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Vendor-neutral sequences and fully transparent workflows improve inter-vendor reproducibility of quantitative MRI

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Abstract

Purpose: We developed an end-to-end workflow that starts with a vendor-neutral acquisition and tested the hypothesis that vendor-neutral sequences decrease inter-vendor variability of T1, MTR and MTsat measurements.

Methods: We developed and deployed a vendor-neutral 3D spoiled gradient-echo (SPGR) sequence on three clinical scanners by two MRI vendors. We then acquired T1 maps on the ISMRM-NIST system phantom, as well as T1, MTR and MTsat maps in three healthy participants. We performed hierarchical shift function analysis in vivo to characterize the differences between scanners when the vendor-neutral sequence is used instead of commercial vendor implementations. Inter-vendor deviations were compared for statistical significance to test the hypothesis.

Results: In the phantom, the vendor-neutral sequence reduced inter-vendor differences from 8 - 19.4% to 0.2 - 5% with an overall accuracy improvement, reducing ground truth T1 deviations from 7 - 11% to 0.2 - 4%. In vivo we found that the variability between vendors is significantly reduced ($p = 0.015$) for all maps (T1, MTR and MTsat) using the vendor-neutral sequence.

Conclusion: We conclude that vendor-neutral workflows are feasible and compatible with clinical MRI scanners. The significant reduction of inter-vendor variability using vendor-neutral sequences has important implications for qMRI research and for the reliability of multicenter clinical trials.

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Introduction

As the invention of MRI approaches its 50th anniversary[1], the notion of image acquisition has almost become synonymous with data collection. A major driving force in the transformation of MR images from mere pictures into mineable data[2] is attributing physiologically relevant physical parameters to the voxels, namely quantitative MRI (qMRI). MRI is not a quantitative measurement device by design. Nonetheless, systematic manipulation of effective micrometer-level MRI parameters via specialized acquisition methods, followed by fitting the resulting data to a signal representation or a biophysical model[3], can yield parametric maps, turning scanners into quantitative diagnostic tools. Despite being as old as MRI itself, most of the qMRI methods have not succeeded to find widespread use in the clinic, at least in part due to a major multicenter reproducibility challenge.

The introduction is organized around two problems hampering multicenter reproducibility of qMRI, which this study seeks to address:

1. Lack of transparency and multicenter consistency in vendor implementations of pulse sequences that are commonly used in qMRI
2. Technical roadblocks in the way of deploying a standardized pulse sequence along with a unified user interface to multiple imaging sites

T1 relaxometry is a clear example of how availability, transparency and multicenter consistency of pulse sequences influence multicenter reproducibility. Several methods such as inversion-recovery spin-echo (IR-SE)[4], variable flip angle (VFA-T1)[5], Look-Locker IR[6] and magnetization-prepared two rapid-echoes (MP2RAGE)[7] have gained popularity in MRI research. Although measured T1 values can exhibit up to 30% inter-sequence variability in the same scan session for the same participant[8], a selected T1 relaxometry method is much more reliable within-site[9,10]. As for the multicenter stability, MP2RAGE appears to be a promising T1 mapping method at 7T with a single vendor considered[11]. On the other hand, substantial multicenter variability is reported for another popular whole-brain imaging method VFA-T1, both in-vivo and in phantoms[12,13]. Several factors contribute to the variability of the VFA-T1 measurement, including B1 field inhomogeneity[8], incomplete spoiling[14], sequence parameters and bore temperature[13], and uncontrolled magnetization transfer (MT) effects[15]. Because of all these diverse confounders of T1 stability, the healthy range of in-vivo T1 values at 3T remains elusive[16,17]. This constitutes a critical problem for the potential use of T1 relaxometry in clinics.

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Considerable amount of research has focused on the measurement bias due to acquisition-related imperfections. However, the reproducibility of the developed techniques is often hindered by *problem 1*. For example, a simple yet powerful B1 correction framework for VFA-T1 has been established[18], but such methods are typically not available in commercial systems, or the available ones vary across vendors. This not only imposes a practical challenge in evaluating the reliability of VFA-T1 measurements across vendors[13,19], but the differences between vendor-native B1 mapping methods can aggravate the instability[20]. Another example is the spoiling gradient area and RF spoiling phase increment in the commercial implementations of spoiled gradient-echo (SPGR) sequences. Both parameters determine the accuracy of VFA-T1 mapping. However, vendors are known to set different defaults for these parameters, rendering some of them unfit for this application[14]. Similarly, fundamental properties of the excitation pulse (e.g., pulse shape, time-bandwidth product, duration) are not disclosed and it is not known how these properties are adjusted under different SAR requirements. To achieve a standardized SPGR acquisition for T1 mapping, such parameter configurations should be disclosed, made accessible and standardized across scanners for eliminating systematic biases. Recently, Gracien et al. showed a successful example of how this solution can reduce systematic biases in relaxometry mapping between two different scanner models from the same vendor[21].

Addressing inadequacies of model assumptions constitutes another solution toward improving the reliability of qMRI methods[3]. For example, balancing the total amount of RF power deposited by each run of a VFA acquisition, Teixeira et al. enforced two-pool MT systems to behave like a single pool MT system[15]. They showed that the measurement reliability increases by making the single pool assumption valid through controlled saturation of MT. Although this technique holds important implications for multicenter reproducibility of qMRI, deploying it to multiple sites is not a straightforward process. Moreover, proprietary programming libraries of different manufacturers may not allow identical implementations, exemplifying the constraints imposed by *problem 2*. Another model-related improvement has been recently introduced to reduce the B1 dependency of MTsat maps by replacing the fixed empirical B1 correction factor of the MT saturation-index (MTsat)[22] with a correction factor map[23]. The proposed methodology requires the details of the saturation and excitation pulses (e.g., shape, offset, duration, etc.) as the correction framework is simulation-based. From the standpoint of *problem 1,* such information is not easily accessible in the stock sequence, so the correction cannot be applied. From the perspective of *problem 2,* deploying sequences in multiple centers with known saturation and excitation pulse parameters may not be realistic due to vendor restrictions. Even though both studies made their

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code publicly available to facilitate the reproducibility of their work[24], black-box vendor strategies thwart these valuable efforts.

Fortunately, there are several open-source pulse sequence development platforms to contend with *problem 2*[25-31]. These platforms can interpret and translate the same sequence logic for multiple vendors, considerably reducing multi-center development efforts and minimizing implementation variability. Another advantage of these tools is to attract community-driven development. For example, Pulseq has received considerable community attention to motivate the development of sequences in Python[28], or even going beyond code to graphically assemble[32] Pulseq descriptions using Pulseq-GPI[33]. Currently, Pulseq can be operated on two major clinical scanners (Siemens and GE) and three pre-clinical scanner platforms. There is recent literature showing the feasibility of Pulseq for performing multicenter qMRI studies. For example, a standardized chemical exchange saturation (CEST) protocol has been developed and deployed on three Siemens scanners, where two of the systems had different vendor software versions[34]. Results by Herz et al. showed multicenter consistency for an advanced CEST method, which has been made publicly available for both Python and Matlab users. Another recent Pulseq study performed inversion-recovery T1 mapping and multi-echo spin-echo T2 mapping on two Siemens scanners at 1.5 and 3T in phantom[35]. In that study the reference T1 mapping method[36] accurately estimated T1 values within an 8% error band, whereas the T2 accuracy was slightly reduced. Taken together, these studies reveal the vital role of vendor-neutral pulse sequences in standardizing qMRI across centers. However, whether a vendor-neutral approach can improve quantitative agreement between scanners from different vendors has remained an open question.

The focus of earlier open-source pulse sequence platforms was providing a rapid and unified prototyping framework for facilitating interoperability, so some of the most adjusted scan parameters (e.g., field of view) had to be fixed once the sequence was downloaded to the scanner. More recent solutions such as GammaStar[31] can remove this limitation by enabling user interaction trough the vendor's user interface to modify fundamental protocol settings during the imaging session. Offering a more complete solution to *problem 2* through on-the-fly sequence updates, GammaStar eases the collaborative sequence development process by providing a web-based interface. Although such technical improvements reduce the barrier to entry for free sequence development, exchange and standardization, the validation aspect of open-source sequences has remained elusive. Recently, Tong et al. (2021) proposed a framework for testing, documenting and sharing open-source pulse sequences[35], which adds an important missing piece to the community-driven MRI development puzzle.

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RTHawk[37] is another vendor-neutral solution, which is a proprietary platform for MRI software development. As it is utilizing the same infrastructure as an FDA approved (510(k), No: K1833274) cardiac imaging platform, it ensures operation within MRI hardware and safety limits. Unlike the above-mentioned solutions, RTHawk provides a remote procedure call (RPC) server that replaces the vendor's pulse sequence controller to orchestrate vendor-specific low-level hardware instructions. The RPC pulse sequence server receives control commands and relevant sequence components (i.e., RF and gradient waveforms, ADC and timing events designed in SpinBench, as shown in Fig. 1c) directly from a standalone Ubuntu workstation connected to the scanner network (Fig. 1a). This gives the flexibility to issue synchronous or asynchronous updates to a sequence in real-time, such as scaling/replacing waveforms between TRs or changing the volume prescription. As the sequence control manager is decoupled from the vendor's workstation, RTHawk makes it possible to develop a vendor-neutral unified user interface (UUI) per application (Fig. 1b). In addition, the collected raw data is streamed over to the standalone Ubuntu workstation through a real-time transport protocol (RTP). The RTP data manager enables adding or changing the metadata associated with each observation, which enables exporting raw and reconstructed images in community data standards (Fig. 1d).

Aside from vendor-neutral experiments, researchers looked at improving qMRI stability by customizing vendor-native implementations and equalizing parameters to the utmost extent possible[21,38,39]. Nevertheless, downstream data harmonization methods were still needed to correct for certain inter-vendor differences[39], or some of the bias could not be removed altogether[38]. This is because vendor-native sequence customization may not offer a standard qMRI protocol, even for scanners with comparable hardware specs, as the selection of sequence design elements is exclusive to each manufacturer.

In this study, we test the hypothesis that vendor-neutral sequences reduce inter-vendor variability of T1, MTR and MTsat measurements. To test this hypothesis, we developed an end-to-end solution starting with a pulse sequence developed on RTHawk, followed by a fully transparent qMRLab workflow. We compared vendor-native T1, MTR and MTsat maps[40] with those obtained using the developed vendor-neutral sequence (VENUS) workflow in three healthy participants, across three different scanners models from two manufacturers at 3T.

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Methods

Vendor-neutral pulse sequence development

We deployed vendor-neutral pulse sequences developed in RTHawk v3.0.0 (rc4-28-ge3540dda19) (HeartVista Inc., CA, USA) on three 3T systems: (G1) GE Discovery 750 software version DV25 (R02_1549.b) (GE Healthcare, Milwaukee, MI, USA), (S1) Siemens Prisma software version VE11C (N4_LATEST_20160120) (Siemens Healthineers, Erlangen, Germany) and (S2) Siemens Skyra with the same software version as (ii). Throughout the rest of this article, these scanners will be referred to as G1, S1 and S2, respectively. Fig.-1a illustrates the hardware and software components of the experimental setup.

General design considerations

All vendor-neutral protocols were based on a 3D SPGR pulse sequence[41], with the RF, gradient waveforms, and the readout scheme developed as independent sequence blocks in SpinBench-v2.5.2 (Fig. 1c). To modify these sequence blocks, an RTHawk application and an additional UUI were developed for quantitative imaging, allowing the user to manage relevant acquisition parameters (e.g., FA, TR, and MT pulse for MTsat) from one simple panel that is vendor-neutral (Fig. 1b). Identical scan geometry and pre-acquisition settings were transferred between each individual acquisition. To avoid signal clipping, the highest SNR acquisition (i.e., T1w acquisition of the MTsat protocol) were run first. A simple sum-of-squares multi-coil reconstruction was developed with a Fermi filter (transition width = 0.01, radius = 0.48, both expressed as a proportion of the FOV) (Fig. 1d).

All the metadata annotations, accumulation logic of the collected data and naming of the exported images were designed according to the community data standards: ISMRM-RD[42] for the k-space data and the Brain Imaging Data Structure (BIDS) for the reconstructed images[43,44].

The vendor-neutral protocol

A slab-selective (thickness = 50mm, gradient net area = 4.24 cyc/thickness) SINC excitation pulse (time-bandwidth product ($T\Delta f$) = 8, duration = 1.03ms, Hanning windowed) was implemented with a quadratic phase increment of 117° for RF spoiling. This was followed by a fully-sampled 3D cartesian readout. The default geometry properties were 256x256 acquisition matrix, 25.6 cm

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FOV and 20 partitions in the slab-selection direction, yielding 1x1x3 mm resolution. The readout gradient had a rewinder lobe with 2 cyc/pixel net area and was followed by a spoiling gradient with an area of 40 mT·ms/m.

For the magnetization transfer (MT) saturation, a Fermi pulse (duration = 12ms, B1rms = 3.64μT, frequency offset = 1.2kHz, transition width = 0.35, max B1 = 5μT, pulse angle= 490°) was designed as an optional block. A loop command was defined for the sequence to iterate through three sets of parameters (i.e., MT, FA and TR), defined by the user in the UUI for a complete MTsat protocol.

From this protocol we acquired three images: (i) PD-weighted SPGR with no MT, FA = 6° and TR = 32ms (ii) MT-weighted SPGR with MT, FA = 6° and TR = 32ms (iii) T1-weighted SPGR without MT, FA = 20° and TR = 18ms. From images (i) and (iii) we computed a T1 map, from images (i) and (ii) we computed an MTR map, and from images (i), (ii) and (iii) we computed an MTsat map.

Data acquisition

Three healthy male participants volunteered for multi-center data collection. Written informed consent was acquired prior to the data collection following a protocol approved by the Ethics Committee of each imaging center.

The participants (P1-3) and the ISMRM-NIST system phantom (HPD Inc., serial number = 42) were scanned on three imaging systems at two imaging sites. In S1 and S2, the phantom was scanned using a 20-channel head coil due to space constraints, whereas a 32-channel coil was used in G1. For in-vivo imaging, 32-channel head coils were used in G1 and S1, whereas a 64-channel coil was used in S2. S1 was equipped with an XR-K2309_2250V_951A (Siemens Healthineers, Erlangen,Germany) gradient system (80 mT/m maximum amplitude and 200 T/m/s slew rate per axis, 50 cm maximum FOV), S2 with an XQ-K2309_2250V_793A (Siemens Healthineers, Erlangen,Germany) gradient system (45 mT/m maximum amplitude and 200 T/m/s slew rate per axis, 50 cm maximum FOV) and G1 with a 8920-XGD (GE Healthcare, Milwaukee, USA) gradient system (50 mT/m maximum amplitude and 200 T/m/s slew rate per axis, 48cm maximum FOV). The nominal field strengths on G1 and S1-2 were 3T and 2.89T, respectively. Before the scan, the phantom was kept in the imaging site for at least a day, and in the scanner room for at

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least 3 hours. The measured bore temperature in G1, S1 and S2 was 20.1°C, 20.2°C and 20.8°C, respectively.

The acquisition parameters were set according to a generic protocol established for MTsat imaging of neural tissue[45]. The vendor-neutral acquisition parameters were identical on all systems. However, it was not possible to equalize all the parameters between the vendor-native protocols. Comparison of vendor-native and vendor-neutral protocols are presented in Table 1. To scan the phantom, prescan measurements were performed as described by Keenan et al. (2021) and the vendor-neutral acquisitions were configured to start the acquisitions with these calibrations[13]. For all acquisitions, the prescan settings of the initial T1w acquisition were used for the subsequent PDw and MTw acquisitions on all vendor systems. For the VENUS acquisitions, B0 shimming gradients were set using a spiral multi-echo gradient-echo sequence. Gradient non-linearity correction was performed as part of the on-site reconstruction pipeline. The warping coefficients were made available for offline reconstruction. For the systems S1-2, the identical protocol was used by exporting the vendor-native protocol files from S2. The protocols for G1 were set on-site.

Data processing

All the processing was performed using data-driven and container mediated pipelines comprised of two docker images (Fig. 2). Quantitative fitting was performed in qMRLab[46] v2.5.0b. Pre-processing steps were performed using ANTs[47] for registration and FSL[48] for automatic gray-matter (GM) and white-matter (WM) segmentation.

For the in-vivo data, between-scan motion correction was performed by aligning PDw and MTw images onto the T1w, followed by MTsat fitting (Fig. 2b). Brain region segmentations were performed on the T1w images and ROI masking was performed to prepare data for statistical analyses (Fig. 2c). The phantom T1 pipeline consisted of linearized VFA-T1 by accounting for varying TRs[22] (Fig. 2a). Resultant phantom maps were then masked using spherical ROIs as described in[49]. Finally, peak SNR (PSNR) values were calculated, and the phantom images were visualized to compare image quality characteristics between vendor-native and VENUS implementations (Fig. 3).

Statistical analyses

All the descriptive statistics were reported by the processing pipeline in tabular format for phantom and in-vivo maps (available at https://osf.io/5n3cu). Vendor-neutral and vendor-native phantom

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measurement performances were compared against the reference (Fig. 4b,c) and percent deviations from the ground truth were reported (Fig. 4d).

Kernel density estimates of the T1, MTR and MTsat distributions in WM and GM were visualized as ridgeline plots for one participant (Fig. 5d-i). Before the statistical comparisons in WM, the outliers were removed from the distributions. The non-outlier range was 0 to 3s for T1, 35 to 70% for MTR and 1 to 8 for MTsat. Filtered distributions were then randomly sampled to obtain an equal number of WM voxels (N = 37,000) for a balanced comparison.

Percentile bootstrap based shift function analysis[50] was performed to compare dependent measurements of T1, MTR and MTsat in WM (N=37,000) between different systems (G1-vs-S1, G1-vs-S2 and S1-vs-S2) for VENUS and for the vendor-native implementations. Deciles of the distributions were computed using a Harrell-Davis quantile estimator[51]. The decile differences were calculated using 250 bootstrap samples to characterize differences at any location of the distributions (Fig. 6a). For convenience, we annotated the 5th decile (median) with the respective percent difference (Fig. 6b-d). To characterize the difference between scanners across the participants, the shift function was extended to a hierarchical design (Fig. 7a). Similarly, percent T1, MTR and MTsat differences between scanners at the median deciles were annotated per subject, and the average percent deviations were reported (Fig. 7b-d). The reader is welcome to reproduce these figures online, where necessary changes can be made to visualize the high-density intervals of the decile differences at https://github.com/qMRLab/VENUS.

Finally, quantitative measurement discrepancies of vendor-native and VENUS implementations between different vendors were compared using Wilcoxon signed rank test. The comparison was performed on the G1-vs-S1 and G1-vs-S2 percent absolute differences of T1, MTR and MTsat in white matter between vendor-native and vendor-neutral implementations. The level of significance was set at $p = 0.05$.

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Results

The contrast characteristics of VENUS and vendor-native T1w phantom images are qualitatively comparable (Fig. 3h-m). In addition, VENUS PSNR values are on a par with those of vendor-native T1w and PDw images (Fig. 3a). The resolution markers are discernible in the vendor-neutral images (Fig. 3b-d) with a slightly lower horizontal resolution compared to the $S1\text{-}2_{NATIVE}$ (Fig. 3f,g). On the other hand, the insert pattern resolution of $G1_{NATIVE}$ (Fig. 3e) appears lower than that of $G1_{VENUS}$ (Fig. 3b).

Overall, the vendor-neutral implementation reduces inter-vendor variability and brings T1 estimations closer to the ground truth of the phantom, particularly for the targeted physiological interval from 0.7 to 1.9s (Fig. 4b). On the other hand, T1 deviations ($\Delta T1$) calculated by percent error indicate that $G1_{NATIVE}$ and $S2_{NATIVE}$ exhibit a persistent overestimation trend, with $S1_{NATIVE}$ showing a relatively better accuracy (Fig. 4c). Within the same interval, the highest deviation is observed for $G1_{NATIVE}$, where $\Delta T1$ ranges from 9.7 to 30.4%. For R4-6, $G1_{NATIVE}$ and $G1_{VENUS}$ T1 measurements straddle the reference, where $G1_{VENUS}$ shows 5.1-13.8% underestimation and the $G1_{NATIVE}$ overestimation remains within the 3.4-10.5% interval (Fig. 4c). For lower T1 reference values (T1 < 170ms), all measurements indicate higher deviations, with $S1\text{-}2_{NATIVE}$ performing better than $S1\text{-}2_{VENUS}$.

When the measured T1 values are averaged over S1-2 ($\bar{S}$), the differences between $G1_{NATIVE}$ and $\bar{S}_{NATIVE}$ are 8, 11, 12.5 and 19.4%, whereas the differences between $G1_{VENUS}$ and $\bar{S}_{VENUS}$ are 5, 2, 2 and 0.2% for R7-10, respectively (Fig. 4d). This reduction in between-vendor differences brought by VENUS is coupled with an improvement in accuracy. When averaged according to the implementation type, average VENUS deviation ($\overline{\Delta T1}_{VENUS}$) falls within the 0.2 - 4% range and $\overline{\Delta T1}_{NATIVE}$ ranges from 7 to 11%. Even though $G1_{NATIVE}$ has the dominant contribution to the higher $\overline{\Delta T1}_{NATIVE}$ values, Fig. 4d shows that $\bar{S}_{VENUS}$ is closer to the reference than $\bar{S}_{NATIVE}$ for most of the R7-10 ($\Delta T1$ of 7.6, 3.5, 5.4, 0.7% and 3.2, 0.9, 2, 1.3% for $\bar{S}_{NATIVE}$ and $\bar{S}_{VENUS}$, respectively). As a result, VENUS reduces between-vendor differences with an overall accuracy improvement.

Figure 5 shows in vivo T1, MTR and MTsat maps from a single participant (P3). While most of the improvements are evident from the maps (5a - 5c), the ridgeline plots (5d – 5i) make it easier to appreciate the VENUS vs vendor-native distribution differences in the GM and WM per metric.

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Consistent with the higher myelin content in WM, T1 values are lower in WM (around 1.1 ∓ 0.2s, Fig. 5d), whereas MTR and MTsat values are higher (around 50 ∓ 8% and 3.8 ∓ 0.9 a.u., Fig. 5 e,f) in comparison to those in GM (1.9 ∓ 0.4s, 40 ∓ 2% and 1.8 ∓ 0.5, for T1, MTR and MTsat, respectively, Fig. 5g-i). The general trend observed in the images is captured by ridgeline plots, showing better agreement between VENUS distributions of G1, S1 and S2. This is further supported by the between-scanner coefficient of variation (CoV) per metric (Table 2), showing that VENUS reduces the CoV from 16.5, 10.1 and 12.5% to 6.1, 4.1 and 4.1% for T1, MTR and MTsat, respectively. This indicates a sizable decrease in between-scanner variability using VENUS compared with vendor-native measurements and the trend is consistent across participants.

Going from vendor-native (top rows, blue panels) to VENUS (bottom rows, red panels), Fig. 6b-d indicates a decrease in T1, MTR and MTsat WM differences between scanners from different vendors (G1-vs-S1 and G1-vs-S2) for P3, without exception and throughout the deciles. One can also appreciate the changes in shift function shapes. For example, the shift function for $G1_{NATIVE}$ vs $S2_{NATIVE}$ MTsat comparison in Fig. 6d shows a positive linear trend, indicating that WM voxels with higher MTsat values tend to show a higher between-vendor difference. On the other hand, the $G1_{VENUS}$ vs $S2_{VENUS}$ MTsat shift function appears flatter, describing a more uniform (and reduced) bias throughout the WM distribution. As for within-vendor comparisons (S1-vs-S2) of the same participant, VENUS reduces difference scores for T1 and MTsat by 5.8 and 7.8% while increasing that for MTR by 5.3% (Fig. 6).

Figure 7 expands on Figure 6 for multiple participants by overlaying individual shift functions (shades of pink) and illustrating the across-participants trend using group shift functions that are red for VENUS and blue for vendor-native differences (Fig. 7a). Overall, VENUS G1-vs-S1 and G1-vs-S2 differences are on the order of 2.3 to 7.9%, whereas the vendor-native variations start from 13.8% and extends up to 25.6%, averaged across participants. The reduction in between-vendor differences achieved by VENUS is significant after correction for multiple comparisons for all maps (p=0.015). Another general observation is that individual shift function shapes are mostly consistent across participants, indicating that the inter-scanner differences between the VENUS and vendor-native implementations are not modified by anatomical differences. However, the magnitude of the difference is participant-specific. For example, P3 shows the highest $G1_{NATIVE}$ vs $S1_{NATIVE}$ T1 difference of 31.2%, which is followed by 20.9 and 14.2% for P2 and P1,

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respectively (Fig. 7b). Finally, within-vendor effect of VENUS remains on the lower side with all participants considered, reducing the S1-vs-S2 difference by 3.2 and 2.0% for T1 and MTsat while increasing that for MTR by 3.7%.

Discussion

In this study, we developed and deployed a vendor-neutral qMRI protocol (VENUS) for T1, MTR and MTsat mapping on three 3T commercial scanners by two vendors. Our findings confirm the hypothesis that vendor-neutral sequences decrease inter-vendor variability of T1, MTR and MTsat measurements. This key improvement addresses *problem 1*, as stated in the Introduction, with open-source pulse sequence descriptions. The developed sequence can be run on most GE and Siemens scanners through RTHawk software and an additional UUI that allows users to prescribe customized file naming entities for exporting reconstructed images in the BIDS[43,44] and k-space data in the ISMRM-RD format[42]. Conforming with community data standards, providing a user-friendly solution with a simplified vendor-neutral deployment, this work offers a complete solution for *problem 2,* and shows a way forward for the standardization of qMRI.

Developing an end-to-end qMRI workflow

First, we created a vendor-native qMRI protocol that is unified across vendors to the greatest extent possible, by keeping contrast, timing, and acquisition geometry identical (Table 1). However, other vendor-native implementation details such as RF spoiling, MT and excitation pulse characteristics were different, as it is commonly the case in multicenter studies[14,38]. Trying to address these issues is difficult with a vendor-native sequence given that the implementations of commercial stock sequences commonly used for qMRI are not open (*problem 1)*. One candidate solution for this problem is modifying sequences on the vendor's proprietary development environment to equalize implementations as much as possible, which has been shown to improve reproducibility to some extent[21]. However, this requires familiarity with multiple sequence development environments and still may fall short in unifying all the aspects on-site. Not only is this approach impractical for the developers, but it is also not a user-friendly solution for clinical use. As we mention in the context of *problem 2,* reproducibility solutions unifying inter-vendor implementations become more favorable if they are designed with clinicians' needs in mind. To that end, we aimed at providing a unified and smooth user experience by developing VENUS as an RTHawk application, which allows implementation details to be shared publicly starting at the pulse sequence level.

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Second, we built from scratch a vendor-neutral sequence that was developed and tested on a single site and then ported to two more scanners from different vendors. In doing so, we adapted a system that is primarily geared toward real-time imaging (RTHawk) to perform quantitative MRI measurements. For example, absolute gradient limits have been allowed to achieve higher spoiling gradient moments and string-valued customized metadata injection has been enabled to follow community data standards[42-44].

Third, we created a fully transparent, container-mediated and data-driven workflow[52,53] that automates the processing and reduces variability introduced by the operators. By design, the workflow operates according to the BIDS qMRI standard[44] for picking up all the necessary data and metadata, and generates outputs following a consistent derivative hierarchy. Moreover, the raw data is exported in the ISMRM-RD format by our vendor-neutral sequence, allowing the use of community developed reconstruction tools by simply adding another container at the beginning of our modular workflow. We envision that using open-source reconstruction tools would be highly favourable for vendor-neutral sequences employing under-sampled k-space with complex trajectories to guarantee reproducibility[54-57].

Reducing inter-vendor variability

Stock sequences are optimized for reliable clinical imaging. These optimizations do not necessarily serve for accuracy when the sequences are used for qMRI experiments. For example, the phase increment values of S1-2$_{\text{NATIVE}}$ sequences (Table 1) are hardcoded to maximize in-vivo signal stability[58], not T1 accuracy in phantoms[59]. On the other hand, the phase increment of G1 has been shown to be unsuitable for T1 mapping, exhibiting severe overestimations[14]. In this study, we set the value (117°) suggested for T1 accuracy[14] while unifying all other aspects of the vendor-neutral acquisition between scanners. The results from the phantom analysis clearly demonstrate that VENUS achieves higher accuracy and a notable reduction in inter-vendor variability compared to its vendor-native counterparts (Fig. 4).

In the absence of an in-vivo ground-truth T1 map (from inversion recovery), we only looked at the agreement between the three implementations and explored whether VENUS brought the T1 values closer across vendors when compared to the vendor-native sequences. Visually (Fig. 5a), the reduction in T1 variability can be appreciated for VENUS within the dynamic range of T1 adjusted for WM/GM. As supported by the ridgeline plots (Fig. 5d,g), the G1$_{\text{NATIVE}}$ T1 distribution

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is globally shifted towards higher values compared to S1-2$_{NATIVE}$, and their central tendency differs. As observed in the phantom, G1$_{VENUS}$ alleviates this discrepancy, shifting the T1 distribution closer to those of S1-2$_{VENUS}$. Interestingly, the WM T1 distributions appear more unimodal on G1 compared to S1-2 (both for VENUS and vendor-native), with a more pronounced bimodal appearance for S1-2$_{VENUS}$. A plausible explanation for that are vendor and implementation specific differences due to B1+ field inhomogeneity. Nevertheless, the VENUS shift functions for G1-vs-S1 and G1-vs-S2 comparisons are flatter than the vendor-native shift functions (Fig. 6b), indicating that the inter-vendor WM T1 statistical distribution characteristics are more similar using VENUS.

Table 2 indicates that reduction in inter-vendor variability is not limited to T1 but persists for all the metrics across all participants. The inter-vendor variability in MTR and MTsat is relatively easier to appreciate visually (Fig. 5b,c). The three MTR and MTsat maps from VENUS are in better agreement, and this is most likely because our unified implementation compensated for the MT saturation pulse differences (Table 1).

Reducing variability matters as much as which tools we use to assess it. Shift functions[50] take the comparison beyond differences in point estimates of centrality and relative spread (CoV) to a robust characterization of differences on the absolute scale of the measurement. This makes the shift function analysis (Fig. 6-7) more informative than CoV (Table 2) by characterizing how distributions differ for P3. For example, Table 2 shows that VENUS reduces CoV from 12.1 to 4.1% for MTsat. Figure 6d explains that most of that reduction is achieved by decreasing the absolute G1-vs-S2 MTsat difference from 1.1 to 0.1 (a.u.), corresponding to a reduction of the inter-vendor difference from 25.7% to 3.2%. In addition, Fig. 6d indicates that higher deciles benefit from the G1-vs-S2 variability reduction more compared to the lower deciles, yielding a flatter shift function for VENUS. This suggests that VENUS not only brings averaged MTsat values closer, but also matches their distribution shape (Fig. 5f).

Implications of vendor-neutrality and the importance of transparency

The most important contribution of this article is the vendor-neutral solution it provides for multi-center qMRI by significantly reducing inter-vendor variability. This issue has been hampering the standardization of qMRI methods for multi-center clinical trials[60], validation[61,62], establishing protocols[17], applied neuroimaging studies[63], determining the range of parameters in pathology[64,65]

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and in health[16,38], scanner upgrades[49] and even for phantom studies[12,13]. By reducing such variabilities, the VENUS approach can bring qMRI closer to teasing out the true biological variability in quantifying in-vivo tissue microstructure[66].

We recognize that part of the RTHawk workflow is proprietary. Hence, we emphasize the importance of the transparency to inter-vendor reproducibility at the level of sequence definitions. RTHawk allows sharing open-source sequences (https://github.com/qMRLab/mt_sat). Note that neither RTHawk nor open-source solutions can access under the hood of vendor-specific drivers to guarantee that open-source sequences are executed according to the published code. To achieve such open-execution[67], vendor-neutral solutions should be coupled with open-hardware[68]. Although RTHawk's pulse sequence and data management servers give more flexibility to the scanner operation at multiple levels of the workflow (e.g., UUI, customized raw data stream, asynchronous real-time updates to sequences, standalone workstation etc.), the conversion of the open-source sequence descriptions to vendor-specific hardware instructions is not transparent. We argue that this is a reasonable trade-off as it peels another layer from a vendor-specific ecosystem, and it does not sacrifice the transparency of sources relevant to a pulse sequence description. The accuracy and reliability of the parameter estimation depend on these descriptions; therefore, for qMRI to work we need to be able to access, modify, and share the methods[69]. Fortunately, the VENUS approach to qMRI is not framework-exclusive and satisfies this key requirement.

Namely, using community developed tools such as Pulseq, GammaStar, SequenceTree, ODIN or TOPPE, interoperable qMRI applications can be developed. A critical step to achieve this is effective communication between method developers to foster compatibility between frameworks. This is nicely exemplified by GammaStar and JEMRIS, as both applications can export Pulseq descriptions. Enabling a similar feature by developing a SpinBench plugin is among our future goals. To facilitate discussions on this topic with vendor-neutral framework developers, we created a forum page on the code repository of this article (https://github.com/qMRLab/VENUS).

Limitations and future directions

The RF transmission systems were different between all the scanners used for data collection. This is indeed a likely cause of variability of T1 and MTsat maps. Therefore, another obvious limitation of this study is the lack of B1+ mapping. Unfortunately, a vendor-native B1+ mapping sequence was not available on G1, and it is also well-known that discrepancies between vendor-native B1+

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mapping contribute to between-scanner bias in T1 mapping[38]. As for the VENUS protocol, the current version of RTHawk did not permit the long gradient durations (e.g., 80ms) needed by AFI implementation to achieve accurate B1+ mapping[70]. Therefore, further investigation is needed to compare vendor-neutral B1+ maps across vendors for isolating the specific contribution of transmit field inhomogeneity.

Another critical factor affecting the accuracy is the calculation of a global RF scaling factor. Vendor-native systems set the transmit gain using their own prescan routine, which may lead to a systematic bias in quantitative mapping. In this work, we implemented prescan for G1 and S1-2 as described by[13] and configured RTHawk to use the same calibration measurements. Nevertheless, it is possible to make this step vendor-neutral as well. For future work, we plan to develop a double-angle VENUS prescan using the same excitation pulses as the qMRI sequences that follow, to determine a global RF scaling factor. Coupled with the use of anatomy-mimicking quantitative MRI phantoms[71], this would offer qMRI-ready adaptive prescan routines and help investigate the effect of standardizing calibration measurements on multicenter accuracy and agreement.

We made the details of the RTHawk reconstruction pipeline publicly available. However, the raw data from the vendor-native acquisitions were not available. Open-source reconstruction tools[54-56] are an important asset to investigate the potential effect of reconstruction pipeline differences on image characteristics, such as the differences between resolution insert patterns observed in Fig. 3b-g. Therefore, future work will enable raw data export from vendor-native systems and add a containerized reconstruction node to the qMRFLow[53] pipeline for investigating potential sources of reconstruction variability.

Finally, the study of measurement stability using VENUS could benefit from recruiting more participants and including more imaging sites. Although the inter-vendor pattern observed in our limited cohort is consistent across 3 scanners, within-vendor (S1-vs-S2) results from vendor-native implementations are more consistent and comparable to VENUS (Fig. 7). Nevertheless, more data is needed for a thorough characterization of subject specific within-vendor effects. Our future study will deploy VENUS on more GE and Siemens sites and recruit more participants to investigate the variability problem from different perspectives, including system upgrades and WM pathology.

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Conclusion

In this article we have demonstrated that vendor-neutral sequences and transparent workflows reduce inter-vendor variability in quantitative MRI. Additionally, these workflows can be deployed on an FDA-approved device, which demonstrates the potential for wide clinical adoption. Quantitative MRI needs to bypass the vendor black boxes to make an impact in the clinic, and this work shows the way forward.

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Tables

Table 1 Comparison of acquisition parameters between vendor-native and vendor-neutral protocols. Parameters that are hardcoded on vendor-native systems are denoted by an asterisk (*).

	Common acquisition parameters			
FA (°) PDw/MTw/T1w	6/6/20			
MT PDw/MTw/T1w	off/on/off			
Voxel size (mm)	1x1x3			
TR (ms) PDw/MTw/T1w	32/32/18			
TE (ms)	4			
FOV (cm)	25.6			
Receiver bandwidth (kHz)	62.5			
MT frequency offset (Hz)*	1200			
Scanner ID and sequence type	**G1NATIVE**	**S1NATIVE**	**S2NATIVE**	**G1, S1-2VENUS**
Sequence name	3D SPGR	3D FLASH	3D FLASH	mt_sat (v1.1.0)
MT pulse shape*	Fermi	Gaussian	Gaussian	Fermi
MT pulse duration (ms)*	8	10	10	12
RF phase increment (°)*	115.4	50	50	117

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Table 2 Coefficient of variation (%) of vendor-neutral (VENUS) and vendor-native quantitative measurements between the scanners for each participant (P1-P3) and across participants.

Participants	**P1**		**P2**		**P3**		**Across**	
Protocol	**NATIVE**	**VENUS**	**NATIVE**	**VENUS**	**NATIVE**	**VENUS**	**NATIVE**	**VENUS**
T1	9.8	1.3	11.7	4.0	16.5	6.1	11.36	4.3
MTR	8.5	3.4	8.5	3.4	10.1	4.1	7.9	3.2
MTsat	13.6	5.9	11.9	3.4	12.1	4.1	10.7	4.2

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Figures

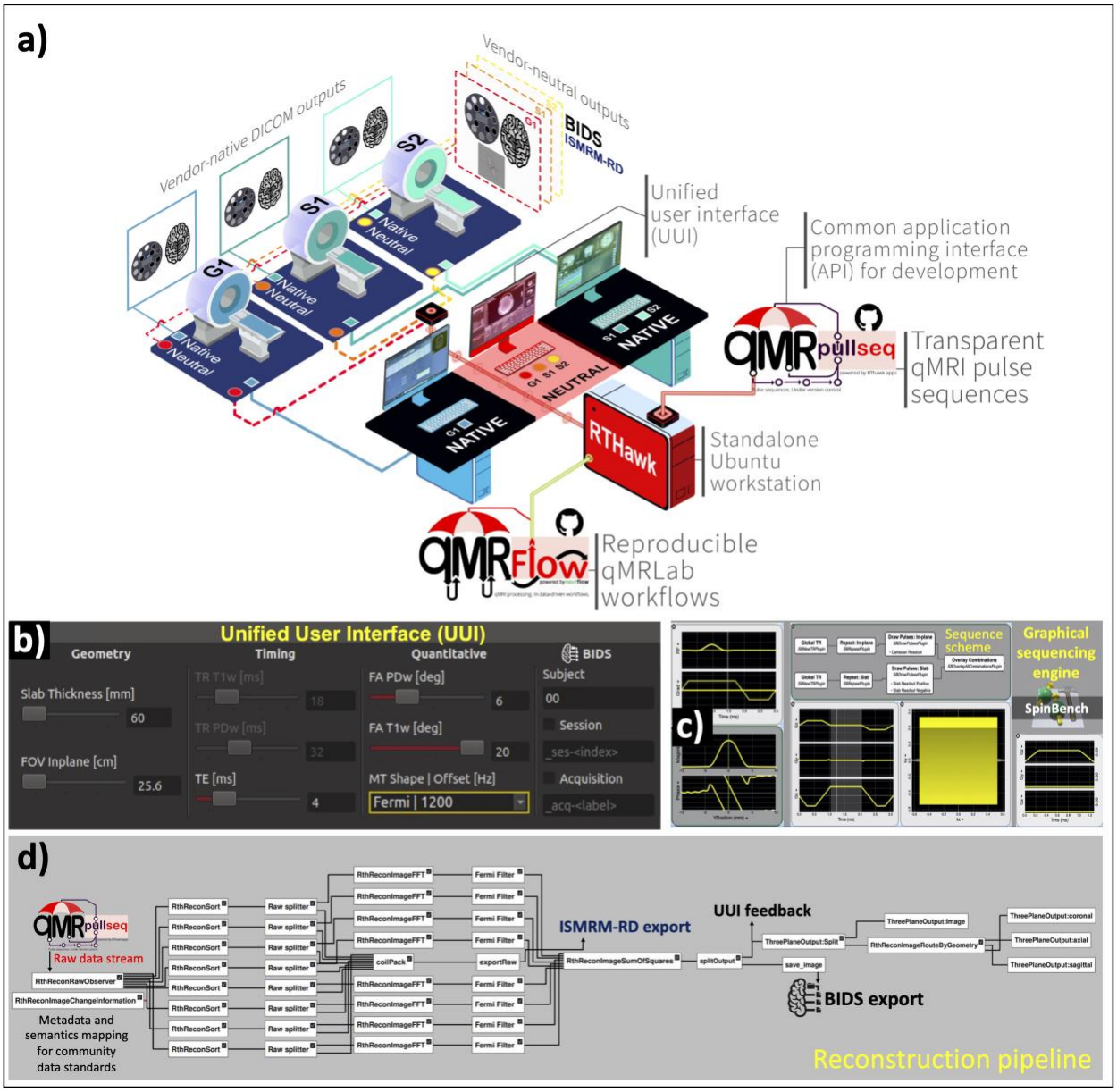

Figure 1 - Schematic illustration of the experimental design for multicenter data collection using vendor-native and vendor-neutral pulse sequences and pulse sequence development components: a) 3 MRI systems are located at 2 different sites and are labeled G1 (GE 750w), S1 (Siemens Prisma) and S2 (Siemens Skyra). Vendor "Native" systems export data in the DICOM format. The proposed vendor-agnostic "Neutral" system can export a complete set of reconstructed images in BIDS and the k-space data in ISMRM-RD format, synchronized across MRI systems. Connecting to the MRI system(s) over the local network, RTHawk (red workstation) can play

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open-source qMRI pulse sequences under version control (qMRPullseq). All the sequences are publicly available at https://github.com/qmrlab/pulse_sequences. Fully containerized qMRFlow data-driven pipelines can connect to the scanner data stream for post-processing on the RTHawk workstation (red workstation). The same pipelines can be reproduced on a local computer, supercomputing clusters or in the cloud. **b)** The acquisitions are controlled using a unified user interface (UUI), providing a consistent user experience across vendors. **c)** RF and gradient waveform stub blocks together with the readout logic are developed using SpinBench. **d)** RTHawk reconstruction pipeline nodes are illustrated for an 8-channel receiver, also indicating how raw and reconstructed data are exported and forwarded to the display tools for on-site visualization.

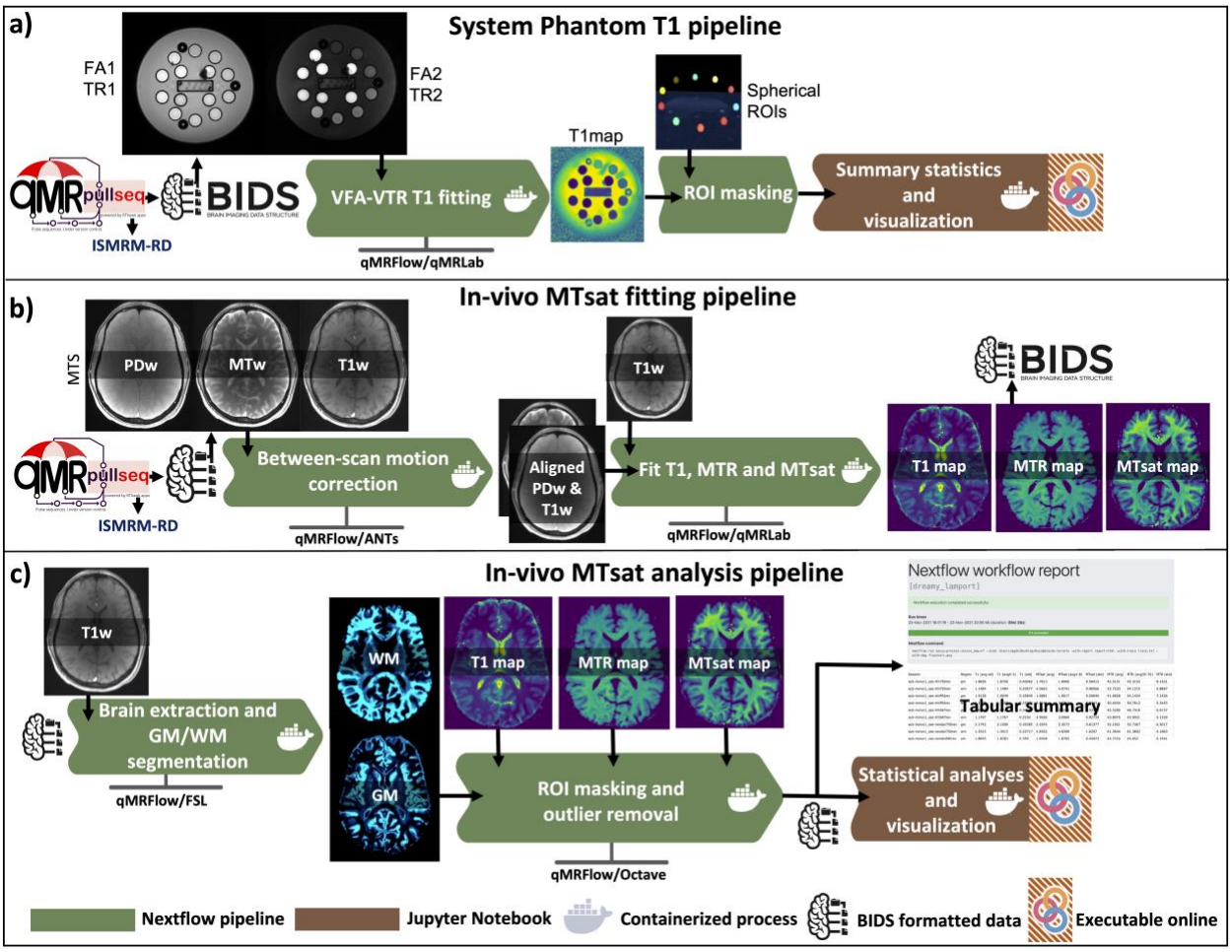

Figure 2 – Image quality assessment using the phantom: a) Peak SNR values (PSNR) from T1w and PDw phantom images are displayed for vendor-neutral (red, orange, and yellow) and vendor-native (blue, cyan, and teal) G1, S1 and S2 scans, respectively. The same color coding is

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used in the following panels. **b-g)** Coronal PDw phantom images, with an inset zoom on two 4x4 grids with 1mm spacing. The brightness of the zoomed-in insets is increased by 30% for display purposes. **h-m)** Coronal T1w phantom images showing the center of the reference T1 arrays. The fine resolution (<0.6mm) inserts located at the center of the T1 array (rectangular area) are not relevant for the present resolution level. These inserts are colored following the same convention described in a) for convenience.

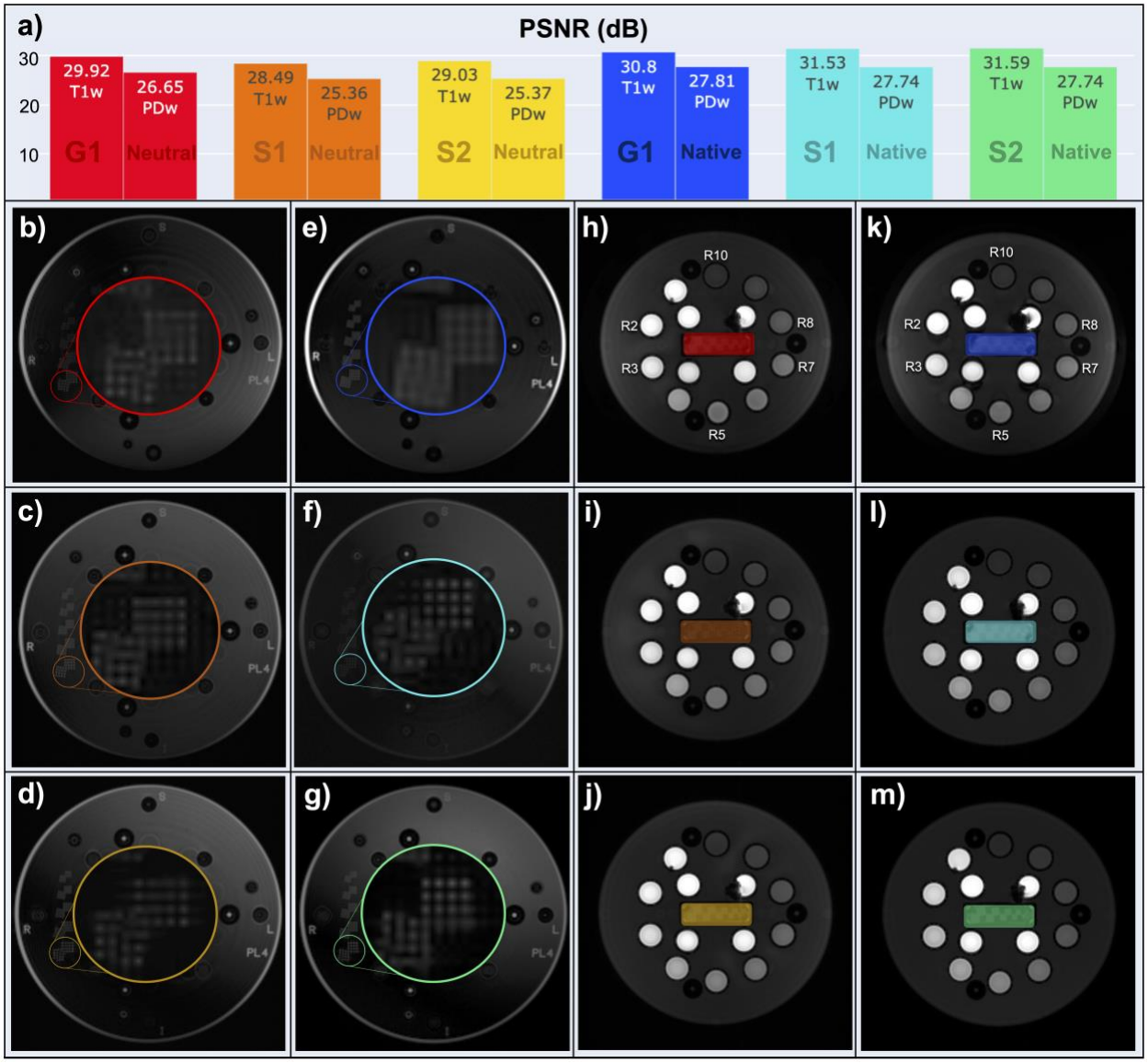

Figure 3 - Overview of the analysis workflow for phantom scans (a) and in vivo scans (b, c). File collection (MTS) and output map names (T1map, MTsat, MTRmap) follow the BIDS standard v1.6.0. **a)** Vendor-neutral and vendor-native phantom images were acquired at two flip angles and

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two repetition times. The output data are then subjected to T1 fitting using qMRLab (Docker container image: qmrlab/minimal:v2.5.0b). The resulting T1 maps are masked using manually prescribed 10 spherical ROIs (reference T1 ranging from 0.9 to 1.9s). **b)** PDw and MTw images are aligned to the T1w image to correct for between-scan motion. The aligned dataset is then subjected to MTsat and MTR fitting in qMRLab to generate T1map, MTRmap and MTsat. **c)** Brain extraction and tissue type segmentation is performed on the T1w images using FSL. Following region masking and outlier removal for each map, vector outputs are saved for statistical analysis and visualization in an online-executable Jupyter Notebook (R-Studio and Python) environment. The tabular summary and the Nextflow pipeline execution report are exported. The pipeline execution report is available at https://qmrlab.org/VENUS/qmrflow-exec-report.html.

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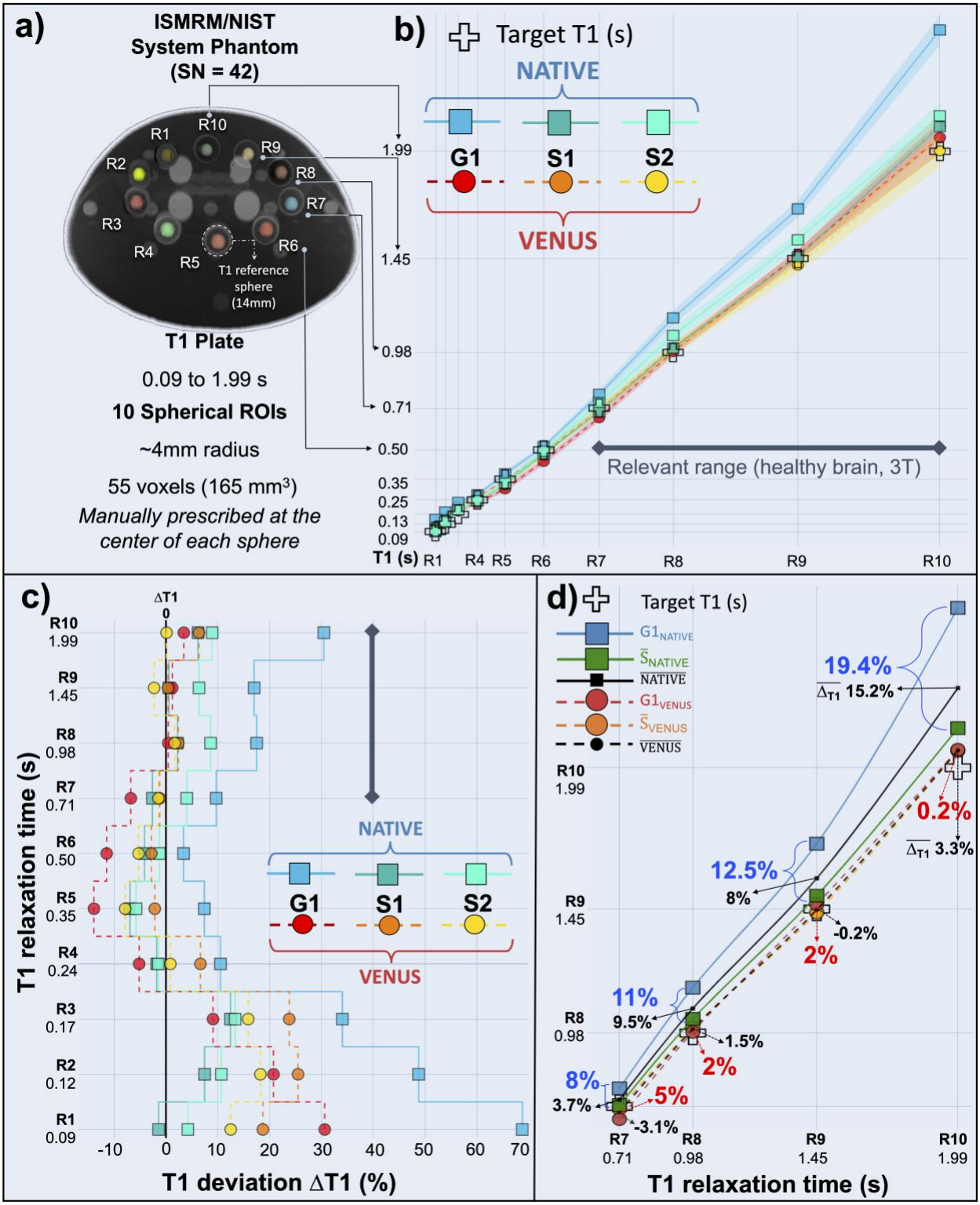

Figure 4 - Comparison of vendor-native and vendor-neutral T1 measurements in the studied range of the phantom reference values, from 0.09 to 1.99s **(a)**. T1 values from the vendor-native acquisitions are represented by solid lines and square markers in cold colors, and those from

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VENUS attain dashed lines and circle markers in hot colors. **b)** Vendor-native measurements, especially $G1_{NATIVE}$ and $S2_{NATIVE}$, overestimate T1. $G1_{VENUS}$ and $S1\text{-}2_{VENUS}$ remain closer to the reference. **c)** For VENUS, ΔT1 remains low for R7 to R10, whereas deviations reach up to 30.4% for vendor-native measurements. **d)** T1 values are averaged over S1-2 ($\bar{S}_{NATIVE}$ and $\bar{S}_{VENUS}$, green square and orange circle) and according to the acquisition type ($\overline{NATIVE}$ and $\overline{VENUS}$, black square and black circle). Inter-vendor percent differences are annotated in blue (native) and red (VENUS). Averaged percent measurement errors ($\overline{\Delta T1}$) are annotated on the plot (black arrows).

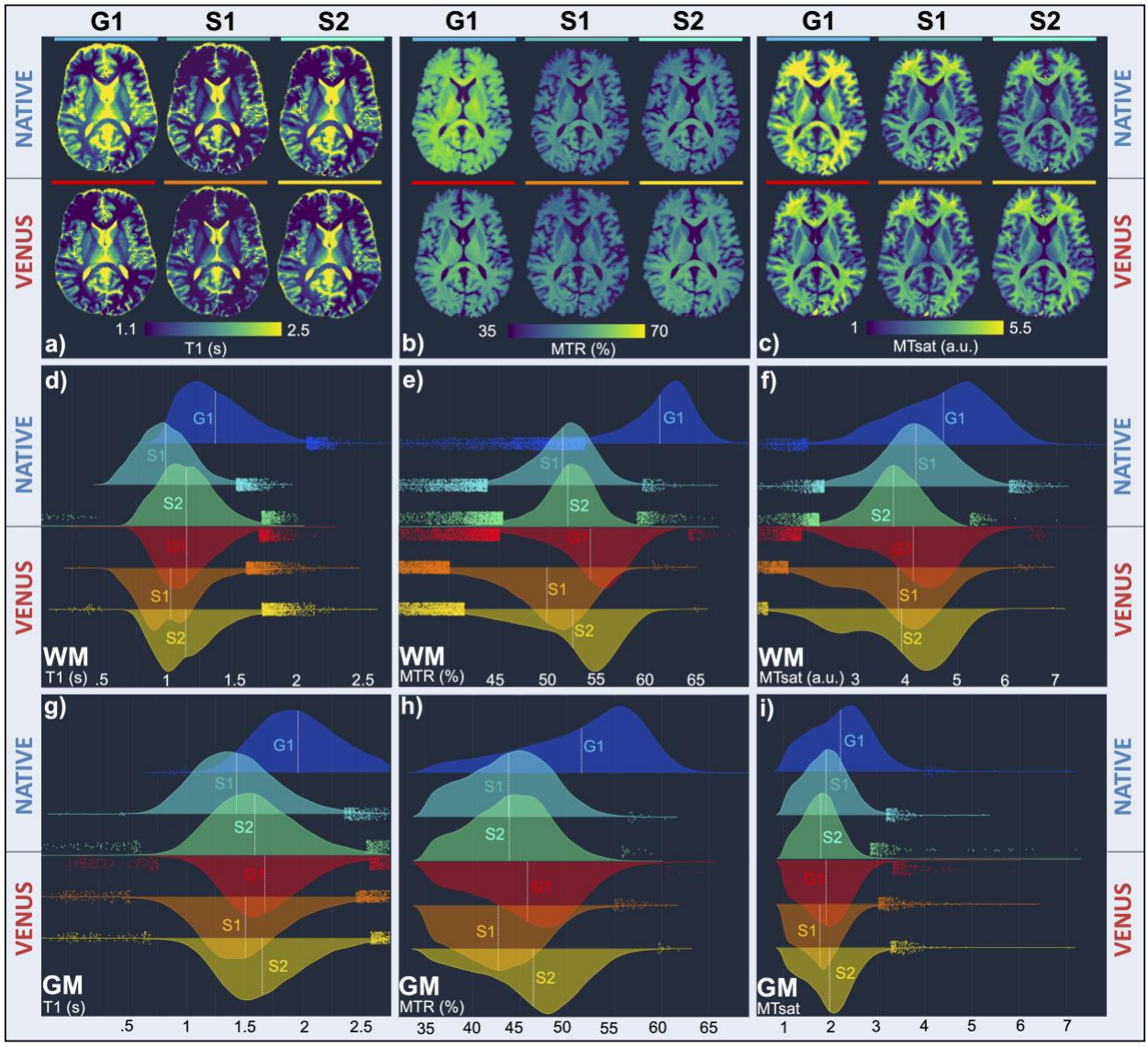

Figure 5- Vendor-native and VENUS quantitative maps from one participant are shown in one axial slice (a-c). Distributions of quantified parameters in white matter (d-f) and gray matter (g-i)

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are shown using ridgeline plots of kernel density estimations. **a-c)** Inter-vendor images (G1 vs S1 and G1 vs S2) appear more similar in VENUS (lower row) than in native (upper row). **d-f)** Distribution shapes and locations agree with visual inspection from (a), indicating closer agreement between VENUS distributions. **g-i)** Superior between-scanner agreement of VENUS persists in GM as well. Compared to WM, GM distributions are in the expected range (higher T1, lower MTR and MTsat values).

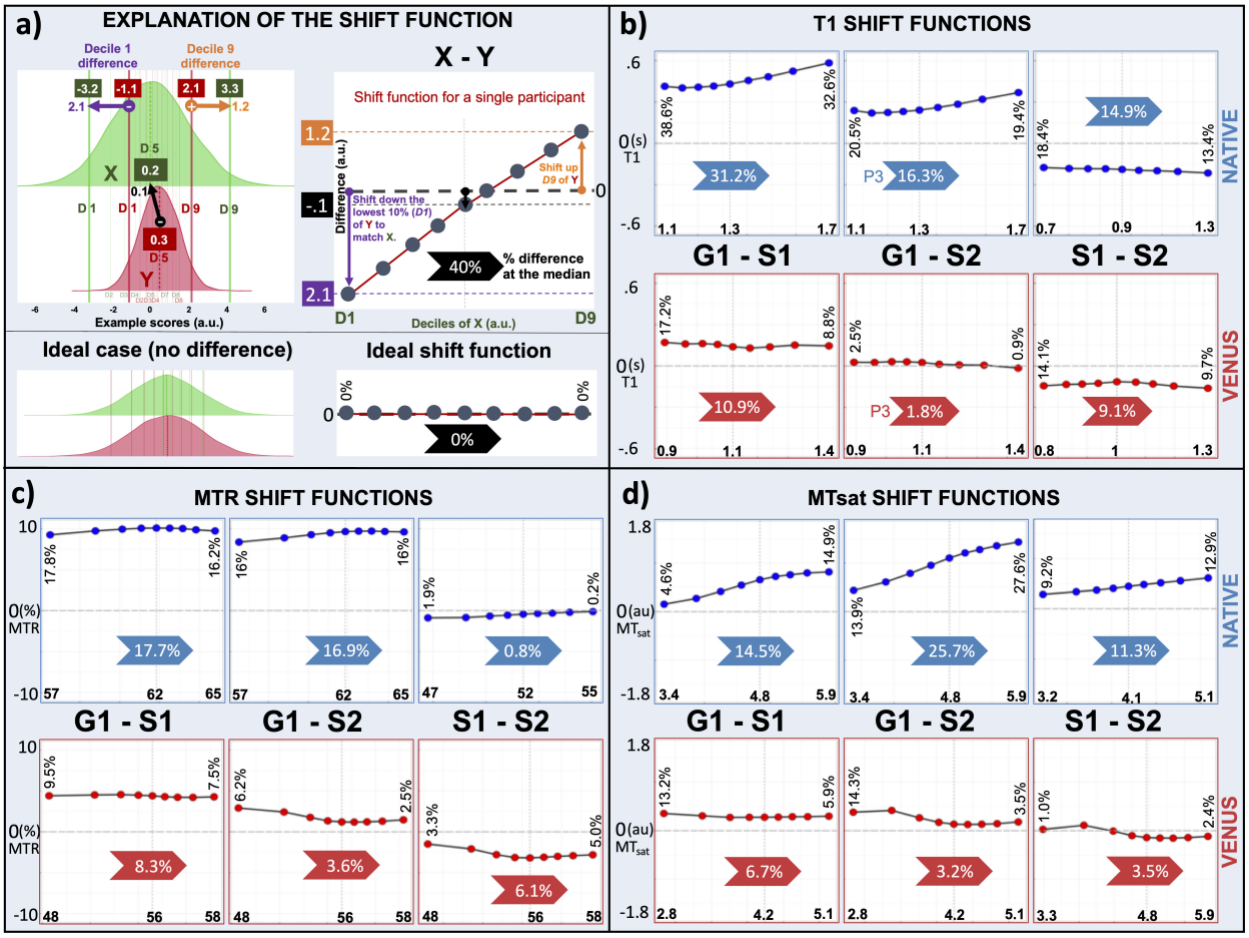

Figure 6 - Shift function analysis of T1, MTR and MTsat results from a single participant in white-matter (WM). a) Shift function analysis is a graphical tool for analyzing differences between two (dependent in this case) measurements at any location of the distributions. It shows 9 markers dividing the distribution into 10 equal chunks; hence the markers represent deciles. The shape of the curve (shift function) obtained by plotting decile differences against the first decile characterizes how distributions differ from each other. **b-d)** Here, shift function plots compare the agreement between different scanners for VENUS (bottom row) and vendor-native (top row)

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implementations in quantifying T1, MTR and MTsat. Across all the comparisons, the apparent trend is that the VENUS inter-vendor variability is lower than for the vendor-native implementations.

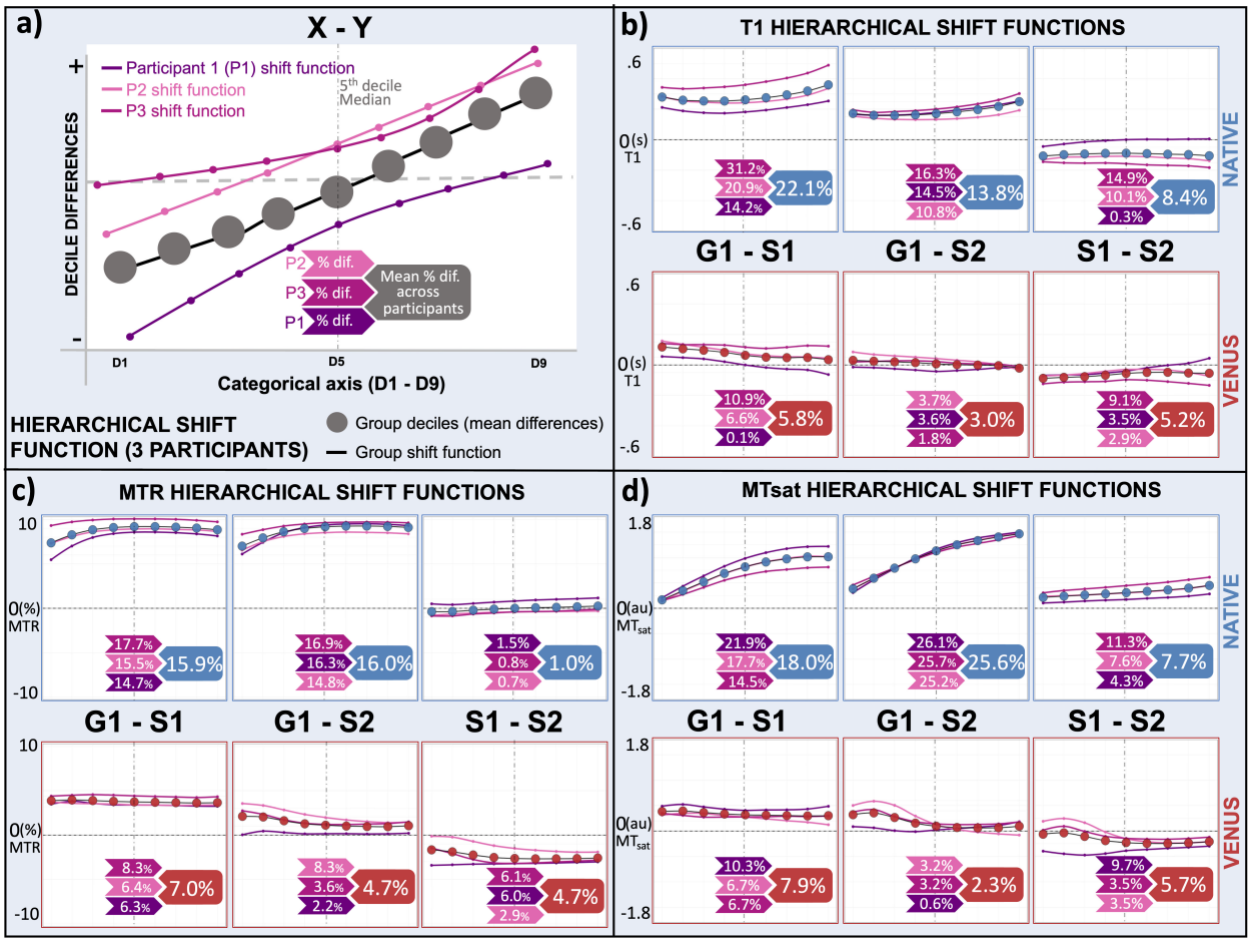

Figure 7 – Hierarchical shift function analysis of T1, MTR and MTsat results from three participants in the white-matter (WM). a) Hierarchical shift function repeats Figure 6 for all participants (shades of pink). Group deciles (red and blue markers for VENUS and vendor-native, respectively) show the average trend of inter-scanner differences across participants. **b-d)** G1-vs-S1 and G1-vs-S2 (inter-vendor) agree in VENUS better than they do in vendor-native for all quantitative maps of T1, MTR and MTsat.

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Data availability statement

All the vendor-neutral pulse sequences are publicly available as git submodules at https://github.com/qmrlab/pulse_sequences and can be run on RTHawk systems v3.0.0 and later. The RF and gradient waveforms (spv files) can be inspected and simulated using SpinBench (https://www.heartvista.ai/spinbench). As per the general design principles of fully reproducible qMRFlow pipelines, we adhered to a one-process one-container mapping for the processing of this dataset. Docker images, BIDS and ISMRM-RD compliant dataset from the current study are freely available at https://doi.org/10.17605/osf.io/5n3cu. Finally, the whole analysis and interactive version of all the figures in this article will be available and executable online at https://github.com/qmrlab/venus.

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