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Title: Reduced Cross-scanner Variability Using Vendor-agnostic Sequences for Single-shell Diffusion MRI

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Abstract (206/250 words)

Purpose: To reduce the inter-scanner variability of diffusion MRI (dMRI) measures between scanners from different vendors by developing a vendor-neutral dMRI pulse sequence using the open-source vendor-agnostic *Pulseq* platform.

Methods: We implemented a standard echo-planar imaging (EPI) based dMRI sequence in *Pulseq*. We tested it on two clinical scanners from different vendors (Siemens Prisma and GE Premier), systematically evaluating and comparing the within- and inter-scanner variability across the vendors, using both the vendor-provided and *Pulseq* dMRI sequences. Assessments covered both a diffusion phantom and three human subjects, using standard error (SE) and Lin's Concordance correlation to measure the repeatability and reproducibility of standard diffusion-tensor imaging (DTI) metrics including fractional anisotropy (FA) and mean diffusivity (MD).

Results: Identical dMRI sequences were executed on both scanners using *Pulseq*. On the phantom, the *Pulseq* sequence showed more than a 2.5× reduction in standard error (variability) across Siemens and GE scanners. Furthermore, *Pulseq* sequences exhibited markedly reduced standard error in-vivo, maintaining scan-rescan repeatability while delivering lower variability in FA and MD (more than 50% reduction in cortical/subcortical regions) compared to vendor-provided sequences.

Conclusion: The *Pulseq* diffusion sequence reduces the cross-scanner variability for both phantom and in-vivo data, which will benefit multi-center neuroimaging studies and improve the reproducibility of neuroimaging studies.

Keywords: dMRI, open-source, reproducibility, vendor-agnostic, Pulseq, open MRI, MRI harmonization

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Introduction

Diffusion magnetic resonance imaging[1] (dMRI) is a non-invasive method that explores the intricate microstructure of biological tissues by observing the random motion of water molecules. Utilizing varying diffusion gradients, diffusion tensor imaging[2] (DTI) can characterize diffusion anisotropy of tissue microstructure. Diffusion-derived quantitative metrics, such as mean diffusivity (MD) and fractional anisotropy (FA) from DTI, have gained prevalence in clinical studies targeting brain diseases like multiple sclerosis[3], epilepsy[4], neurodegenerative disorders[4], and aging[5]. These investigations aim to delineate statistical differences between patients and healthy individuals based on underlying biological factors. Often, these studies encompass multi-center/site approaches to incorporate larger sample sizes, enhancing statistical power for robust analyses.[6–8]

However, when evaluating diffusion measures, a notable challenge emerges due to the inherent variability within and between scanners across multiple sites, primarily attributed to non-biological factors.[9–13] These factors include differences in the hardware provided by different manufacturers, encompassing gradients, radiofrequency (RF) coils, magnetic field (B0) inhomogeneity as well as different shimming conditions. Differences in software versions, heterogeneity in the acquisition parameters (echo time (TE), voxel size, diffusion gradient directions, readout bandwidth, etc.), and vendor-specific reconstruction algorithms further exacerbate the issue. This lack of standardization impedes the joint analysis of dMRI data across sites and scanners, and there is a critical need for methods that facilitate harmonization to enable effective joint analysis.[14,15]

The initial and critical phase for designing multi-site/scanner studies is to standardize the dMRI scanning protocol. However, each vendor has a different design for their dMRI scan and image reconstruction algorithm, and allows only a nominal match of high-level imaging parameters such as TE, repetition time (TR), and voxel size, while many fundamental parameters such as diffusion times (δ and Δ), readout bandwidth, fat suppression method, and RF pulse shape, duration, and time-bandwidth product (TBWP) are still pre-defined and often unchangeable from the scanner console.[16]

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To address the challenge of inter-scanner variability, post-processing techniques for harmonizing dMRI data have been proposed.[14,15,17,18] Although effective in mitigating scanner-induced variations, these post-hoc methods often require traveling or control subjects to estimate scanner effects from each site.[15] Furthermore, the statistical methods require a substantial participant pool for robust statistical analyses, limiting their applicability in studies with small sample sizes.[19]

Recently, vendor-agnostic sequence development tools have been developed and are gaining widespread attention.[20–25] One of them is *Pulseq*[22,26], which is an open-source, vendor-neutral platform for sequence development. Users can describe sequences directly within MATLAB or Python using functions from the *Pulseq* toolbox, simplifying the sequence generation process. Moreover, these sequences can be executed on various vendor platforms using vendor-specific interpreters, ensuring identical execution of the sequences across different MRI systems. Following sequence execution, a consistent reconstruction and post-processing pipeline can be applied. *Pulseq* has been used to develop a range of sequences, including CEST,[27] T_1/T_2 mapping with IRSE and TSE,[28] spiral TSE,[29] T_1 mapping with blipped-bSSFP,[30] and optimized RARE,[31] which reveal the growing appeal of the *Pulseq* platform. However, despite its potential, a gap remains in implementing standard dMRI sequences in *Pulseq* and understanding how *Pulseq* sequences might mitigate inter-scanner variability, particularly concerning quantitative metrics obtained from dMRI. As such, we aim to ascertain the platform's effectiveness in reducing variability in dMRI acquisition across different scanners.

In this technical note, we implemented a standard echo-planar imaging (EPI) based dMRI sequence in *Pulseq*. We tested it on Siemens Prisma and GE Premier scanners, systematically evaluating and comparing the within- and inter-scanner variability (i.e. repeatability and reproducibility) across the vendors, using both the vendor-provided and *Pulseq* dMRI sequences. Our assessment covered a diffusion phantom and three human subjects, using standard error[32] (SE) and Lin's Concordance correlation[33] to quantify the variability of standard DTI measures including MD and FA.

Methods

1. *Pulseq* dMRI sequence development

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Pulseq represents an MRI pulse sequence as a series of non-overlapping blocks[22]. One block represents a basic component of a sequence, and each block can be substituted flexibly for sequence modifications. Our dMRI sequence comprised of five blocks (see Figure 1C):

1. Fat suppression: a non-selective Gaussian pulse and a pair of spoilers along X, Y, and Z gradients were allocated in front of the sequence.
2. Excitation: a Sinc pulse with a duration of three milliseconds, TBWP=4, and a 90^{o} flip angle. A slice selection gradient and its rewinder were also applied to excite a slice at a given location, and an interleaved acquisition was performed to mitigate crosstalk artifact.
3. Diffusion: monopolar diffusion-sensitizing gradients were generated and implemented. First, diffusion gradients along the Z axis were calculated for a given b-value and were then rotated according to the azimuthal and polar angles calculated from the spherical coordinate of the diffusion gradient table.
4. Refocusing: a Sinc pulse with a duration of three milliseconds, TBWP=4, and 180^{o} flip angle, and a slice selection gradient were used for refocusing, and a pair of crushers were added on both sides of the refocusing pulse for the non-diffusion weighted volumes.
5. EPI readout: EPI with ramp sampling was applied for the readout, and the analog-to-digital converter (ADC) sampling rate was set to two. The blip gradient (G_y) was turned off for the first volume to acquire the three-line reference scan to calculate the phase differences between odd and even readout lines.

2. Phantom and participants

An MRI Diffusion Calibration Phantom[34] (M231006, Psychology Software Tools, Inc., Sharpsburg, PA) and three healthy male subjects were recruited for this study after informed consent. All scans and procedures were performed with the approval of the Institutional Review Board of Mass General Brigham.

3. Data acquisition

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The study was conducted on two 3T scanners (Siemens Prisma, version VE11C, and GE Premier, version MR30). Both scanners had a max gradient strength of 80 mT/m and a maximum slew rate of 200 T/m/s.

The vendor-provided diffusion-weighted monopolar spin-echo EPI sequence and *Pulseq*-diffusion sequence were used on each scanner for phantom and in-vivo scans. The high-level scan parameters for all sequences (including the *Pulseq* sequence) were identical: TR/TE/echo spacing=11000/58/0.69 ms, FOV=220×220 mm^2, in-plane resolution=1.5×1.5 mm^2, slice thickness=1.5 mm, 88 slices, in-plane acceleration[35] factor=3, Partial Fourier factor=6/8. The same 60-direction diffusion table was used for all the sequences, as well as b-value=1000 s/mm^2, with one anterior-posterior (AP) b=0 image and one posterior-anterior (PA) b=0 image for correcting susceptibility-induced distortions[36].

During the pre-scan of the product sequences, an EPI and a gradient echo sequence were acquired as the autocalibration signal (ACS) reference scan for Siemens (integrated Parallel Acquisition Technique, iPAT) and GE (Autocalibrating Reconstruction for Cartesian imaging, ARC), respectively. For *Pulseq* sequences, a separate three-shot EPI with matched FOV and distortion was acquired as the ACS reference scan. The developed *Pulseq* sequence (v1.0.0) is available at: https://github.com/HarmonizedMRI/Pulseq-diffusion. Acoustic resonance peaks caused by gradient coil mechanical resonances (also translated as forbidden echo spacings) can be checked while writing *Pulseq* sequences using the Matlab function demoUnsorted/gradSpectrum.m available in our repository.

To assess intra- and inter-scanner variability, a phantom and three subjects underwent scan-rescan sessions. The phantom was removed from the coil and re-scanned after one hour of room temperature adaptation.[37] The in-vivo scans were obtained on the same day (a total of 4 scans per subject spread over two hours).

T_1-weighted structural images were acquired for each subject as the anatomical reference using a 3D T_1-weighted image magnetization-prepared rapid gradient echo (MPRAGE) sequence[38] on the

Siemens Prisma scanner with the following parameters: TR/TE=2300/2.98 ms, FOV=256×240×144 mm^3, resolution=1.0×1.0×1.0 mm^3.

4. Data processing

The *Pulseq* k-space data were converted to ISMRM-RD format[39], and custom MATLAB scripts were used to reconstruct *Pulseq* k-space data, including ramp sampling interpolation, linear Nyquist ghost artifact correction using the three-line reference scan, GRAPPA[35] reconstruction, and Gibbs ringing artifact[40] removal. The code for all these steps is available at https://github.com/QiangLiu0310/Pulseq-diffusion_recon. The reconstructed images for *Pulseq* and exported images from the product sequences were formatted using the Brain Imaging Data Structure (BIDS)[41] convention prior to preprocessing. FSL[42] *eddy*[43] and *TOPUP*[44] corrections were applied to mitigate distortions and head motion for all sequences. *Freesurfer*[45]was used to parcellate the brain using the Deskian-Killiany atlas on the T_1-MPRAGE images, after which Advanced Normalization Tools[46] (ANTs) was used for the rigid registration of the output of *Freesurfer* to the diffusion space for each dMRI acquisition.

For the phantom, MD values were calculated from nine regions of interest (ROIs) with varying diffusivities. FA values were not calculated for the phantom as this version of the phantom lacked anisotropic regions. Each ROI had an area of 15×15 voxels per slice and was combined from three consecutive slices. Based on the calculated MD values, we further divided the selected ROIs into two groups: three ROIs with low MD values and six ROIs with higher MD values. Variability (intra- and inter-scanner) was assessed using Concordance correlation coefficient and standard error (SE) analyses for MD measurements in the phantom. SE ($\hat{\sigma}_e$) was calculated using:

$$\hat{\sigma}_e{}^2 = \frac{1}{n(k-1)} \sum_{i=1}^{n} \sum_{j=1}^{k} \left(y_{ij} - \bar{y}_i\right)^2$$

where n represents the number of ROIs in the case of the phantom and subjects for in-vivo data, i represents the ROI/subject index, j represents the measurement number, k represents the number of measurements: k=2 for intra-scanner session, and k=4 for inter-scanner session including scannerA_scan1, scannerA_scan2, scannerB_scan1, and scannerB_scan2, y_{ij} represents the dMRI

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measure, and $\bar{y}_i$ represents the mean of the measurement for one subject (across an ROI). SE was calculated separately for each ROI in the phantom and in-vivo data.

For the in-vivo data, MD and FA values were computed, after which the SEs of MD and FA were calculated across three subjects. Employing *Freesurfer* parcellations, the SE was analyzed in two ways: first, the SEs of subcortical, cortical, and white matter regions were calculated. SEs were further calculated for each of the *Freesurfer* ROIs within each of the subcortical, cortical, and white matter regions. To maintain statistical robustness, only ROIs with volumes in the top 75 percentile in each group were included in the analysis.

Results

Figure 1 shows sequence diagrams for both the product (Siemens and GE) and *Pulseq* diffusion sequences. Figure 1(A) shows the EP2D sequence sourced from the Siemens IDEA platform, while Figure 1(B) was obtained using Plotter, a tool provided by GE Healthcare. Additionally, Figure 1(C) presents the sequence diagram of *Pulseq*-diffusion. A comparative analysis between the product diffusion sequences reveals several notable differences. First, the Siemens sequence employs a pair of spoilers placed at the beginning of the TR, whereas GE incorporates an additional spoiler along the Z-axis at the end of the TR. Second, there are differences in the RF pulse shapes used for fat suppression, potentially yielding differing fat suppression effects. Third, the excitation and refocusing pulse shapes are different, notably in the side lobes, which could impact the resulting slice profiles. Finally, upon the addition of diffusion-sensitizing gradients, GE retains a pair of crushers, introducing variations in diffusion times between Siemens and GE sequences. When implementing *Pulseq*-diffusion sequences, all these differences were removed, and identical sequences were executed on both Siemens and GE scanners (referred to as vendor A and vendor B respectively, hereafter).

Figure 2(A) shows nine ROIs in the phantom with varying diffusivities on an example slice. Figure 2(B) displays the SE of the MD values in both scan-rescan and inter-scanner sessions. Overall, the lowest variability was observed using *Pulseq* sequences. Compared to the vendor-provided sequences, the *Pulseq* sequence exhibited superior inter-scanner reproducibility (better by a factor

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of ~2.5×; see Fig.2(B) (all nine ROIs)), particularly for ROIs with lower MD values. Paired differences of the MD values in the inter-scanner session with bootstrapped confidence interval were also calculated and are shown in Figure S1, where *Pulseq* showed lower paired differences than the product sequences.

Figure 2(C) shows Lin's Concordance correlation of MD values between scan-rescan sessions and across different scanners. The inter-scanner correlation coefficient (ρ_c= 0.9670, 95% confidence interval: [0.9221,0.9862]) for the *Pulseq* diffusion sequences was close to the scan-rescan correlations (ranging from 0.9303 to 0.9973) and much higher than the correlation obtained from vendor product sequences (ρ_c= 0.7310, 95% confidence interval: [0.4973,0.8658]).

Figure 3 shows a representative DWI slice and diffusion-derived metrics, including MD, FA, and color-encoded FA maps obtained using vendor-provided and *Pulseq* sequences on both scanners from one subject. As can be seen, the anatomical details are similar between the *Pulseq* and product scans. We estimated the noise map (please see Figure S2(A)) for each of the scans using the homomorphic algorithm[47] and found them to be quite comparable across sequences although a bit lower (i.e. better SNR) in the *Pulseq* scans: 0.5023±0.2277 (vendor A), 0.5044±0.2060 (vendor B), 0.4433±0.1836 (*Pulseq* on A), and 0.4781±0.1844 (*Pulseq* on B). We also estimated the angular contrast-to-noise ratio (CNR) (Figure S2(B)) of each scan using FSL *eddy* and found that vendor A provided dMRI images with the highest angular CNR among all scans: 1.1577±0.6767 (vendor A), 1.0742±0.5449 (vendor B), 0.8547±0.4687 (*Pulseq* on A), and 0.6981±0.3415 (*Pulseq* on B). This can be attributed to specialized (proprietary) post-processing/filtering done by vendor A during data reconstruction.

Figure 4 shows the standard errors calculated from the three subjects for vendor and *Pulseq* sequences. Figure 4(A) compares the SE in three brain regions (subcortical gray, cortical gray, and white matter), while Figure 4(B) shows the distribution of the SE across *Freesurfer* ROIs within these regions. Notably, the SE using *Pulseq* sequences across different scanners exhibited lower variation, about half in cortical and subcortical regions and 35% lower in white matter, while maintaining similar within-scanner variability. Furthermore, the distribution of the SE across all *Freesurfer* ROIs (large and small) for the *Pulseq* sequence is much tighter compared to product

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sequences. This shows that a unified acquisition and reconstruction platform (*Pulseq*) can reduce inter-scanner variability across different vendors.

Similarly, Figure 5 displays the standard error in MD values. *Pulseq* sequences showed comparable SE in subcortical regions but 22% and 19% lower variability in cortical and white matter regions, respectively. The distribution of SEs across all *Freesurfer* ROIs for *Pulseq* sequences is also notably narrower compared to product sequences.

Discussion

In this work, we implemented standard dMRI sequences on a vendor-neutral sequence development platform *Pulseq*. We demonstrated promising results with the proposed harmonized acquisition, which enhanced the reproducibility and consistency of dMRI measurements across scanners from two different vendors. On the phantom, the *Pulseq* sequence showed more than a 2.5× reduction in standard error (variability) across Siemens and GE scanners. Furthermore, on the human in-vivo data, *Pulseq* sequences exhibited remarkably reduced standard error, maintaining scan-rescan repeatability while delivering lower variability in FA and MD (more than 50% reduction in cortical/subcortical regions) compared to vendor-provided sequences.

Our primary focus was to address the critical challenge of reducing inter-scanner variability in dMRI for multi-center/site studies. Efforts to standardize dMRI protocols across different scanners encounter significant technical barriers due to vendor-specific implementations and limitations. Although attempts have been made to align high-level imaging parameters,[12] considerable differences in diffusion-specific parameters and other fundamental sequence components remain largely unchangeable. To combat the challenge, this study leveraged the *Pulseq* platform, recognized for its capacity to implement vendor-neutral MRI sequences. Beyond aligning basic imaging parameters like FOV and matrix size, our approach combined five sequence blocks within the *Pulseq*-dMRI sequence, precisely matching sequence timing, fat suppression method, RF pulse, and gradient waveform shapes. This synchronization effectively tackled the first problem of variation in data acquisition. Moreover, our unified reconstruction pipeline contributed to mitigating challenges associated with reconstruction algorithms. This comprehensive solution not

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only ensured the standardization of the sequence itself but also bolstered the reproducibility of dMRI measurements across diverse scanners. Thus, the *Pulseq*-dMRI sequence has significant potential to become an indispensable asset in advancing and standardizing multicenter dMRI studies.

Despite the improvement in the reproducibility of diffusion measures using the Pulseq diffusion sequence, it is important to note that the inter-scanner variability of the Pulseq-dMRI sequence remained slightly higher than the intra-scanner variability for both FA and MD. This discrepancy might be attributed to variations in hardware among different manufacturers, specifically differences in the scanner bore size, the use of receiver coils with varying channel numbers, magnetic field strength differences (3.0T vs 2.89T), and the application of different shimming methods. For instance, on one scanner, a 32-channel coil with high-order shimming was utilized, whereas on the other scanner, a 48-channel coil with linear shimming was employed. These distinct factors might significantly influence the signal-to-noise ratio[48,49] (SNR) and geometric fidelity of the dMRI images. Besides different shimming methods, differences in prescan calibrations (e.g., transmitter and receiver gain adjustments) provided by different vendors may also introduce variations to the measured image signal, which will propagate to the proton density image without influencing the diffusion measures. Although our study did not cover scanners with various software versions, it is also worth noting that scanner upgrades will also introduce variability in the measurements, likely due to updates to image reconstruction or the pre-calibration methods.[50] Such differences in data due to hardware and software variations can be mitigated with post-processing methods. [14,15]

This study also has some limitations. First, the image reconstruction of the *Pulseq* diffusion sequence is limited to offline. With the help of IceGadgetron[51,52] (Siemens) or Orchestra (GE), *Pulseq* data could be reconstructed online, even with advanced imaging features such as in-plane acceleration or ramp sampling. The second limitation is that our scan protocol only covered single-shell DTI acquisition. With the flexibility of sequence development using *Pulseq*, other dMRI acquisition protocols and dMRI models can also be investigated[53,54]. In this first study, we implemented the standard single-band diffusion EPI sequence. Future work could investigate the reproducibility of the *Pulseq*-dMRI sequence using blipped-CAIPI-multiband sequence[55]. While

this study focused on two scanner vendors, extending this evaluation to other MRI platforms would bolster the generalizability of our findings.

Conclusion

To conclude, we demonstrated that the *Pulseq* diffusion sequence reduced the inter-scanner variability of dMRI data in phantom and in-vivo subjects, and could immensely benefit multi-center neuroimaging studies.

Data Availability Statement

The source code to produce the standard diffusion sequence for use with the *Pulseq* sequence programming environment is available at: https://github.com/HarmonizedMRI/Pulseq-diffusion, the corresponding reconstruction code is available at: https://github.com/QiangLiu0310/Pulseq-diffusion_recon.

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References

1. Johansen-Berg H, Behrens TEJ. Diffusion MRI: From Quantitative Measurement to in Vivo Neuroanatomy. 2013
2. Le Bihan D Mangin JF PCCCAPSMNCH. Diffusion tensor imaging: Concepts and applications. J Magn Reson Imaging (ISSN: 1053-1807, 1522-2586electronic) 2001; 5422:534–546.
3. De Santis S, Bastiani M, Droby A, et al. Characterizing Microstructural Tissue Properties in Multiple Sclerosis with Diffusion MRI at 7 T and 3 T: The Impact of the Experimental Design. Neuroscience 2019; 403:17–26.
4. Tae WS, Ham BJ, Pyun SB, Kang SH, Kim BJ. Current clinical applications of diffusion-tensor imaging in neurological disorders. Journal of Clinical Neurology (Korea) 2018; 14:129–140.
5. Beer AL, Plank T, Greenlee MW. Aging and central vision loss: Relationship between the cortical macro-structure and micro-structure. Neuroimage 2020; 212
6. Koller K, Rudrapatna U, Chamberland M, et al. MICRA: Microstructural image compilation with repeated acquisitions. Neuroimage 2021; 225
7. Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K. The WU-Minn Human Connectome Project: An overview. Neuroimage 2013; 80:62–79.
8. Froeling M, Tax CMW, Vos SB, Luijten PR, Leemans A. "MASSIVE" brain dataset: Multiple acquisitions for standardization of structural imaging validation and evaluation. Magn Reson Med 2017; 77:1797–1809.
9. Magnotta VA, Matsui JT, Liu D, et al. MultiCenter Reliability of Diffusion Tensor Imaging. Brain Connect 2012; 2:345–355.
10. Helmer KG, Chou M-C, Preciado RI, et al. Multi-site study of diffusion metric variability: characterizing the effects of site, vendor, field strength, and echo time using the histogram

Author Manuscript

distance. Medical Imaging 2016: Biomedical Applications in Molecular, Structural, and Functional Imaging, 2016; 97881G
11. Vollmar C, O'Muircheartaigh J, Barker GJ, et al. Identical, but not the same: Intra-site and inter-site reproducibility of fractional anisotropy measures on two 3.0T scanners. Neuroimage 2010; 51:1384–1394.
12. Palacios EM, Martin AJ, Boss MA, et al. Toward precision and reproducibility of diffusion tensor imaging: A multicenter diffusion phantom and traveling volunteer study. American Journal of Neuroradiology 2017; 38:537–545.
13. Zhu T, Hu R, Qiu X, et al. Quantification of accuracy and precision of multi-center DTI measurements: A diffusion phantom and human brain study. Neuroimage 2011; 56:1398–1411.
14. Mirzaalian H, Ning L, Savadjiev P, et al. Inter-site and inter-scanner diffusion MRI data harmonization. Neuroimage 2016; 135:311–323.
15. Cetin Karayumak S, Bouix S, Ning L, et al. Retrospective harmonization of multi-site diffusion MRI data acquired with different acquisition parameters. Neuroimage 2019; 184:180–200.
16. Warrington S, Ntata A, Mougin O, et al. A resource for development and comparison of multi-modal brain 3T MRI harmonisation approaches. bioRxiv 2023
17. De Luca A, Karayumak SC, Leemans A, et al. Cross-site harmonization of multi-shell diffusion MRI measures based on rotational invariant spherical harmonics (RISH). Neuroimage 2022; 259
18. Fortin JP, Parker D, Tunç B, et al. Harmonization of multi-site diffusion tensor imaging data. Neuroimage 2017; 161:149–170.
19. Pinto MS, Paolella R, Billiet T, et al. Harmonization of Brain Diffusion MRI: Concepts and Methods. Front Neurosci 2020; 14
20. Jochimsen TH, Von Mengershausen M. ODIN - Object-oriented Development Interface for NMR. Journal of Magnetic Resonance 2004; 170:67–78.
21. Magland JF, Li C, Langham MC, Wehrli FW. Pulse sequence programming in a dynamic visual environment: SequenceTree. Magn Reson Med 2016; 75:257–265.
22. Layton KJ, Kroboth S, Jia F, et al. Pulseq: A rapid and hardware-independent pulse sequence prototyping framework. Magn Reson Med 2017; 77:1544–1552.
23. Nielsen JF, Noll DC. TOPPE: A framework for rapid prototyping of MR pulse sequences. Magn Reson Med 2018; 79:3128–3134.
24. Cordes C, Konstandin S, Porter D, Günther M. Portable and platform-independent MR pulse sequence programs. Magn Reson Med 2020; 83:1277–1290.
25. Karakuzu A, Biswas L, Cohen-Adad J, Stikov N. Vendor-neutral sequences and fully transparent workflows improve inter-vendor reproducibility of quantitative MRI. Magn Reson Med 2022; 88:1212–1228.
26. Ravi K, Geethanath S, Vaughan J. PyPulseq: A Python Package for MRI Pulse Sequence Design. J Open Source Softw 2019; 4:1725.
27. Herz K, Mueller S, Perlman O, et al. Pulseq-CEST: Towards multi-site multi-vendor compatibility and reproducibility of CEST experiments using an open-source sequence standard. Magn Reson Med 2021; 86:1845–1858.
28. Tong G, Gaspar AS, Qian E, et al. A framework for validating open-source pulse sequences. Magn Reson Imaging 2022; 87:7–18.
29. Hennig J, Barghoorn A, Zhang S, Zaitsev M. Single shot spiral TSE with annulated segmentation. Magn Reson Med 2022; 88:651–662.
30. Gaspar AS, Silva NA, Price AN, Ferreira AM, Nunes RG. Open-source myocardial T1 mapping with simultaneous multi-slice acceleration: Combining an auto-calibrated blipped-bSSFP readout with VERSE-MB pulses. Magn Reson Med 2023; 90:539–551.
31. Dang HN, Endres J, Weinmüller S, et al. MR-zero meets RARE MRI: Joint optimization of refocusing flip angles and neural networks to minimize T2-induced blurring in spin echo sequences. Magn Reson Med 2023; 90:1345–1362.

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32. Matheson GJ. We need to talk about reliability: Making better use of test-retest studies for study design and interpretation. PeerJ 2019; 2019
33. Lin LI-K. A Concordance Correlation Coefficient to Evaluate Reproducibility. Biometrics 1989; 45:255–268.
34. Reischauer C, Staempfli P, Jaermann T, Boesiger P. Construction of a temperature-controlled diffusion phantom for quality control of diffusion measurements. J Magn Reson Imaging 2009; 29: 692–698.
35. Griswold MA, Jakob PM, Heidemann RM, et al. Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA). Magn Reson Med 2002; 47:1202–1210.
36. Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. Magn Reson Med 1995; 34:65–73.
37. Teipel SJ, Reuter S, Stieltjes B, et al. Multicenter stability of diffusion tensor imaging measures: A European clinical and physical phantom study. Psychiatry Res Neuroimaging 2011; 194:363–371.
38. Brant-Zawadzki M, Gillan GD, Nitz WR. MP RAGE: a three-dimensional, T1-weighted, gradient-echo sequence–initial experience in the brain. Radiology 1992; 182:769–775.
39. Inati SJ, Naegele JD, Zwart NR, et al. ISMRM Raw data format: A proposed standard for MRI raw datasets. Magn Reson Med 2017; 77:411–421.
40. Lei T, Udupa JK. Gibbs ringing artifact and spatial correlation in MRI. Medical Imaging 2003: Physics of Medical Imaging, 2003; 961
41. Gorgolewski KJ, Auer T, Calhoun VD, et al. The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. Sci Data 2016; 3
42. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004; 23:S208–S219.
43. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 2016; 125:1063–1078.
44. Andersson JLR, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage 2003; 20:870–888.
45. Fischl B. FreeSurfer. Neuroimage 2012; 62:774–781.
46. Avants BB, Tustison N, Johnson H. Advanced Normalization Tools (ANTS) Release 2.x. 2014
47. Aja-Fernández S, Pięciak T, Vegas-Sánchez-Ferrero G. Spatially variant noise estimation in MRI: A homomorphic approach. Med Image Anal 2015; 20:184–197.
48. Farrell JAD, Landman BA, Jones CK, et al. Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5T. Journal of Magnetic Resonance Imaging 2007; 26:756–767.
49. Polders DL, Leemans A, Hendrikse J, Donahue MJ, Luijten PR, Hoogduin JM. Signal to noise ratio and uncertainty in diffusion tensor imaging at 1.5, 3.0, and 7.0 Tesla. Journal of Magnetic Resonance Imaging 2011; 33:1456–1463.
50. Lee Y, Callaghan MF, Acosta-Cabronero J, Lutti A, Nagy Z. Establishing intra- and inter-vendor reproducibility of T1 relaxation time measurements with 3T MRI. Magn Reson Med 2019; 81:454–465.
51. Xue H, Inati S, Sørensen TS, Kellman P, Hansen MS. Distributed MRI reconstruction using Gadgetron-based cloud computing. Magn Reson Med 2015; 73:1015–1025.
52. Hansen MS, Sørensen TS. Gadgetron: An open source framework for medical image reconstruction. Magn Reson Med 2013; 69:1768–1776.
53. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage 2012; 61:1000–1016.

54. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: The quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med 2005; 53:1432–1440.
55. Setsompop K, Gagoski BA, Polimeni JR, Witzel T, Wedeen VJ, Wald LL. Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. Magn Reson Med 2012; 67:1210–1224.

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Figure Caption

Figure 1. Sequence diagrams for product and *Pulseq* diffusion sequences. Figure 1(A): EP2D sequence from Siemens IDEA platform. Figure 1(B): diffusion EPI sequence from GE plotter. Figure 1(C): *Pulseq*-diffusion sequence. Even though the high-level sequence parameters were set the same for Siemens and GE product sequences, differences are still observed in the fat suppression pulse, spoiler, crusher, and excitation and refocusing radiofrequency (RF) pulses.

Figure 2. (A) Diffusion phantom and the selected nine ROIs with varying diffusivities. (B) The standard errors in MD values for scan-rescan and inter-scanner sessions. (C) Lin's Concordance correlation for MD between scan-rescan sessions and across different scanners for vendor-provided dMRI and *Pulseq*-diffusion sequences. *Pulseq* shows a significantly higher correlation in MD between scanners compared to product sequences.

Figure 3. A representative slice showing dMRI data and derived diffusion metrics on in-vivo data from the same subject using both product and *Pulseq* sequences on GE and Siemens scanners.

Figure 4. The standard error (quantifying within- and between-scanner variability) in FA in subcortical, cortical, and white matter regions is shown in (A). In each 4×4 matrix, within-scanner variabilities are shown in the left-top 2×2 corner (scans from vendor A are labeled as A1, A2; whereas using *Pulseq* are labeled PA1, PA2) and right-bottom 2×2 corner (scans from scanner B are labeled B1, B2; and using *Pulseq* as PB1, PB2), and between-scanner variability is shown in the left-bottom 2×2 corner. The distribution of the SE (the horizontal bar is the median) across different *Freesurfer* regions is shown in (B). About 50% reduction in inter-scanner variability is seen in cortical and subcortical regions using *Pulseq* (A) with 35% reduction in white matter.

Figure 5. The standard error in MD values. Subcortical, cortical, and white matter standard errors are shown in (A), and region-based standard errors are shown in (B). 22% and 19% reduction in variability is seen in cortical and white matter regions.

Figure S1. Paired differences of the MD values in the inter-scanner session with bootstrapped confidence interval. *Pulseq* showed lower paired differences than the product sequences.

Figure S2. Noise map (A) for each of the scans using the homomorphic algorithm and the angular contrast-to-noise ratio (CNR) (B) of each scan using FSL *eddy*.

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