How to do a STRUCTURAL multicenter neuroimaging study

Matt A. Bernstein Ph.D
Departments of Radiology, Physiology, and Biomedical Engineering
Professor of Radiologic Physics
Mayo Clinic, Rochester, MN U.S.A.

GENERAL ISSUES

Multicenter studies are an important tool to validate and establish MRI methodology, particularly for their use as a biomarker. Multicenter studies are also widely used in clinical trials to evaluate pharmaceuticals, MRI-compatible devices, and related technology. The design of a multicenter study that employs MRI and in particular the design of the MR imaging protocol, is driven by the requirements of the study. These requirements follow from the scientific aims of study, and typically reflect engineering and other practical considerations. In particular, several questions to consider are:

1) *Can the study be performed on a homogeneous set of MRI equipment? That is, can the study be performed with all of the participating sites using the same field strength (1.5 or 3T), a single vendor's equipment, running the exact same revision of software, and using the same model of gradient and RF coils?*

If the answer to this question is "yes", then clearly the design and execution of the study are simplified greatly. If, however, site selection for the study is driven by patient recruitment (rather than by the technology available at the sites) the answer invariably will be "no". If the answer is no and there is heterogeneous equipment supported in the study, then a related question arises: Should the MR imaging protocol be standardized to "one-size-fits-all" (also called "the least common denominator" approach), or should the protocol be tailored to take advantage of capabilities present at the individual sites? For example, because phased array head coils have increased SNR and compatibility with parallel imaging methods, it is usually possible to reduce scan time at sites with newer RF hardware, compared to older MRI systems that only have access to a single-channel head coil. Whether or not to standardize the protocol, i.e., use the longer scan time at all sites, is a judgment call for the study designers.

2) *Are there experienced personnel at each site such as MR physicists who can provide local support for the study?*

The presence of those personnel at the sites greatly facilitates the setup and execution of a multicenter study, but they are less likely to be available at a community hospital than at an academic medical center.

3) *Will the use of works-in-progress (WIPS) pulse sequences (also known as "prototype" or "research" pulse sequences) be permitted in the study?*

If not, the study is restricted to the use of commercially available pulse sequences. This means that all the pulse sequences have received FDA 510(k) clearance or the international equivalent. If the goal of the multicenter study is to evaluate the WIPS pulse sequence itself, then clearly the answer must be "yes". In some cases, the answer is also "yes" because tailored pulse sequences are needed in order to reduce vendor-to-vendor differences (or software revision-to-revision differences within a single vendor) down to an acceptable level.

Use of a non-FDA 510(k) cleared pulse sequence complicates a multicenter study. Not only does the WIPS pulse sequence have to be created and validated, but also other issues can arise including, but not limited to: a) Requirement that the binary executable files be properly distributed at the start of the study and again whenever any site upgrades its scanner's software revision. b) Need for each of the sites to enter into a research agreement with their own MR vendor. c) If a goal of the multicenter study is to acquire MR image data in preparation for a future FDA submission of a pharmaceutical, then the use of a non-FDA cleared imaging technique could somewhat complicate that later submission. d) Potential patent licensing issues with certain techniques running on certain vendor's platforms.

4) *Will the MR imaging protocol be distributed in electronic form or paper form? (Note that the electronic imaging protocol is a collection of imaging parameters, which is distinct from the pulse sequence discussed in question 3)?*

The use of electronic format for the MR imaging protocol avoids many transcription errors and greatly increases the reliability of installing the accurate MR imaging protocol on the scanners at the sites. The advent of new software features (e.g., "Phoenix" and others) offered by some vendors allows the electronic protocol to be distributed via the DICOM image header, making the task easier. On older model scanners, however, the task is usually more challenging.

5) *How will the images obtained from the participating study sites be checked at a central location?*

Even when the imaging protocol is electronically distributed, many other types of errors can occur and the images obtained from the sites need to be reviewed. This review ideally includes a visual check by a skilled observer located at a central site. It is also useful to perform an automated check of the DICOM image header to verify that key imaging parameters are consistent (to within a predetermined tolerance) with those distributed in the electronic protocols.

6) *Will a phantom be used for quality control?*

Use of a phantom provides an objective measure of system performance. Phantom data are particularly useful for crossover tests spanning system software and hardware upgrades. Readily available phantoms such as the American College of Radiology (ACR) MRI phantom can be used, which provides data on low-contrast dectectability, spatial resolution, uniformity and other metrics. For more specialized tests such as 3D spatial linearity and gradient fidelity [1,2], a dedicated phantom [2] such as the ADNI phantom [3,4] can be useful.

7) *Does the study require a preparatory (prep) phase*? A prep phase is a mini-clinical trial that serves as a dry run before the actual study begins patient recruitment. It allows the study designers to test the MRI protocols and to work out the issues and tradeoffs discussed in this (and the next) section. During a prep phase, a few study sites, generally with a high level of local support, install and test tentative MR imaging protocols. Necessary changes to the protocol are allowed during a prep phase before the protocol parameters are frozen. A prep phase is essential for a complex multicenter study and needs to be scheduled and budgeted. For a very simple study, however, prep phase might not be required. The transition threshold is a subjective call of the study designers.

TECHNICAL ISSUES FOR A STRUCTURAL NEURO IMAGING STUDY

The general questions raised above apply to virtually any multicenter study employing MRI methods. For a structural neurological imaging study, some specific technical considerations and tradeoffs are particularly relevant. Most structural studies of the brain include a T1-weighted 3D volumetric gradient echo acquisition, either without inversion preparation (SPGR, spoiled FLASH, T1-FFE, etc.) or with inversion preparation, such as MP-RAGE, IR-FSPGR, etc. This section discusses some more specific considerations about the MR imaging protocol, focusing on the context of the T1-weighted volumetric series.

Field strength: Will the study be restricted to 1.5T or 3T or use a mixture of both? 3T is now more widely available, and today it is feasible to perform most multicenter studies at 3T. As a rule of thumb, holding SNR and chemical shift (in mm) constant, 3T allows an approximately $\sqrt{2}$ -times smaller voxel volume, which is an advantage for some structural studies. There is also a consensus that many of the emerging MRI methods such as parallel imaging with high channel count coils and acceleration factors, diffusion tensor imaging, resting state fMRI, and arterial spin labeling work better at 3T than at 1.5T. On the other hand, the 4-fold increase in SAR, the increased susceptibility artifacts, and the sometimes unfamiliar contrast properties at 3T due to the elevated T1 of some tissues are all potential drawbacks. Also, there are safety concerns at 3T for some patient populations, such as those with implanted aneurysm clips. 3T head imaging produces a more pronounced central brightening artifact due to nonuniformity of the B1 transmit field, but this artifact can be suppressed with post-processing methods such as N3 [5,6]. Overall, there is no single answer to the question of the optimal field strength mix for a multicenter study; these tradeoffs need to be considered on an individual basis for each study.

RF coil: For head exams there are two main choices: phased-array coils and single-channel coils. The latter are often, but not always, transmit/receive. When available, phased-array head coils are usually preferred because of their improved SNR and compatibility with parallel imaging methods. Most MRI vendors now offer a B1-uniformity correction (e.g., CLEAR, PURE, prescan normalize, etc.) [7] to reduce or eliminate the effect of high-intensity “hotspots” that appear on the image near the coil elements.

Spatial resolution: For effective brain segmentation using a 3D, T1-weighted gradient echo scan, typically the acquired (as opposed to interpolated with zero-filling or a related method) voxel dimension should be no larger than 1.5 mm in any of the three directions. The lower limit of the voxel dimension is determined by SNR and scan duration considerations. Even if allowed by SNR or other considerations, the advantage of sub-millimeter spatial resolution can be lost when there is even minor patient motion. Consequently, spatial resolution in the 1.0-1.5 mm range is typical. Isotropic spatial resolution is usually desirable, but might not be required.

Imaging plane: For brain and head studies, the use of each of the three orthogonal planes has its own advantages. In multicenter studies, use of the oblique plane is generally avoided because the subject-to-subject variability in angulation in turn introduces subject-to-subject variation in gradient performance, which can affect parameters such as minimum TE and echo spacing. Consequently, proper training of the technologists at the study sites to standardize patient positioning is necessary.

For 2D acquisitions, we typically follow conventional clinical practice for the choice of imaging plane, e.g., T2-weighted head images are acquired in the axial plane, and FLAIRs to visualize the hippocampus are acquired coronally.

For 3D acquisitions the axial plane often offers the fastest acquisition for whole-brain (as opposed to whole-head), but requires the use of slab-selective RF pulse to avoid aliasing or wraparound artifact. Also, especially on high SNR images, even minor imperfections in the RF slab profile can cause aliasing artifacts and slice-to-slice intensity variation. The sagittal and coronal planes are acquired with the frequency-encoded direction head-foot (S/I) to minimize aliasing or wraparound and do not require good slab-selective RF when the entire head is covered. For a fixed slice thickness, the sagittal plane requires fewer slices than the coronal plane to cover the brain. Depending on the nesting order of the loops of the two phase-encoded directions in the pulse sequence, image artifacts from the eye motion can be more likely to overlap the brain region on sagittals than coronals, or vice versa. If the in-plane phase encode (i.e., the *y*- or primary-phase encode) is the outermost loop (i.e., more slowly varying), then use of the coronal plane sometimes offers an advantage.

Chemical shift direction: For sagittal and coronal acquisitions of the brain, the fat-shift direction should be caudal (i.e., inferior). This chemical shift direction for the shift makes it easier to segment the resulting images, because overlap between the brain and lipid signal is minimized.

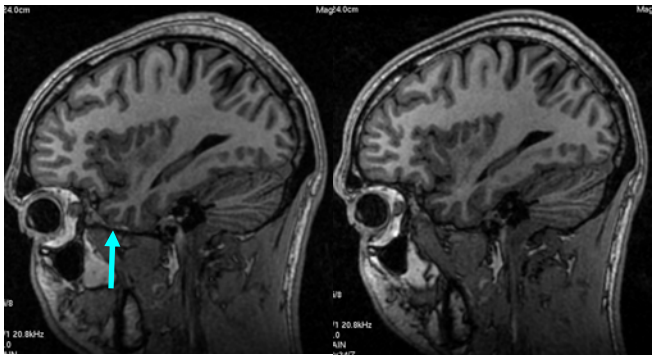

Figure 1. For sagittal and coronal brain imaging, chemical shift of lipid signal in the caudal direction (right) facilitates brain segmentation by reducing signal overlap (arrow).

Coverage: Usually, it is a requirement of the study to cover the whole brain. It is also important to make the MR technologist's job as easy as possible for multicenter studies. For example, the graphic prescription box should be easy to prescribe from the scout (i.e., localizer) images. A 3D sagittal head prescription with *at least* 170 1.2-mm thick slices meets this requirement, as the resulting 204 mm covers the right-left extent of most people's heads.

Imaging time: It is important to minimize imaging time on any one series in order to reduce patient motion artifacts. Provided the other requirements of coverage, spatial resolution, artifact reduction, and SNR are met, the shorter the imaging time, the better. There is no absolute cutoff, but in general, a scan duration of approximately 10 minutes per series is considered an upper limit. Use of 3T imaging in conjunction with a head coil with at least 8-12 channels enables the use of parallel imaging techniques such as GRAPPA. Typically, parallel imaging can cut the acquisition time for a high-resolution, whole-head MP-RAGE scan from 9 minutes to 4-5 minutes with minimal loss of image quality.

It is also important to minimize the length of the entire subject exam, especially for longitudinal studies where subject retention is critical to success. Exams with total duration of 30 minutes or less generally place minimal burden on the subject and are well tolerated.

Contrast: Like all the other tradeoffs discussed here, the decision about contrast is driven by the specific requirements of each multicenter study. For example, in a brain imaging study, what will

the 3D T1-weighted images be used for? If the sole goal is to measure whole-brain volume, then the contrast between gray matter and CSF should be maximized. In this case, maximizing gray matter SNR is useful to get a distinct CSF-gray matter boundary. If, on the other hand the goal is measure cortical thickness, then CSF signal should still be minimized, but gray matter intensity should be approximately midway between the white matter and CSF intensity to facilitate segmentation.

Post-processing: Post-processing steps might include the two types of B1 uniformity corrections mentioned earlier and 3D gradient distortion correction (i.e., gradwarp). Applying the gradient distortion correction is useful for longitudinal volumetric studies, because it relaxes the need for landmark and gradient isocenter to correspond to exactly the same anatomy for each scanning session.

THE ADNI STUDY, AND LESSONS LEARNED.

Many of the tradeoffs discussed in the previous two sections were considered in the development the MR imaging protocol for the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The ADNI [8, 9] is a six-year, publicly and privately funded partnership to assess how well the combined information obtained from MRI, PET, other biological markers, and clinical and neuropsychological assessment can measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). This observational study acquires serial data at approximately 60 sites in North America from patients with MCI (n = 400), mild AD (n = 200), and controls (n = 200). All patients are scanned with 1.5T MRI, and a subset (25%) with 3T MRI. Half of the subjects also receive FDG PET, and 120 subjects receive PIB PET. A total of approximately 5500 MRI exams are planned over the Execution Phase of the study, which is scheduled to be completed in 2010. All of the image data are readily available via the Internet to any researcher.

Details about the ADNI MR imaging protocol and its development process are documented in [9]. A total of 89 scanners with 38 discrete combinations of vendor/field strength/software revision/hardware configuration are supported. Detailed lists of parameters for those configurations are posted and are publicly available at http://www.loni.ucla.edu/ADNI/Research/Cores/ . Here, with benefit of hindsight, a few lessons learned are listed:

1. A multicenter study is a guest, i.e., a low-priority user, at the MRI sites. For example, system hardware and software upgrades proceed based on the clinical considerations of the site and not based on the convenience of the multicenter study.

2. Communication between each site and the study is essential. In addition to a receiving a detailed procedure manual, representatives from each site participated in a telephone call with Bret Borowski RT (ADNI's MRI site liaison) to work out any local issues with the study prior to site qualification.

3. A prep phase as described earlier, is essential for a study of the scale of ADNI.

4. It is necessary to work closely with representatives of the MR vendors. The vendors benefit the study by providing advanced warning of system upgrades, giving suggestions about how to standardize the MR imaging protocol across vendors and software releases, and in many other ways. The study can benefit the vendors by providing valuable quality control information about

their own systems. In ADNI, several faulty RF coil components (from two different vendors) were first discovered during routine QC of the study images. Naturally, intervendor confidentiality is respected.

5. As described in the preceding sections, expect many tradeoffs while developing the MR imaging protocol. There is no absolute correct protocol design, but rather a range of protocols that meet the requirements. Transparency such as the public posting of the image parameters as was done in ADNI, is very useful, especially given the long delay time for publication at scientific journals. ADNI also enlisted the advice from three external advisers, Professors Gary Glover, John Gore, and John Mugler, to review the protocols and the prep phase data. Their experienced advice greatly improved the quality of the study.

ACKNOWLEDGEMENT:
This work is supported by the Alzheimer's Disease Neuroimaging Initiative (ADNI), Michael Weiner, MD, PI, NIH grant number U01 AG024904. I also thank all my colleagues at the Mayo ADIR Lab, particularly Jeff Gunter PhD, Bret Borowski RT, and Denise Reyes and its leader, Cliff Jack MD.

1. Baldwin L, Wachowicz K, Thomas S, Rivest R, Fallone G, 2007. Characterization, prediction, and correction of geometric distortion in 3T MR images, Medical Physics, vol. 34, pp. 388-399.

2. Wang D, Strugnell W, Cowin G, Doddrell D, Slaughter R, 2004. Geometric distortion in clinical MRI systems Part I: evaluation using a 3D phantom, Magnetic resonance imaging, vol. 22, pp.1211-1221.

3. Gunter JL, Bernstein MA, Borowski BJ, Felmlee JP, Blezek DJ, Mallozzi RP, Levy JR, Schuff N, Jack Jr CR. Validation Testing of the MRI Calibration Phantom for the Alzheimer's Disease Neuroimaging Initiative Study. International Society for Magnetic Resonance in Medicine, Seattle, WA, May 2006.

4. Gunter J, Bernstein MA, Borowski BJ, Britson PJ, Ward CP, Jack CR. Phantom correction of human images for spatial scaling errors. International Society for Magnetic Resonance in Medicine, Toronto, Canada, May 2008.

5. Sled JG, Zijdenbos AP, Evans, AC, 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17, 87-97.

6. Boyes R, Gunter J, Frost C, Janke A, Yeatman T, Hill DLG, Bernstein MA, Thompson PM, Weiner MW, Schuff N, Alexander GE , Killiany RJ, DeCarli C, Albert M, Fox N, Jack CR. Intensity non-uniformity correction using N3 on 3-T scanners with multichannel phased array coils. Neuroimage 2008 15;39(4):1752-1762.

7. Narayana PA, Brey WW, Kulkarni MV, Sievenpiper CL, 1988. Compensation for Surface Coil Sensitivity Variation in Magnetic-Resonance Imaging. Magnetic Resonance Imaging 6, 271-274.

8. Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, Trojanowski JQ, Toga AW, Beckett L. Ways towards an early diagnosis in Alzheimer's disease: The Alzheimer's disease neuroimaging initiative. Alzheimers Dement. 2005 ;1(1):55-66.

9. Jack CR, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, Whitwell J, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DLG, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzer GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Alber M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI Methods. J Magn Reson Imaging 2008 ;27(4):685-91.