launch in 2004, the overarching aim of the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been realized in informing the design of therapeutic trials in Alzheimer's disease (AD). ADNI3 continues the previously funded ADNI1, ADNI-GO, and ADNI2 studies that have combined public/private collaborations between academia and industry to determine the relationships between the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of sporadic late onset AD.

Our strategy is based on the concept that AD can be characterized by the accumulation of Aβ and phosphorylated tau, synaptic loss, and neurodegeneration that leads to a decline in cognition. Clinical/cognitive measures lack both sensitivity and specificity to detect AD pathologic changes. Instead, biomarkers are more reliably used to identify participants at risk for cognitive decline and to measure disease progression. This project will involve collecting MRI (anatomic, diffusion, perfusion, and resting state images); amyloid PET using florbetapir F18 (florbetapir) or florbetaben F18 (florbetaben); ^{18}F-FDG-PET (FDG PET); CSF for Aβ, total tau, phosphorylated tau, and other proteins; AV-1451 PET; and genetic and autopsy data to determine the relationship of these biomarkers to baseline clinical status and cognitive decline.

2.1. MRI Human Scan Protocol

1. 3 Plane Scout
2. Sagittal 3D Accelerated MPRAGE/IRSPGR
3. Sagittal 3D FLAIR
4. Axial T2 Star/GRE or Axial 3TE T2 Star/GRE
5. Axial 3D pCASL, Axial 3D PASL or Axial 2D PASL
6. Axial DTI or Axial MB (multi band) DTI
7. Axial Field Mapping Sequence
8. Axial fcMRI or Axial MB fcMRI
9. Accelerated High Resolution Hippocampus Scan

3. UNDERSTANDING CHANGES IN ACQUISITION PROTOCOL FROM ADNI1 TO ADNI3

3.1. History of ADNI MRI

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal natural history study. Data from ADNI is publicly available (http://adni.loni.usc.edu). The third phase of ADNI (ADNI3) began in late 2016, with subject imaging beginning around mid-2017.

The MRI protocol for ADNI1 (2004-2009) focused on consistent longitudinal structural imaging on 1.5T scanners using T1- and dual echoT2-weighted sequences. One-fourth of ADNI1 subjects were also scanned using essentially the same protocol on 3T scanners.

In ADNI-GO/ADNI2 (2010-2016), imaging was performed at 3T with T1-weighted imaging parameters similar to ADNI1. In place of the dual echo T2-weighted image from ADNI1, 2D FLAIR and T2*-weighted imaging was added at all sites. Both fully sampled and accelerated T1-weighted images were acquired in each imaging session. Advanced imaging was included depending on scanner manufacturer: diffusion imaging on GE scanners, resting state functional MRI on Philips scanners and arterial spin labeling on Siemens scanners. There were several reasons for this manufacturer-specific use of advanced sequences; for example, ASL was not available as product on all vendor systems at that time, product diffusion MR was highly variable, etc.

ADNI3 imaging is being done exclusively on 3T scanners. Nearly all of the imaging sequences from ADNI2 have been updated for inclusion in ADNI3. Each of the ADNI2 "advanced imaging" sequences is now included in the "basic" ADNI3 protocol with a few site-wise exceptions related to sequence license issues.

3.2. Scope of ADNI

ADNI imaging is carried out at 57 imaging centers on subjects enrolled at 59 clinical sites. Two of the imaging centers each serve two enrolling sites. Scanners from the three largest MRI vendors (GE, Philips and Siemens) are supported across nearly all of the current software configurations. ADNI subjects are only a small part of the workflow at each imaging center so ADNI has no control over scanner type or model or system upgrades to the scanner used for ADNI subjects.

3.3. Product Sequence Considerations

ADNI is funded through a public/private partnership in order to establish multi-site imaging methods suitable for inclusion in drug studies. In order to create imaging protocols that can be used to support drug studies, it is necessary to restrict the sequences employed to those commercially available on scanners.

3.4. Advanced vs. Basic

There is a broad gap between older MRI systems and the state-of-the-art systems within each vendor's product line. The range of scanners being qualified for use in ADNI scanning as of late 2016 is given in the Scanner Table.

A two-tiered approach is taken to accommodate the range of variability in scanners. Thus, "ADNI3 Basic" and "ADNI3 Advanced" protocols have been created. An underlying assumption is that all scanners will be

upgraded and some will be replaced over the lifespan of ADNI3 leading to increased use of the ADNI3 Advanced protocols.

Structural T1-weighted, 3D FLAIR, T2* GRE, ASL, and high resolution images of the hippocampus are common across basic and advanced protocols within each vendor.

The Advanced diffusion MRI and Resting State fMRI scans take advantage of simultaneous multi-slice acceleration for echo-planar images (EPI). For longitudinal consistency, they can be down-sampled post-scan to match the Basic sequences.

3.5. Scanner Breakdown

Running the Advanced protocol requires both hardware and software support.

Hardware: a high channel count receiver array and high performance imaging gradients are taken as requisite to run the ADNI3 Advanced protocol.

Commonly, suitable hardware to run the ADNI3 Advanced protocols has become available ahead of software support. This table speculates, based largely on hardware, which protocols may be in use circa 2018-2019.

Scanner Make and Model	No. in ADNI3	Capable of Advanced	Comment
GE 750	8	Y	Contingent on high channel count receive coil with diffusion in software DV26; fMRI possibly in DV27 (no release date)
GE 750W	3	N	Wide bore gradient performance
Siemens Prisma / PrismaFit	18	Y	32 or 64 channel receive array, SW VE11C and up. SMS license required
Siemens Skyra	7	Y	Wide bore gradient performance (Can run advanced but will be slow). 32 or 64 channel receive array, SW VE11C and up. SMS license required
Siemens Verio	5	N	Wide bore gradient performance

Siemens Trio / TIM	5	N	Out of production
Philips Achieva	6	?	Software level 5.3 and up
Philips Ingenia 3T CX	5	Y	Wide bore gradient performance (Can run advanced but will be slow)

3.6. ADNI3 Sequences

Parameters of the ADNI3 sequences given below are approximate. Parameters will vary based on system hardware and software.

Unless otherwise stated, the ADNI3 Basic and Advanced protocols share the same parameters. For example, the MPRAGE is the same in both protocols while diffusion and fMRI differ.

Choice of ASL sequence is driven almost entirely by sequence availability: 3D pCASL being preferred if available and 2D PASL the least desirable.

ADNI3 data and protocol information is maintained at http://adni.loni.usc.edu

Sequence Name	Geometry (FOV @ reconstructed resolution) in mm	Timing Parameters (ms)	Time (m:ss)	Purpose	Notes
Accelerated MPRAGE	208x240x256 mm @ 1x1x1 mm	TE = min full echo TR = 2300 TI = 900	6:20	T1-weighted structure analysis; also may be used as source of spatial information in PET imaging	2X accelerated image acquisition
3D FLAIR	256x256x160 mm @ 1.2x1x1 mm	Effective TE = 119 TR = 4800 TI = 1650	5:30	White matter disease, infarction, pathology. May be used in conjunction with MPRAGE for multi-spectral	Sequence is sensitive to implementation details. TE definition varies by vendor, effective TE is

				tissue segmentation	quoted
High Res Hippo	175x60x175 mm @ 0.39x2x0.39 mm	TE = 50 TR = 8020	4:20	Hippocampal subfield measurement	Oblique acquisition with 2 mm thick slices perpendicular to long axis of hippocampi
T2* GRE	220x220x176 mm @ 0.85x0.85x4 mm	TE = 20 TR = 650	4:10	Cerebral microbleed assessment	GRE as opposed to SWI because GRE is more universally available
ASL	240x240x160 mm @ 1.9x1.9x4 mm	TE = 10.5 TR = 4885 PLDelay = 2000	4:00	Perfusion	3D pCASL implementation on GE (all) and Philips SW version 5.3 (planned); 3D PASL on Siemens; 2D PASL on Philips SW version <5.3
Diffusion	ADNI3 Basic 232x232x160 mm @ 2x2x2 mm	TE = 56 TR = 7200	7:30	DTI	Single b = 1000 s/mm^2 shell b = 0 images interleaved throughout if possible in product sequence
	ADNI3 Advanced 232x232x160 mm @ 2x2x2 mm	TE = 71 TR = 3300	7:10	Tractography + better tissue characterization than can be done with DTI	Three shells: b = 500,1000, 2000 s/mm^2 (112 total diffusion weighted directions)

EPI-BOLD	ADNI3 Basic 220x220x163 mm @ 3.4×3.4×3.4 mm	TE = ~30 TR = 3000 FA = 90°	10:00	RSfMRI analysis	2X accelerated (even/odd interleave) P>>A phase encoding
	ADNI3 Advanced 220x220x160 mm @2.5x2.5x2.5 mm	TE = ~30 TR = 600ms FA = 53°	10:00	RSfMRI analysis	64 slices of SMS = 8 acquired, CAIPI-shift = 4 (Time chosen to be 10 wall clock minutes)

4. LONI

Investigators desiring access to the MRI or other ADNI data can apply online. Applications are generally reviewed within one week. Details about applying may be found on the ADNI website: http://adni.loni.usc.edu/

4.1. LONI User Manual

Instructions on searching for and downloading data may be found in the LONI IDA user manual: **https://ida.loni.usc.edu/services/Menu/PDF/IDA_User_Manual.pdf**

5. ANALYSIS OF THE MRI DATA

The following data types and responsible PIs that are provided by the MR Core are listed below. These numeric data types are provided for each MR exam in ADNI3.

5.1. Structural MRI

Four ADNI MR Labs are funded to analyze 3D T1 scans:

Paul Thompson (USC), tensor based morphometry;
Nick Fox (UCL), boundary shift integral;
Dugyu Tosun (UCSF), Freesurfer;
Matthew Senjem (Mayo Clinic), tensor based morphometry–symmetric normalization (TBM-SyN).

5.2. FLAIR

Charles DeCarli (UCD) - cerebrovascular disease metrics: white matter hyperintensity volume and brain infarctions

5.3. T2 GRE

Mayo Clinic provides data on number and location of all cerebral microbleeds and superficial siderosis

5.4. DTI

Paul Thompson (USC) and Charles DeCarli (UCD) provide analyses of regional fractional anisotropy, diffusivity and more advanced metrics from diffusion-weighted imaging (DWI). After visual inspection and automated brain extraction ("skull-stripping"), all raw DWI are corrected for motion, eddy-current and echo-planar imaging (EPI) induced susceptibility artifacts. A single diffusion tensor (DTI) is fitted to corrected DWI scans with FSL's *dtifit*; scalar fractional anisotropy (FA) and mean, radial and axial diffusivity (MD, RD, AD) maps are obtained from the resulting tensor eigenvalues. These corrected DWI and scalar maps are also made available for download. The FA image from the JHU DTI atlas (Mori et al., 2008) is warped to each subject and the deformation applied to the stereotaxic JHU "Eve" white matter (WM) atlas labels. For each subject, the average FA, MD, RD, and AD are subsequently extracted from 57 WM regions of interest (ROIs) and are made available for download. For a complete list of ROIs and pre-processing steps, please refer to Nir et al. (2013) or the ADNI website. As ADNI3 collects multi-shell and higher angular resolution DWI, we are currently also evaluating beyond-tensor diffusion metrics for monitoring brain aging, such as TDF-FA and related metrics (Nir et al., *Magn. Res. Med*., 2017).

5.5. fMRI

Jeff Gunter and David Jones (Mayo Clinic) provide a summary connectivity metric for all scans

5.6. ASL

Dugyu Tosun (UCSF) provides regional perfusion measures

5.7. Hippocampal T2

Paul Yushkevich and Sandy Das (UPenn) provide volumetric measurements of hippocampal subfields and extra-hippocampal medial temporal cortex subregions. These measurements are generated by applying ASHS software (https://sites.google.com/site/hipposubfields/) to the hippocampal T2-weighted MRI scan. If you are going to use these for analysis, here are the things to keep in mind:

1. Take note of the QA columns, which describe image quality on a scale from 0 (worst) to 4 (best). These represent overall usability of the T2-weigthed images and we don't recommend using volumetric data for any image with a QA rating <= 1. Common factors contributing to low QA score are motion artifacts and slab orientation and positioning errors.
2. For extra-hippocampal cortical regions ERC, PHC, BA35 and BA36, use a normalized volume which can be obtained by dividing the raw volumes by the number of slices in which the ROI appears. This is because the segmentation of these regions along the MRI slice direction is partial. See Yushkevich et al. (PMID: 25181316) for additional details.
3. CA2 and CA3 measurements are noisy due to the small size of these subfields. We recommend using CA1, or a combined CA (1+2+3) in your analysis if you can.

If you are going to be generating the segmentation yourself using the ASHS software, here are the things to keep in mind:

1. Make sure to use an appropriate atlas. For ADNI data, you should use the 3T Penn Memory Center atlas.
2. The manual segmentation protocol fully labels a certain number of coronal slices. However, the variability of the slice orientation across subjects may result in the automatic segmentation having straddler voxels labeled as one of the cortical regions at the anterior/posterior-most slices. You may want to disregard these voxels when estimating volumes. A heuristic we use is to discard all extra-

hippocampal voxels in a slice when the number of such voxels is below 25% of the median across slices.

6. IMAGE DATA PREPROCESSING

Mayo Clinic provided intensity normalized and gradient un-warped #DTI image volumes for all ADNI1 and many ADNI2 exams. As MR vendors offered these corrections online as part of the product, ADNI stopped performing its own preprocessing and instead employed the preprocessing performed by vendor product. Consequently, no offline 3DTI image preprocessing is now needed and none is done in ADNI3.

All ADNI3 T1 images include an on-scanner non-uniformity correction, this may not fully eliminate non-uniformity. Many volumetric analysis pipelines now include bias field correction; however, users not using such a pipeline and performing analysis which may be influenced by non-uniform intensities within the image may wish to apply an additional bias field correction such as N4 (Tustison et al. IEEE TMI 2010, 29(6))

7. QUALITY CONTROL

Each series in each exam undergoes quality control at Mayo Clinic. Two levels of quality control are performed; adherence to the protocol parameters and series-specific quality (i.e., subject motion, anatomic coverage, etc.). Scan quality is graded subjectively by trained analysts: 1-3 is acceptable and 4 is failure (unusable). This QC information will eventually be available for each series on LONI. Thus, users will be able to easily employ exam level QC information as filters in data collections.

8. SCANNER CHANGES

MR scanners routinely undergo upgrades. These can be relatively minor (SW version) or major (hardware changes, e.g. head coil). In some cases, the scanner itself will be replaced at an ADNI site. One of the research objectives of the MR Core in ADNI3 will be to assess the impact of these various types of scanner change on the consistency of different data types over time. Results of these investigations will not be available until adequate longitudinal data becomes available. Until then, we advise the following:

1. Assume that longitudinal within subject data is not compatible before vs after a change in scanner.
2. Assume that longitudinal within subject data is not compatible before vs after a major hardware change – e.g., change in head coil.
3. Assume that longitudinal within subject data maybe compatible before vs after a SW version change, but be advised that this may not be shown to be true eventually for some types of SW changes.

All technical scanner information is available in the DICOM headers; however, this is not easily searchable at present (January 2018). Eventually, the relevant technical scanner information will be easily available and downloadable at the exam level for ADNI users at the time they create either image or numeric data collections. Thus, users will be able to easily employ exam level technical scanner information as filters in data collections.

9. ADNI2 TO ADNI3 PROTOCOL COMPATIBILTY

Our approach to developing the ADNI3 protocol was that the ADNI3 protocol had to be modernized even if this introduced non-compatibility between ADNI2 and ADNI3 data for some series. By series type, we note the following:

3D T1 – spatial resolution was improved slightly in ADNI3 to 1 mm cubed. We believe this should not have a dramatic effect on longitudinal within person analyses.

FLAIR – changed from 2D to 3D in ADNI3. This introduces a significant improvement in spatial resolution plus a change in the contrast model. It is doubtful that this data type will be consistent from ADNI2 to ADNI3 without significant data processing to account for the change in acquisition.

GRET2* – no change from ADNI2 to ADNI for GE or Philips scanners. A 3-echo train GRE sequence is acquired on Siemens scanners with phase and magnitude volumes saved for each echo. This will allow creation of pseudo quantitative susceptibility maps. The magnitude 20 ms volume (3rd echo), from these Siemens GRE acquisitions is compatible with GRE scans acquired in ADNI-GO/2.

Hi resolution coronal for hippocampal subfields – little change, should be compatible from ADNI2 to ADNI3.

ASL – 2D PASL was used in ADNI2 and 3D (PASL or pCASL) are used wherever possible in ADNI3. Thus, this data type is unlikely to be compatible between ADNI2 and ADNI3.

DTI – ADNI3 uses 2.0 mm isotropic voxels, but ADNI2 used 2.7 mm, with b = 0 and 1000 s/mm^2 weighted volumes. ADNI3 Basic and Advanced both provide b = 0 and 1000 s/mm^2 weighted volumes, but the b = 500 and 2000 s/mm^2 volumes of Advanced would have to be excluded before comparison with ADNI2.

fMRI – the Basic version of each of these should be fairly compatible, but the Advanced ADNI3 version will not be compatible with ADNI2 data.