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, Minnesota, U.S.A.

When designing a multicenter trial that includes MR structural imaging, questions about the choice of field strength and RF coil often arise. There are also tradeoffs to consider about spatial resolution, imaging time, acquisition plane, and several other factors. 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. In this abstract, these issues are discussed, focusing on the context of the T1-weighted volumetric series.

Use of a phantom 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 detectability, spatial resolution, uniformity and other metrics. For more specialized tests such as 3D spatial linearity and gradient fidelity [1, 2], a dedicated phantom such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) phantom [3, 4] can be useful.

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 and other artifacts [5, 6], and the sometimes less familiar 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 non-uniformity of the B1 transmit field, but for low-flip angle gradient echo acquisitions, this artifact generally can be corrected well with post-processing methods such as N3 [7,8], provided any applied RF inversion pulses are adiabatic. 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.) [9] to reduce or eliminate the effect of high-intensity "hotspots" that appear on the image near the coil elements. So typically phased-array coils are chosen. The advent of commercially available 32-channel coils raises another question: If only a fraction of the sites have access to a 32-channel head coil available, should those sites be allowed to use them in the study, or should the study revert to the "least common denominator"? Again, there is no single

Proc. Intl. Soc. Mag. Reson. Med. 18 (2010)

answer to this question; instead, this tradeoff between performance and standardization needs to be considered on a study-by-study basis.

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 desirable but is usually not 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. In some cases, it might be acceptable to use auto-alignment software, which can reduce scan-rescan positioning errors. For 3D acquisitions, those positioning errors are not too problematic, even for serial studies, because the image sets are typically registered. Also, it should be verified beforehand, however, that variation introduced into parameters such as minimum TE and echo spacing by the auto-alignment is within acceptable limits.

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 for suppression of eye-motion artifacts in the brain.

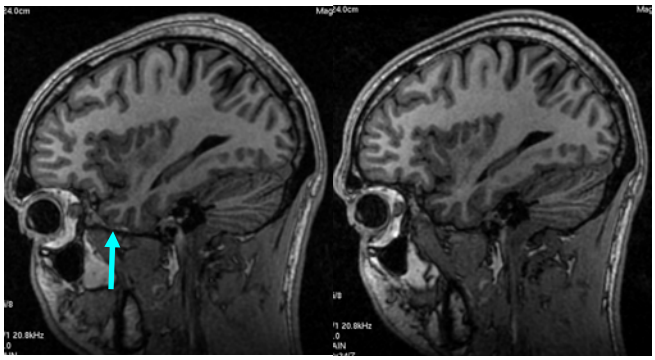

Figure 1. For sagittal and coronal brain imaging, chemical shift of lipid signal in the caudal direction (right) facilitates brain segmentation by reducing signal overlap (arrow).

Chemical shift direction: As shown on Fig. 1, 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.

Coverage: Usually, it is a requirement for the 3D acquisition 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 8-12 or more 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 (i.e., serial) 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.

Tissue 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 to 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. The MP-RAGE parameters used in the ADNI study [10, 11] provide a fairly good compromise for a general purpose structural MRI protocol.

Post-processing: Post-processing steps might include the two types of B1 uniformity corrections mentioned earlier [7, 9] and 3D gradient distortion correction. 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 here were considered in the development the MR imaging protocol for the ADNI study. ADNI [10, 12] 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 [10]. 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 [11]. 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 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. For a large-scale study such as ADNI, it is useful to run a "prep phase", i.e., a dry-run or mini study at a few sites prior to the start of the main study. The prep phase allows the protocol to be tested on the main scanner platforms to work out any bugs and, if necessary, to provide data for any final decisions about protocol tradeoffs.

4. It is very valuable to work closely with representatives of the MR vendors. The vendors benefit the study by providing advanced notice 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, in turn, 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, inter-vendor confidentiality is respected.

5. As described, 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 scientific aims of the study. Transparency, such as the public posting of the image parameters as was done in ADNI is 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 2007; 34: 388-399.

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

3. Gunter JL, Bernstein MA, Borowski BJ, Ward CP, Britson PJ, Felmlee JP, Schuff N, Weiner M, Jack CR. Measurement of MRI scanner performance with the ADNI phantom. Medical Physics 2009; 36(6): 2193-205.

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. Bernstein MA, Huston J 3rd, Ward HA. Imaging artifacts at 3.0T. J Magn Reson Imaging 2006; 24(4):735-46.

6. Dietrich O, Reiser MF, Schoenberg SO. Artifacts in 3-T MRI: physical background and reduction strategies. Eur J Radiol. 2008; 65(1):29-35.

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

8. 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; 39:1752-1762.

9. Narayana PA, Brey, WW, Kulkarni MV, Sievenpiper CL, Compensation for surface coil sensitivity variation in magnetic-resonance imaging. Magnetic Resonance Imaging 1998; 6: 271-274.

10. 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.

11. http://www.loni.ucla.edu/ADNI/Research/Cores/ , accessed November 24, 2009.

12. 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 Dementia 2005; 1(1): 55-66.