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Magnetic resonance imaging in Alzheimer's Disease Neuroimaging Initiative 2

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Abstract

Introduction: Alzheimer's Disease Neuroimaging Initiative (ADNI) is now in its 10th year. The primary objective of the magnetic resonance imaging (MRI) core of ADNI has been to improve methods for clinical trials in Alzheimer's disease (AD) and related disorders.

Methods: We review the contributions of the MRI core from present and past cycles of ADNI (ADNI-1, -Grand Opportunity and -2). We also review plans for the future-ADNI-3.

Results: Contributions of the MRI core include creating standardized acquisition protocols and quality control methods; examining the effect of technical features of image acquisition and analysis on outcome metrics; deriving sample size estimates for future trials based on those outcomes; and

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piloting the potential utility of MR perfusion, diffusion, and functional connectivity measures in multicenter clinical trials.

Discussion: Over the past decade the MRI core of ADNI has fulfilled its mandate of improving methods for clinical trials in AD and will continue to do so in the future.

Keywords: Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative; ADNI; Diffusion; MRI; Neuroimaging; Perfusion; Resting functional MRI

1. Introduction

The overarching objective for the Alzheimer's Disease Neuroimaging Initiative (ADNI) magnetic resonance imaging (MRI) core has been to improve methods for clinical trials in Alzheimer's disease (AD) and related disorders. Our approach has included the following elements: develop standardized MRI protocols; port these to all needed platforms of the three major MR vendors (GE, Siemens and Philips); qualify all scanners at baseline and requalify following upgrades; perform near real time quality control (QC); perform and post publicly, quantitative measurements that are relevant to AD clinical trials on all scans [1].

ADNI-1 focused primarily on structural MRI to study morphological changes associated with AD [1]. Although the ADNI cohort was recruited to study AD, not vascular disease, ADNI-1 included a T2/proton density sequence to ascertain incidental vascular changes. Subjects with hemispheric infarctions at baseline were excluded from ADNI-1, but white matter hyperintensities of any severity were not excluded. ADNI-GO/2 retained this focus on anatomic changes in AD but added a Fluid Attenuation Inversion Recovery (FLAIR) sequence to better depict cerebrovascular disease and also added a T2* gradient echo sequence for the detection of cerebral microbleeds (CMB) [2]. ADNI-GO/2 also added "experimental" sequences for perfusion MRI (arterial spin labeling, ASL), diffusion MRI (diffusion tensor imaging, DTI), and task-free functional MRI (TF-fMRI) also known as resting fMRI [3]. These sequences were selected because they are a major focus of modern imaging science (more so than anatomic MRI). Our thinking was that functional measures, particularly ASL and TF-fMRI, might be more sensitive to early disease-related effects than anatomic measures. A fourth experimental sequence was added after ADNI-GO/2 had begun—a high-resolution coronal T2 fast spin echo for the purpose of measuring hippocampal subfield volumes [4]. These "experimental" sequences were performed in a vendor-specific manner to pilot their potential use in multicenter clinical trials: DTI on GE systems; TF-fMRI on Philips systems; ASL; and coronal T2 on Siemens systems. Reasons for this approach were: (1) We used only vendor product sequences in ADNI-GO/2 (i.e. no works in progress sequences were used, because these require a research license for each site), and some of these sequences were not available as product from all MR vendors at the time ADNI-GO/2 began, and (2) implementation of these sequences was highly variable across vendors. To optimize the uniformity of acquisition we limited each of these sequences to a single vendor [3].

This report is divided into two major sections—the first outlines contributions of the ADNI MRI core to date (i.e. ADNI-1, GO/2) and the second outlines plans for ADNI 3.

2. Accomplishments of the ADNI-MRI core to date

2.1. Technical standards

A major goal of ADNI-MRI was the standardization of imaging methods to facilitate MRI in clinical trials. Ideally, variation in quantitative measures across subjects and over time should be a product of disease effects, not due to nonuniform imaging methods. To achieve the goal of standardized acquisitions across all scanners and across time, protocols were developed that were compatible with a variety of hardware/software configurations within each of the three major MRI vendors' product lines [1]. A total of 59 3T systems and 40 1.5T scanners have been qualified and requalified over time as needed with upgrades. This resulted in a large infrastructure of harmonized MRI scanners at ADNI sites which have been used in various clinical trials in AD and related disorders. Vendor- and version-specific protocols are publically posted which resulted in the wide use of the ADNI-MRI protocols both by the pharmaceutical industry and academic entities.

ADNI methods also include near real-time QC of all examinations. QC results are used within ADNI to identify subjects who may have medical problems, to select subjects with failed examinations for rescans, and to label the quality of scans for analysis purposes. QC was managed by the Mayo group. Once uploaded, every MR study was examined by a fully automated software program created at Mayo to check tens of imaging parameters in each image file against the protocol standard (which was specific for vendor/scanner model/software version). Scans were also viewed and graded manually by a MR technologist to ascertain quality problems such as motion artifact and also potential medical findings. Scans that failed protocol checking or visual quality prompted a rescan. All scans with potential medical findings were reviewed by MDs (CRJ or KK) at Mayo.

The ADNI phantom was designed at the beginning of ADNI-1 to address the need for a high-resolution three-dimensional (3D) geometric phantom for quantitative structural MRI. The ADNI phantom was initially used to correct for changes in scanner geometric scaling over time, scanner