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Standardization of Analysis Sets for Reporting Results from ADNI MRI Data

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Abstract

The ADNI 3D T1-weighted MRI acquisitions provide a rich dataset for developing and testing analysis techniques for extracting structural endpoints. To promote greater rigor in analysis and meaningful comparison of different algorithms, the ADNI MRI Core has created standardized analysis sets of data comprising scans that met minimum quality control requirements. We

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encourage researchers to test and report their techniques against these data. Standard analysis sets of volumetric scans from ADNI-1 have been created, comprising: screening visits, 1 year completers (subjects who all have screening, 6 and 12 month scans), two year annual completers (screening, 1, and 2 year scans), two year completers (screening, 6 months, 1 year, 18 months (MCI only) and 2 years) and complete visits (screening, 6 months, 1 year, 18 months (MCI only), 2, and 3 year (normal and MCI only) scans). As the ADNI-GO/ADNI-2 data becomes available, updated standard analysis sets will be posted regularly.

Introduction

One of the primary goals of the Alzheimer's Disease Neuroimaging Initiative (ADNI) is to develop improved methods for clinical trials by providing a large, publicly available database of biomarkers for further analysis and exploration. The ADNI project(1, 2) provides a rich set of imaging (MRI and PET), cerebral spinal fluid (CSF) and blood biomarkers, and several clinical and neuropsychological measures acquired from healthy controls (normals), mild cognitive impaired (MCI) subjects and Alzheimer's disease (AD) subjects followed over the course of 3 years (available at: www.loni.ucla.edu/ADNI) with up to an additional 6 years of data currently being acquired in the ADNI-GO and ADNI-2 projects (3). The MRI data include MPRAGE T_1- weighted 3D scans (or equivalent) acquired at regular (6 or 12 monthly) intervals and intended for morphometric analysis (4) including volumetric measures of whole brain and regional structures, as well as cortical thickness and atrophy. These quantitative endpoints represent promising imaging biomarkers which are thought to be particularly sensitive to disease progression in the MCI and AD stages (3).

With numerous researchers working with the same dataset, there is the potential for direct comparisons of the various endpoints of brain structures as well as the algorithms and preprocessing steps used to extract these structural measures. To ensure these comparisons are meaningful, it is desirable to define standardized datasets that multiple researchers can use for making methodological comparisons, thereby mitigating the risk that some of the observed differences in algorithm performance are an artifact of the use of different input data. Thus, in order to ensure meaningful side-by-side comparisons of structural MRI endpoints, the ADNI MRI-Core proposes:

1. To define and make publicly available defined "standard analysis sets" of the structural MRI scans comprising only image data that have passed quality control (QC) assessments conducted at the Aging and Dementia Imaging Research Laboratory at the Mayo Clinic (See (4) and http://adni.loni.ucla.edu/research/protocols/mri-protocols/)
2. To encourage any group publishing results using ADNI structural MRI data either to use one of these defined standard analysis sets of data or to justify the exclusion of any scans from their analysis and then to publish the actual data sets used.

In the following we expand on the motivation and the details of the proposal.

Motivation

Seven different research groups were funded to perform analyses of the ADNI-1 MRI data (3). In addition, many other researchers have published analyses with ADNI-1 MRI data (5). A PubMed search conducted on Feb. 15, 2012 using the key terms "ADNI", "MRI", and "Volume" identified 46 matching articles. While a few of these could be discounted as not directly involving the ADNI data, it still shows the impact of this very rich dataset in exploring various hypotheses and developing new analysis techniques. As pharmaceutical

and biotech companies try to apply this knowledge into their AD treatment trials they are faced with deciding which biomarkers and which analysis techniques are best suited to the needs of the trial. For example, there is great interest in determining which of the many reported techniques is most sensitive for measuring changes in brain or hippocampus volume. In addition to determining the most sensitive technique there may be other metrics of interest for comparison such as measurement bias. Unfortunately *every reported study to date on volume techniques based on the ADNI MRI data has used a different subset of data*, confounding direct side-by-side comparisons--a key ADNI aim.

While some of these differences are a result of availability of data at the time of publication, others are likely due to the variations in the robustness of a given technique or the imposition of additional QC standards on the dataset. The ADNI data go through an initial quality control (QC) process and only data that passes the predefined criteria are released for further analysis. The QC process includes a comparison of image acquisition parameters in the DICOM header against the expected protocol, a visual check of the image quality by an experienced image analyst, and a quantitative check of the geometric accuracy of the scanner by analyzing data acquired with the ADNI phantom (4). However, many algorithms may require additional QC steps to ensure successful processing or, alternatively, when the algorithm fails, the data are deemed to be unanalyzable and not reported in the final analysis. This exclusion of subjects may thus obscure the real-world performance of a technique expected in a realistic clinical trial setting. For example, an algorithm that appears to work well but excludes half the data as being unsuitable for analysis would require a larger number of subjects if used as an endpoint in a trial than another technique which may in testing appear to be less effective but is able to run on the full dataset with no exclusions. When reporting an interventional drug study the final disposition of all subjects must be accounted for. A-priori QC standards or reasons for drop-out or unanalyzable endpoints need to be identified and summarized across all subjects not included in the analyses. This need for clear criteria for technical failure during analysis is described in the recent FDA draft guidance on standards for clinical trial imaging endpoints (6). However, this type of rigor is seldom applied in studies aimed at developing new analysis techniques. In order to properly compare and contrast multiple techniques, it is important that each method is run on the same set of subjects and time points and that the largest available dataset be used so that the robustness of the techniques can be understood. We propose the higher level of rigor of drug studies can and should be adopted for all analysis studies using the ADNI MRI data thereby permitting fairer evaluation and direct comparison between techniques.

Proposal

ADNI-1

In order to ensure consistency in the analysis of ADNI-1 MRI data, we have defined five standard analysis datasets (Table 1). Researchers are encouraged to use these datasets and present results obtained using the most appropriate dataset for their study. These five datasets differ based on the time points selected for inclusion. All subjects were included in the standardized analysis dataset if the MRI of at least one of the two replicate T_1-weighted volumetric sequences passed the quality control conducted by the Mayo Clinic (4) for all of the visits defined by the analysis set. The subjects also had to have all their scans performed on the same scanner since an analysis conducted on a subject scanned on different MR equipment is likely to be technically inconsistent. During the 6 years of the ADNI-1 study the scanners at some enrollment sites were replaced by the imaging department. This was the case for 42 ADNI subjects whose data were removed from the multi-visit standardized analysis sets because at least one visit was conducted on a different scanner than that used at their screening visit, typically because of the decommissioning or major upgrade of the original scanner.

In ADNI-1, 818 subjects received screening MRIs, met the study entry criteria and were randomized. Of these 818 subjects, 197 subjects were assigned to receive 1.5T MRI only, 419 to receive 1.5T MRI and FDG-PET and 203 were assigned to receive both 1.5T and 3.0T MRI. By design, the sequence of post baseline scanning time points differed by clinical diagnosis in that only MCI subjects received an M18 scan while only Normal and MCI subjects received the M36 scan. Table 1 summarizes the standardized datasets from the 818 subjects receiving 1.5T scans.

The instrumental variability of 3.0T MRI equipment at some of the sites at the start of the ADNI study in 2005 resulted in additional quality issues with the 3.0T ADNI-1 MRI data. Specifically, some sites had older 3.0T scanners (e.g. Siemens Allegra or GE VH3), which were limited to the use of a single-channel head coil. This resulted in reduced SNR and image contrast compared to their multichannel counterparts, given the constraints of the desired spatial coverage and spatial resolution ($1.0\times1.0\times1.2$ mm^3) and maximal scan time of 9–10 minutes. These issues resulted in data that were generally of poorer quality which can be problematic for further processing and analysis. Because all modern 3.0T scanners now have multichannel capabilities, those older, single-channel 3.0T scanners are no longer representative of equipment readily available today for multicenter trials. Consequently, it was decided by the ADNI MRI-Core that the 3.0T images from sites with single-channel coils would be excluded from the standardized sets. Thus, of the 203 subjects who received a baseline 3.0T MRI only the 151 who received passing quality checks were included in the standardized dataset for the baseline visit. Table 2 summarizes the standardized datasets from these 151 subjects who received 3.0T scans.

It should be noted that the clinical diagnosis (Normal, MCI, AD) was evaluated at screening and even though some subjects changed diagnosis (e.g., progressed from MCI to AD) at subsequent visits they are still maintained in these lists under the original diagnosis. However, the change in diagnosis and when it occurred are available on the ADNI website.

ADNI-1 data are available with different levels of pre-processing to reduce known image nonidealities. Most publications to date have been written using data that have been through gradient non-linearity and intensity inhomogeneity correction (7). These files are labeled GW_N3 in the ADNI database found on the LONI website (see http://adni.loni.ucla.edu/). Additionally, images with phantom-based distortion correction (8) are available and have filenames with the suffix “scaled” or “scaled2”. It is not the intent of creating standard data sets to limit options available to the research community. An investigator could eschew all the corrections and begin with DICOM image data as it was acquired from the scanner. Or an investigator could choose to use data in which phantom-based scaling has not been applied, instead relying on their own methods to correct for scanner calibration drift over time.

ADNI-GO/ADNI-2

The standard analysis data sets described above are considered to be “frozen” at this point for the ADNI-1 project because all normal and MCI subjects have completed their final 3 year visits and all AD subjects have completed their 2 year visits. However, the ADNI-GO and ADNI-2 projects are still ongoing and will be collecting data for several more years. The ADNI-2 exams are acquired exclusively at 3T, and although its protocol differs substantially from that of ADNI- 1 (2, 3), it continues to include an unaccelerated volumetric T1-weighted scan, with additions of an accelerated T1-weighted volumetric scan, a fluid attenuation inversion recovery (FLAIR), and a T2*-weighted gradient echo. Arms of the ADNI-2 study also include arterial spin labeling (ASL) MRI on Siemens scanners, resting state functional MRI (rs-fMRI) on Philips scanners and diffusion tensor imaging (DTI) on GE scanners. In order to balance rigor and consistency with reporting along with

timely dissemination of results, regular updates of the currently-available "standard analysis sets" will be provided on an annual basis. Researchers reporting prior to the final subject visits for a given analysis set should use the latest officially defined set available at a given point and explicitly state the version of the full analysis set used (e.g., the available standard analysis set as of 3Q2012). Details of the latest standard analysis sets of available ADNI-GO/ADNI-2 data can be found on the ADNI standardization website as described in the next section.

Accessing data

For each of the ADNI-1, and ADNI-GO/ADNI-2 standardized analysis sets described above in Tables 1 and 2 a complete listing of the subject IDs, scan dates and unique image series ID's can be found on the website: http://adni.loni.ucla.edu/research/mri-analysis/adni-standardized-data. In addition collections of the images included in the lists have been created for download through the Image Data Archive on LONI. Further directions for accessing these image collections can be found on the above website.

Cross-validation Studies

Some algorithms require cross-validation on the same data that are separate from the data used to develop the algorithm. This is usually done by dividing the data into separate testing and training sets and sometimes a third validation set. The test/training split is highly dependent on the technique and may vary between assigning the majority of the data to the testing set and assigning the majority of the data to the training set. The ADNI Biostatistics Core has provided researchers with guidance on conducting cross-validation studies and a predefined full analysis set split of the 818 subjects in ADNI by 40% for training set and 60% for testing as well as for a 10-fold cross-validation. This can be found at http://www.adniinfo. org/Scientists/CrossValidation.aspx. Assignments were blocked by diagnosis at screening, age (<76, >76), and arm (1.5T only, 1.5T + 3.0T, 1.5T + FDG-PET). Researchers are encouraged to use the proposed cross-validation methods and test set where appropriate and if a different cross-validation split is required to publish the actual subject IDs used in each split.

Publication Standards

Any researcher conducting analysis on the ADNI structural MRI data is strongly encouraged to use one of the standard analysis data sets. It is understood that any algorithm or technique will potentially fail on a subset of data due to poor image quality, secondary quality control or other factors. These analysis exclusions or failures should be explicitly noted as this is extremely important for the assessment of the robustness of a given technique and in order to determine realistic sample size calculations. If for other reasons the study must use a different subset of the data, then the researcher is again strongly encouraged to publish a list of subjects and time points used in the final analysis either as supplemental material on the publishing journal's website or their own publicly available website. This list of subjects should then be referenced in the journal publication. These steps will result in greater rigor in the reporting of structural MRI analyses based on ADNI data and will permit replication of results and side-by-side comparisons with other techniques. This will also help to understand the differences between image analysis techniques.

A standard metric on which different algorithms are compared is the sample size needed to detect a hypothetical treatment effect – for example, a 25% reduction in the rate of atrophy in AD subjects with standard power (e.g. 80%) and type 1 error metrics (9). An algorithm that fails to finish on a large portion of scans may on the surface perform well on this sample size metric. Yet in reality such an algorithm would perform poorly in a clinical trial due to the large number of exclusions required. Therefore, we encourage all investigators who

publish sample size estimates to include failed scans *in the sample size estimates* by amplifying the required sample size similar to how one might do so to account for attrition. This is the only way that different algorithms can be compared head-to-head on an even footing.

To help promote the use of these formally defined analysis datasets, we are asking the ADNI publications committee to encourage adherence in submitted manuscripts as well as asking journal editors and reviewers to insist on the use of either an official standard analysis dataset or the inclusion of a supplemental file detailing the actual analysis set used.

Discussion/Issues

There are a number of occasions when use of a standard analysis set may not be appropriate for study and publishing. For example, a number of exploratory studies or new technique development studies will use a small subset of the data for proof of concept. In these cases analysis of the full dataset may be deferred due to time or cost involved. Likewise it may be desirable to use all available data regardless of missing visits or to create alternative datasets; for example, a dataset with all subjects who had two or more visits may be useful for a biomarker prediction study. In these exceptions, it would still be appropriate to publicly identify the subject IDs actually used in the study.

The concept of standard analysis datasets becomes more complicated when combining biomarkers across modalities or where critical clinical data is lacking for correlative studies. For example, a comparison of MRI volumes with amyloid PET imaging endpoints or CSF biomarkers necessitates selecting the dataset defined by the intersection of the combined biomarkers. To facilitate this we are encouraging the other ADNI Cores to publish standard datasets of their respective biomarkers. Researchers reporting on multiple biomarkers are encouraged to continue to use the principle of using all the available data, explicitly accounting for any excluded subjects or time points, and reporting all subject IDs included in the final analysis.

A good example of a side-by-side comparison of multiple ADNI biomarkers can be found in Beckett et al (9). They compared FDG-PET and MRI biomarkers using nine different analysis approaches from different labs, but ultimately had to limit the analysis comparison to the 69 subjects that had complete analysis across all nine methods. The greatest limitation of the data was due to the inclusion of the FDG-PET modality in the analysis, as only about half the subjects received a FDG-PET scan whereas all subjects received MRI scans. However, we also note that the five MRI techniques used in this study were reported on different numbers of subjects with no clear explanation offered to explain differences in subject selection. While this does not necessarily undermine the conclusions drawn, the additional rigor obtained by using more complete and identical datasets for analysis would greatly strengthen the comparisons and conclusions that can be drawn from them.

Many factors, however, can influence results of analyses such as the number of people needed to detect a 25% reduction in a parameter. The overarching goal of our approach is to reduce study-to-study variability due to which specific scans are included in analyses. This approach does not address other concerns, such as the extent to which a particular outcome may be modifiable by a particular intervention. For example, one can imagine study 1 finds sample size of n(1) people needed to detect a 25% reduction in parameter p(1), while study 2 finds sample size of n(2) needed to detect a 25% reduction in p(2). If an intervention causes much greater change in p(1) than in p(2), then study 1’s technique may be preferred, even if n(2) is less than n(1). In essence, the initiative proposed here will address some of the technical details of comparing methods, but the appropriateness of any particular method as

an outcome for a study will still require scientific reasoning and detailed understanding of biological equivalency. Conversely, methods such as factor analysis (10) can be used to see if differing measures (e.g. FDG, MRI, DTI) have shared or unique explanatory power related to rates of biological change in AD. Further research, therefore, should consider the concept of biological equivalency when comparing various methods.

Another issue to consider is that there is a wealth of structural MRI ADNI studies previously published with variable subsets of the data. It is not the intent of this proposal to request authors to retrospectively reanalyze those studies. While we do encourage these researchers to make available the list of subject IDs used, the aim of this proposal is to encourage adherence for future publications.

It should be noted that the concepts of presenting the analyses with respect to a standard dataset and providing full disclosure of unanalyzable data are not unique to ADNI MRI volumetric analysis. These principles should be applied to the analysis of any of the other ADNI data or any other scientific study. We present the details for achieving these goals with the ADNI structural MRI data and hope that the concepts will propagate beyond this scope.

We realize that there is no way to rigorously enforce to this set of proposals and the success of this concept will depend on its general acceptance by the MRI AD research community. However, the advantages of using standard analysis sets include:

- greater rigor in reporting,
- the ability to compare various techniques side-by-side,
- the ability to evaluate robustness of a given technique, and
- the ability to replicate methods.

These advantages will help promote the goals of ADNI in developing the tools needed to eventually develop effective treatments for AD.

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Table 1

ADNI-1 subjects available for standard analysis datasets at 1.5T

Screening visits		
Normal, N=229	MCI, N=401	AD, N=188
Complete year 1 visits (SC, M06, M12)		
Normal, N=195	MCI, N=311	AD, N=133
Complete annual year 2 visits (SC, M12, M24)		
Normal, N=169	MCI, N=234	AD, N=101
Complete 2 year visits (SC, M06, M12, M18*, M24)		
Normal, N=168	MCI, N=212	AD, N=99
Complete visits (SC, M06, M12, M18*, M24, M36)**		
Normal, N=135	MCI, N=148	AD, N=99

SC = screening, MCI = mild cognitive impairment, AD = Alzheimer's disease, SC = screening, M06 (M12, M18, M24, M36) = month 6 (12, 18, 24, 36),

* M18 imaging was conducted only on MCI subjects,

** M36 imaging was only conducted on Normal and MCI subjects.

Table 2

ADNI-1 subjects available for standard analysis datasets at 3.0T

Baseline visits		
Normal, N=47	MCI, N=71	AD, N=33
Complete year 1 visits (BL, M06, M12)		
Normal, N=39	MCI, N=56	AD, N=24
Complete annual year 2 visits (BL, M12, M24)		
Normal, N=34	MCI, N=37	AD, N=18
Complete 2 year visits (BL, M06, M12, M18*, M24)		
Normal, N=33	MCI, N=35	AD, N=18
Complete visits (BL, M06, M12, M18*, M24, M36)**		
Normal, N=22	MCI, N=20	AD, N=18

BL = baseline, MCI = mild cognitive impairment, AD = Alzheimer's disease, SC = screening, M06 (M12, M18, M24, M36) = month 6 (12, 18, 24, 36),

* M18 imaging was conducted only on MCI subjects,

** M36 imaging was only conducted on Normal and MCI subjects.