The Influence of Radio-Frequency Transmit Field Inhomogeneities on the Accuracy of G-ratio Weighted Imaging

Emmenegger, Tim M; David, Gergely; Ashtarayeh, Mohammad; Fritz, Francisco J; Ellerbrock, Isabel; Helms, Gunther; Balteau, Evelyne; Freund, Patrick; Mohammadi, Siawoosh

Abstract: G-ratio weighted imaging is a non-invasive, in-vivo MRI-based technique that aims at estimating an aggregated measure of relative myelination of axons across the entire brain white matter. The MR g-ratio and its constituents (axonal and myelin volume fraction) are more specific to the tissue microstructure than conventional MRI metrics targeting either the myelin or axonal compartment. To calculate the MR g-ratio, an MRI-based myelin-mapping technique is combined with an axon-sensitive MR technique (such as diffusion MRI). Correction for radio-frequency transmit (B1+) field inhomogeneities is crucial for myelin mapping techniques such as magnetization transfer saturation. Here we assessed the effect of B1+ correction on g-ratio weighted imaging. To this end, the B1+ field was measured and the B1+ corrected MR g-ratio was used as the reference in a Bland-Altman analysis. We found a substantial bias (-89%) and error (37%) relative to the dynamic range of g-ratio values in the white matter if the B1+ correction was not applied. Moreover, we tested the efficiency of a data-driven B1+ correction approach that was applied retrospectively without additional reference measurements. We found that it reduced the bias and error in the MR g-ratio by a factor of three. The data-driven correction is readily available in the open-source hMRI toolbox (www.hmri.info) which is embedded in the statistical parameter mapping (SPM) framework.

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Keywords: myelin volume fraction, axon volume fraction, radio-frequency transmit field inhomogeneities, B1+ correction, multi-parameter mapping, diffusion MRI, magnetization transfer saturation, MR g-ratio

INTRODUCTION

The g-ratio [i.e., the ratio between the inner (r) and outer (R) radius of an axon with myelin sheath (g-ratio = r/R)] of a given axon quantifies the degree of relative myelination, ranging between 0 (no axon) and 1 (no myelin). The g-ratio captures both axonal and myelin damage by incorporating axonal and myelin volumes in one metric, making it potentially more specific to tissue integrity than...
In this study, we investigate the effect of B1+ inhomogeneities on MR g-ratio maps when omitting the B1+ correction. As a reference, we use the B1+ corrected MR g-ratio from a dataset of healthy controls. We compare the reference MR g-ratio values against (i) values obtained without B1+ correction and (ii) values obtained with B1+ correction using the data-driven UNICORT approach.

**MATERIALS AND METHODS**

**Subjects**

This study included 25 healthy control subjects (12 females, age (mean ± standard deviation) of 25.4 ± 2.4 years). They were recruited at the University Medical Centre Hamburg-Eppendorf and screened for neurological or psychiatric illness. The study was in agreement with the Declaration of Helsinki and was approved by the local ethics committee (Ärztekammer Hamburg #PV5141).

**Data Acquisition**

Each subject was scanned twice within 1 week in a whole-body 3T Tim TRIO MR scanner (Siemens Healthcare, Erlangen, Germany) using the body RF-coil for transmission and a 32-channel radiofrequency (RF) head coil for signal reception, respectively. The MR acquisition on both scan days included a multi-parameter mapping (MPM) (Weiskopf et al., 2013; Callaghan et al., 2015b) and a diffusion-weighted imaging (DWI) protocol. The MPM protocol consists of three differently weighted 3D-multi-echo spoiled gradient echo sequences (Siemens FLASH). The echo train length and flip angle for the proton density (PD) weighted, T1-weighted, and magnetization transfer (MT) weighted sequences were 8/6, 8/21, and 6/6\(^{\circ}\), respectively. The MT-weighted sequence had a Gaussian RF pulse (2 kHz off resonance with 4 ms duration and a nominal flip angle of 220\(^{\circ}\)). All other sequence parameters were the same for the three sequences: repetition time (TR) 25 ms, echo spacing, resolution 0.8 mm isotropic; field of view (FoV) 166 × 224 × 256 mm\(^3\), readout bandwidth 488 Hz/pixel, partially parallel imaging using the GRAPPA algorithm was employed in each phase-encoded direction (anterior-posterior and right-left) with 40 reference lines and a speed up factor of two, total acquisition time: ~25 min. The B1+ field reference map was acquired using the three-dimensional echo-planar imaging (3D EPI) method, including field maps for distortion correction (Lutti et al., 2010).

The DWI sequence was a twice-refocused single-shot spin-echo EPI scheme (Reese et al., 2003), consisting of 12 non-diffusion-weighted images (b0 images), equidistantly distributed across the diffusion weighted images. The diffusion-weighted images were acquired at two b-values (1000 and 2000 \(\frac{mm^2}{s}\)), sampled along 60 unique diffusion-gradient directions within each shell. The entire protocol was repeated with identical parameters but with reversed phase encoding direction (anterior-posterior) to correct for susceptibility-related image distortions (blip-up, blip-down correction). In total, 264 images were acquired per subject (120 diffusion-weighted images, 12 b\(_0\) images, each acquired twice). Other acquisition parameters were:

| Sequence     | TR (ms) | TE (ms) | b-value (mm\(^2\)/s) | Echo Train Length | Flip Angle (°) |
|--------------|---------|---------|-----------------------|-------------------|----------------|
| PD           | 8       | 6       | 1000                  | 8                 | 220            |
| T1           | 8       | 21      | 8                     | 8                 |                |
| MT           | 6       | 6       | 2000                  | 6                 |                |

**Correction in G-ratio Imaging**

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86 slices with no gap, TR = 7.1 s, TE = 122 ms, an isotropic voxel size of (1.6 mm)$^3$, FoV $= 224 \times 224 \times 138$ mm$^3$, 7/8 partial Fourier imaging in phase encoding direction, readout bandwidth. To accelerate the data acquisition, GRAPPA (in-plane acceleration with factor two) and simultaneous multi-slice acquisitions (“multiband,” slice acceleration factor two) (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013) were used as described in Setsompop et al. (2012). The image reconstruction algorithm was provided by the University of Minnesota Centre for Magnetic Resonance Research. The total acquisition time was $\sim$37 min.

Data Processing

MT$_{sat}$ maps were generated in the SPM-based hMRI toolbox (Tabelow et al., 2019). Note that the hMRI toolbox also generates additional maps of longitudinal ($R_1$) and effective transverse relaxation rates ($R_2^*$) and PD. Three MT$_{sat}$ maps were generated: (i) MT$_{sat}^{NO}$ maps, without B$_1^+$ correction; (ii) MT$_{sat}^{B1}$ map, using the reference B$_1^+$ field map for correction (Lutti et al., 2010); and (iii) MT$_{sat}^{UN}$ maps, using the data-driven UNICORT approach for B$_1^+$ estimation (Weiskopf et al., 2011; see Supplementary Figure 2). UNICORT is a probabilistic framework for unified-segmentation based correction of R$_1$ maps for B$_1^+$ inhomogeneities. The framework incorporates a physically informed generative model of smooth B$_1^+$ inhomogeneities and their multiplicative effect on R$_1$ estimates (Weiskopf et al., 2011). Parameters used in UNICORT such as the smoothness and regularization were optimized for R$_1$ B$_1^+$ correction in a 3T scanner (i.e., Tim Trio scanner—Weiskopf et al., 2011).

For B$_1^+$ correction, we used the following heuristic correction factor as detailed in Helms (2015), and Helms et al. (2021):

$$MT_{sat}^{Corr} = MT_{sat}^{NO} \frac{1 - C}{1 - CB_1^+} \quad (1)$$

where $C$ has been calibrated to be 0.4 for the MT pulse used in this paper. B$_1^+$ can be either measured ($MT_{sat}^{Corr} = MT_{sat}^{B1}$) or estimated with the UNICORT approach ($MT_{sat}^{Corr} = MT_{sat}^{UN}$).

The DWI data were processed based on the pipeline described in Ellerbrock and Mohammadi (2018) using the SPM-based ACID toolbox$.^2$ It included several artifact corrections such as Rician signal bias correction (i.e., denoising) (André et al., 2014), correction for eddy current and motion artifacts (Mohammadi et al., 2010, 2014), and correction for image distortions due to susceptibility artifact using reversed phase encoding (Ruthotto et al., 2012, 2013; Macdonald and Ruthotto, 2018). The corrected images were fitted with the NODDI signal model (Zhang et al., 2012) to estimate the intra-cellular volume fraction ($\nu_{icvf}$), the isotropic volume fraction ($\nu_{iso}$), and the orientation dispersion index (ODI) in each voxel.

Spatial Alignment

Co-registration

The voxel-wise arithmetic between the MT$_{sat}$ and $\nu_{icvf}$ maps, necessary for MR g-ratio computation, requires an accurate spatial alignment between the two maps (Mohammadi et al., 2015). To this end, we created two white matter (WM) tissue probability maps (TPMs) based on the ODI and MT$_{sat}$ maps, respectively (Figure 1). To reduce the influence of contrast-specific artifacts (e.g., due to subject motion) on the registration quality, the WM TPM of the ODI map was co-registered to the WM TPM of the MT$_{sat}^{B1}$ map using rigid-body registration (spm_coreg algorithm, SPM toolbox). The estimated transformation parameters were applied to all other NODDI maps as well. Note that the segmentation quality of the second session was unsatisfactory for two subjects, and the R$_1^{B1}$ map (R$_1$ with B$_1^+$ inhomogeneities bias correction using the B$_1^+$ reference measurements) was used to generate the WM TPM instead. In another subject, the $\nu_{iso}$ was segmented instead of the ODI to achieve satisfactory WM segments.

Normalization

Spatial normalization was performed in four steps. First, a rough alignment of the MT$_{sat}^{B1}$ maps with the T1-weighted MNI template image was achieved using the Auto-Reorient function (hMRI toolbox) and this was applied on the NODDI maps as well. Second, both MT$_{sat}^{B1}$ maps of each subject (corresponding to two sessions) were registered to the mid-point average using the Pairwise Longitudinal Registration (SPM12). Hereby, values below zero and above 10 were excluded to improve the registration. Third, the resulting mid-point average image was normalized to the MNI space using the DARTEL-based (Ashburner, 2007) Spatial Processing module (hMRI toolbox). Fourth, a combined deformation field was generated per subject and session, combining the deformation fields from steps 2 and 3.

Computation of MVF$_{MR}$, AVF$_{MR}$ and g$_{MR}$

In this section, our approach to estimating MVF and AVF from the measured MR parameters is introduced. The MR-based MVF (MVF$_{MR}$) was assumed to be proportional to MT$_{sat}$ without intercept, following (Mohammadi and Callaghan, 2020):

$$\text{MVF}_{MR} = \alpha MT_{sat} \quad (2)$$

The proportionality constant $\alpha$ was estimated from Equation (2) in a region where the histological MVF (MVF$_{hist}$) was known. Due to the lack of own histological data, we used published histological data which contain the frequency distribution of inner-axon radius ($r$) and myelin sheath thickness (m) of 2,400 myelinated fibers in the medullary pyramids of a 71 years old human (see Table 1 in Graf von Keyserlingk and Schramm, 1984). The total volume (TV) of the sample is the sum of the total volume of myelinated axons (TAV$_{m}$), unmyelinated axons (TAV$_{u}$), myelin volume (TMV), and extracellular volume (TEV). TAV$_{m}$ was calculated as $\sum_{i=1}^{N_m} \pi r_i^2$ with $i$ indexing the $N_m$ myelinated axons only, and TMV was computed as $\sum_{i=1}^{N_m} \pi (r_i + m_i)^2 - TAV_m$. TAV$_{u}$, while not reported in Graf von Keyserlingk and Schramm (1984), was found to be

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$^2$http://www.diffusiontools.com
approximately 43% of TAV$_m$ for multiple mammals (Swadlow et al., 1980; LaMantia and Rakic, 1990; Olivares et al., 2001; Wang et al., 2008; Liewald et al., 2014). Note that the aforementioned papers typically reported the unmyelinated axons as 30% of the total volume of axons, which corresponds to 43% ($= \frac{0.3}{0.3+0.7} \cdot 100$) of TAV$_m$. EVF was estimated to be 25%, according to Lehmenkühler et al. (1993), Nicholson and Hrabìtová (2017), Tønnesen et al. (2018). Finally, MVF was calculated as

$$\text{MVF}_{\text{hist}} \approx \frac{1}{TV} \sum_{j=1}^{N} \pi \left( r_j + m_j \right)^2 - r_j^2 \quad (3)$$

with j indexing all N fibers, yielding MVF$_{\text{hist}} \approx 0.3623$. Plugging this value into Equation (2) (assuming that MVF$_{\text{MR}} \approx$ MVF$_{\text{hist}}$) along with the group-average MT$_{\text{sat}}$ within the medullary pyramids (see Figure 2 for ROI definition) yielded an $\alpha$ of 0.2496 for MT$_{\text{B1 sat}}$, 0.2414 for MT$_{\text{UN sat}}$ and 0.2884 for MT$_{\text{NO sat}}$.

The MR-based AVF (AVF$_{\text{MR}} = (1 - \text{MVF}_{\text{MR}}) \cdot \text{AWF}_{\text{MR}}$) was calculated as

$$\text{AVF}_{\text{MR}} = (1 - \alpha_{\text{MT}_{\text{sat}}}) \left( 1 - \nu_{\text{iso}} \right) \nu_{\text{cvf}} \quad (4)$$

where AWF $= (1 - \nu_{\text{iso}}) \nu_{\text{cvf}}$ is the axonal water fraction estimated from the NODDI parameters (Stikov et al., 2015) and MVF$_{\text{MR}} = \alpha_{\text{MT}_{\text{sat}}}$. The MR g-ratio was then computed according to Stikov et al. (2011, 2015)

$$g_{\text{MR}} = \sqrt{\frac{1 - \text{MVF}_{\text{MR}}}{\text{MVF}_{\text{MR}} + \text{AVF}_{\text{MR}}}} \quad (5)$$

Note that three versions of MT$_{\text{sat}}$, AVF$_{\text{MR}}$, and g$_{\text{MR}}$ were generated according to notation in section "Data Processing": (i)
Definition of White Matter Masks

As g\textsubscript{MR} and its constituents (MVFM\textsubscript{MR}, AVFM\textsubscript{MR}) are defined only in the WM, we restricted the analysis to the WM by creating binary WM masks (Mohammadi and Callaghan, 2020). WM tissue probability maps (WM-TPM) were created for each subject by segmenting AWF and MT\textsuperscript{B1\textsubscript{sat}} using the hMRI toolbox, and taking their intersection according to Mohammadi and Callaghan (2020). In two subjects, the MT\textsuperscript{B1\textsubscript{sat}} segmentation was of insufficient quality for segmentation and was replaced by the R\textsubscript{B1} map. A group-specific binary WM mask (WM\textsubscript{group}) was generated by averaging all individual WM-TPMs in the MNI space and thresholding it at 0.95.

A so-called high-SNR WM\textsubscript{group} was also defined by taking the intersection of the WM\textsubscript{group} and a binary signal-to-noise ratio (SNR) map. Hereby, the latter was used to reduce the number of voxels with unrealistically high values of V\textsubscript{ref} (V\textsubscript{ref} ≥ 0.999). In 6 of 25 subjects, an SNR map was created by dividing the mean b\textsubscript{0} image by a single noise estimate in the native space and multiplied by the square root of the number of b\textsubscript{0} images per DWI dataset (n = 12). The noise was estimated within a noise ROI outside the brain in 72 images (6 subjects, both timepoints and 6 b\textsubscript{0} images.
FIGURE 3 | Relationship between signal-to-noise ratio (SNR) and unrealistically high $\nu_{icvf}$ values—here defined as $\nu_{icvf} \geq 0.999$. (A) Sagittal, coronal, and axial view of the whole-brain SNR map (i), with a zoom-in view of the brainstem (ii). The brainstem is characterized by low SNR due to the spatial characteristics of the receive coil array (iii) and high occurrence of unrealistically high $\nu_{icvf}$ (iv), also shown as a binary mask (v). (B) Given the co-occurrence of low SNR and unrealistically high $\nu_{icvf}$, a binary SNR mask was created to exclude low-SNR voxels. To determine the optimal threshold for the SNR mask, the ratio between the number of voxels with unrealistically high $\nu_{icvf}$ and the total number of voxels within the mask were plotted against the SNR threshold. The solid dots and error bars represent the group mean and group standard deviation of the ratio, respectively. The SNR value that yielded the minimum of this ratio was considered optimal (SNR = 39, shown in red).

FIGURE 4 | Location of the ROIs used for analysis. The 21 high-SNR ROIs (listed in Table 1) are part of the JHU-ICBM-DTI-81 WM atlas (Hua et al., 2008) and are displayed here on the group-averaged normalized MTB1 image. Note that for ROI analysis, the ROIs were projected into the native space using the inverse of the combined deformation field.

each) using the ACID toolbox, with the values averaged to obtain a single noise estimate. The threshold for SNR maps to create binary SNR map was chosen such that it minimizes the ratio between the number of artifactual voxels where $\nu_{icvf} \geq 0.999$ and the total number of voxels in the SNR mask (Figure 3B), yielding a value of 39. This was motivated by the observation that unrealistically high $\nu_{icvf}$ values typically occur in low-SNR areas (Figures 3Aii,iii). This threshold selection represents a trade-off between removing unrealistic voxels while retaining as many voxels as possible.
TABLE 2 | Summary statistics of $g_{\text{MR}}^{B1}$, AVF$^{B1}_{\text{MR}}$, and MVF$^{B1}_{\text{MR}}$.

|         | $\Delta_{\text{DR}}$ | $\text{min}_{\text{ROI}}$ | $\text{max}_{\text{ROI}}$ | mean | SD  |
|---------|----------------------|--------------------------|--------------------------|------|-----|
| $g_{\text{MR}}^{B1}$ | 0.048                | 0.642                    | 0.688                    | 0.664 | 0.014 |
| AVF$^{B1}_{\text{MR}}$ | 0.076                | 0.308                    | 0.384                    | 0.337 | 0.020 |
| MVF$^{B1}_{\text{MR}}$ | 0.037                | 0.408                    | 0.445                    | 0.425 | 0.010 |

This table lists the dynamic range ($\Delta_{\text{DR}}$), lowest ($\text{min}_{\text{ROI}}$) and highest ($\text{max}_{\text{ROI}}$) ROI average value, mean value of the 21 analyzed ROI’s (mean) with its corresponding standard deviation (SD).

Region of Interest Selection
For the region of interest (ROI) analysis, the JHU-ICBM-DTI-81 WM atlas (Hua et al., 2008) was transformed into the native space using the inverse of the combined deformation field. Two sets of ROIs were defined: (i) whole-WM ROIs and (ii) high-SNR ROIs, used for the main analysis. The whole-WM ROIs included those of the JHU-ICBM-DTI-81 WM atlas that were completely in $\text{WM}_{\text{group}}$ defined in 2.6, yielding 43 ROIs (out of 48, leaving out the column and body of the fornix, the left and right cingulum part in the vicinity to the hippocampus, and the left and right uncinate fasciculus). The high-SNR ROIs included only those whole-WM ROIs that overlapped with the high-SNR $\text{WM}_{\text{group}}$ to at least 95%, yielding 21 ROIs (Figure 4 and Table 2). For the analyses, group-averaged $g_{\text{MR}}$, AVF$_{\text{MR}}$, and MVF$_{\text{MR}}$ were calculated within the $\text{WM}_{\text{group}}$. Note that averaging included both sessions of each subject for all analyses except for the analysis in section “Test-Retest Analysis of the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction.”

Test-Retest Analysis of the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction
The group-averaged $g_{\text{MR}}^{B1}$ of the first and second session were compared within the previously mentioned 21 high-SNR ROIs using Bland-Altman plots (Bland and Altman, 1986). In the Bland-Altman plots, the differences in...
The computed $\delta_i$ between the first ($g_{B1, i}^{MR}$) and second ($g_{B1, i}^{\text{retest}}$) session ($\delta^{\text{retest}}_i = (g_{B1, i}^{MR}) - (g_{B1, i}^{\text{retest}})$) were plotted against their means ($\text{mean}_i^{\text{retest}} = \frac{1}{21} \sum_{i=1}^{21} g_{B1, i}^{\text{retest}}$), where $i$ is the index of ROI $i$. Bias captures the offset ($\delta_i^{\text{retest}} = \frac{1}{21} \sum_{i=1}^{21} \delta_i^{\text{retest}}$), while error ($\epsilon_{B1} = \sqrt{\frac{1}{21} \sum_{i=1}^{21} (\delta_i^{\text{retest}} - \delta_i^{\text{retest}})^2}$) captures the variation between the first and second scan within the $i$th ROI. The computed $\delta_i^{\text{retest}}$ and $\epsilon_{B1}$ were normalized by the dynamic range ($\Delta_{DR}$) of $g_{B1}^{MR}$ within the high-SNR ROIs, defined as $\Delta_{DR} = \max_{i \in \text{ROI}} (\text{mean}_i^{\text{retest}}) - \min_{i \in \text{ROI}} (\text{mean}_i^{\text{retest}})$, yielding the relative error ($\epsilon_{DR\%}^{\text{retest}} = \frac{\epsilon_{B1}^{\text{retest}}}{\Delta_{DR}} \cdot 100$) and relative bias ($\delta_{DR\%}^{\text{retest}} = \frac{\delta_i^{\text{retest}}}{\Delta_{DR}} \cdot 100$). The same procedure was also applied to $AVF_{B1}^{MR}$ and $MVF_{B1}^{MR}$.

The distinction between bias and error is important, because while a potential bias can be retrospectively corrected, the error in the MR g-ratio method defines its sensitivity to detect differences between individuals, groups, or time points. To reliably capture these differences, the error must be significantly lower than the expected effect size.

### Influence of $B1+$ Correction in the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction

Bland-Altman analysis was used to compare $g_{B1}^{MR}$ with and without $B1+$ correction. In particular, the difference $\delta_i^{B1}$ in $g_{B1}^{MR}$ between $(g_{B1, i}^{MR})$ and second ($g_{B1, i}^{\text{retest}}$) session ($\delta^{\text{retest}}_i = (g_{B1, i}^{MR}) - (g_{B1, i}^{\text{retest}})$) were plotted against their means ($\text{mean}_i^{\text{retest}} = \frac{1}{21} \sum_{i=1}^{21} g_{B1, i}^{\text{retest}}$), where $i$ is the index of ROI $i$. Bias captures the offset ($\delta_i^{\text{retest}} = \frac{1}{21} \sum_{i=1}^{21} \delta_i^{\text{retest}}$), while error ($\epsilon_{B1} = \sqrt{\frac{1}{21} \sum_{i=1}^{21} (\delta_i^{\text{retest}} - \delta_i^{\text{retest}})^2}$) captures the variation between the first and second scan within the $i$th ROI. The computed $\delta_i^{\text{retest}}$ and $\epsilon_{B1}$ were normalized by the dynamic range ($\Delta_{DR}$) of $g_{B1}^{MR}$ within the high-SNR ROIs, defined as $\Delta_{DR} = \max_{i \in \text{ROI}} (\text{mean}_i^{\text{retest}}) - \min_{i \in \text{ROI}} (\text{mean}_i^{\text{retest}})$, yielding the relative error ($\epsilon_{DR\%}^{\text{retest}} = \frac{\epsilon_{B1}^{\text{retest}}}{\Delta_{DR}} \cdot 100$) and relative bias ($\delta_{DR\%}^{\text{retest}} = \frac{\delta_i^{\text{retest}}}{\Delta_{DR}} \cdot 100$). The same procedure was also applied to $AVF_{B1}^{MR}$ and $MVF_{B1}^{MR}$, comparing them to their respective reference method and $g_{B1}^{MR}$ between $(g_{B1, i}^{MR})$, when using no (k = NO) or UNICORT (k = UN) $B1+$ correction, and $(g_{B1, i}^{MR})$, when using no (k = NO) or UNICORT (k = UN) $B1+$ correction: $\delta_i^{B1} = (g_{B1, i}^{B1}) - (g_{B1, i}^{MR})$ was plotted against their mean: mean$_i^{B1} = \frac{1}{21} \sum_{i=1}^{21} (g_{B1, i}^{B1})$, with $i$ being the index of the 21 high-SNR ROIs. The bias and error associated with the lack of (or UNICORT) $B1+$ correction are defined as $\delta = \frac{1}{21} \sum_{i=1}^{21} \delta_i^{B1}$ and $\epsilon^{B1} = 1.96 \cdot \sqrt{\frac{1}{21} \sum_{i=1}^{21} (\delta_i^{B1} - \delta)}$, respectively.

The computed $\delta_i^{B1}$ and $\epsilon_i^{B1}$ were normalized by the dynamic range of $g_{B1}^{MR}$ within the high-SNR ROIs, yielding the relative error ($\epsilon_{DR\%}^{B1} = \frac{\epsilon_i^{B1}}{\Delta_{DR}} \cdot 100$) and relative bias ($\delta_{DR\%}^{B1} = \frac{\delta_i^{B1}}{\Delta_{DR}} \cdot 100$). The same procedure was also applied to $AVF_{B1}^{MR}$ and $MVF_{B1}^{MR}$, comparing them to their respective reference method and $g_{B1}^{MR}$.

### Table 3: Bias and error between scans, in $g_{B1}^{MR}$, $AVF_{B1}^{MR}$, and $MVF_{B1}^{MR}$

| MAP       | $\delta_{B1}^{\text{retest}}$ | $\epsilon_{B1}^{\text{retest}}$ | $\delta_{DR\%}^{\text{retest}}$ | $\epsilon_{DR\%}^{\text{retest}}$ |
|-----------|-------------------------------|----------------------------------|----------------------------------|-----------------------------------|
| $g_{B1}^{MR}$ | 0.0021                        | 0.0102                           | 4.57                             | 22.17                             |
| $AVF_{B1}^{MR}$ | 0.0006                        | 0.0156                           | 0.79                             | 20.53                             |
| $MVF_{B1}^{MR}$ | -0.0031                      | 0.0076                           | -8.38                            | 20.54                             |

List of the bias ($\delta^{\text{retest}}$) and error ($\epsilon^{\text{retest}}$) values, defined as in Figure 7, along with their relative value with respect to the dynamic range $\Delta_{DR}$: $\epsilon_{DR\%}^{\text{retest}} = \frac{\epsilon^{\text{retest}}}{\Delta_{DR}} \cdot 100$; $\delta_{DR\%}^{\text{retest}} = \frac{\delta^{\text{retest}}}{\Delta_{DR}} \cdot 100$. 

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**FIGURE 6** | Violin plots representing the distribution of $g_{B1}^{MR}$ (A), $MVF_{B1}^{MR}$ (B), and $AVF_{B1}^{MR}$ (C) across the group and in 21 high-SNR ROIs listed in Table 1. The mean and standard deviation of the distribution are indicated by solid dot and whiskers, respectively.
FIGURE 7 | Depicted are scatter and Bland-Altman plots of $g^{B1}_{MR1}$ (first row), $AVF^{B1}_{MR1}$ (second row), and $MVF^{B1}_{MR1}$ (third row) from two sessions across 21 WM regions (denoted high-SNR ROIs, see Figure 4). The Bland-Altman plot illustrates the differences between values obtained from the two sessions (e.g., $g^{B1}_{MR1}$ vs. $g^{B1}_{MR2}$; $\delta_{\text{retest}}^i = (g^{B1}_{MR1})^i - (g^{B1}_{MR2})^i$) against their mean (e.g., $\text{mean}_{\text{retest}}^i = \frac{(g^{B1}_{MR1})^i + (g^{B1}_{MR2})^i}{2}$, with $i$ indexing the $i$th ROI). Each point in the scatter plot represents the group-averaged value in a single ROI. The bold black line represents the bias ($\delta_{\text{retest}}^i$) against their mean, while the dashed line shows error ($\epsilon_{\text{retest}} = 1.96 \cdot \text{SD}(\delta_{\text{retest}}^i)$) between the two sessions.

dynamic range. For $MVF_{MR}$, the Bland-Altman analysis was additionally done using the whole-WM ROIs instead of the high-SNR ROIs (see section “Region of Interest Selection”) to assess the influence of including low-SNR voxels in the analysis.

Group Variability in MR G-ratio, Axon, and Myelin Volume Fraction
To assess group variability for each correction method, the coefficient-of-variation (CoV) across subjects and sessions was
calculated for MVF\textsubscript{MR}, AVF\textsubscript{MR}, and \g\textsubscript{MR} in the MNI space after applying tissue-weighted smoothing (Tabelow et al., 2019), yielding: CoV\textsubscript{B1\textsuperscript{MR}}, CoV\textsubscript{UN\textsuperscript{MR}}, and CoV\textsubscript{NO\textsuperscript{MR}}, where MR \in {\text{gMR, AVFMR, and MVFMR}}. For tissue-weighted smoothing, a full width at half maximum Gaussian smoothing kernel of 6 mm was used. Bland-Altman analysis (see section “Test-Retest Analysis of the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction”) was used to compare CoV\textsubscript{B1\textsuperscript{MR}} and CoV\textsubscript{NO\textsuperscript{MR}} against CoV\textsubscript{B1\textsuperscript{MR}} based on the reference method, yielding bias ($\overline{\epsilon}$CoV) and error (\epsilon CoV) values. A higher variability across the brain is expected to increase $\overline{\epsilon}$CoV whereas a higher local variability is expected to increase \epsilon CoV.

### RESULTS

#### G-ratio, Myelin, and Axonal Volume Fraction Across the White Matter

Voxel-wise maps of group-averaged g\textsubscript{B1\textsuperscript{MR}}, AVF\textsubscript{B1\textsuperscript{MR}}, and MVF\textsubscript{B1\textsuperscript{MR}} in WM are shown in Figure 5. The group-averaged mean and standard deviation of g\textsubscript{B1\textsuperscript{MR}}, MVF\textsubscript{B1\textsuperscript{MR}}, and AVF\textsubscript{B1\textsuperscript{MR}} in 21 high-SNR ROIs are reported in Table 1 and Figure 6. The dynamic range (\Delta DR), minimum and maximum values, and mean and standard deviation of g\textsubscript{B1\textsuperscript{UN}}, AVF\textsubscript{B1\textsuperscript{UN}}, and MVF\textsubscript{B1\textsuperscript{UN}} across ROIs are listed in Table 2. The largest g\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} and AVF\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} were found in the right anterior limb of the internal capsule (0.688 and 0.384, respectively), while the largest MVF\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} was in the genu of corpus callosum (0.445), where also the lowest g\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} (0.037), followed by g\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} (0.046) and AVF\textsubscript{B1\textsuperscript{B1\textsuperscript{MR}}} (0.076).

#### Table 4: Bias and error between methods, in g\textsubscript{MR}, AVF\textsubscript{MR}, and MVF\textsubscript{MR}.

| MAP               | $\overline{\epsilon}$B1 | \\$\epsilon$B1 | $\overline{\epsilon}$DR | \$\epsilon$DR |
|-------------------|--------------------------|-----------------|-------------------------|--------------|
| $g_{\text{B1}\text{MR}}$ vs. $g_{\text{B1}\text{UN}}$  | -0.041                   | 0.017           | -89.13                  | 36.96        |
| $g_{\text{B1}\text{MR}}$ vs. $g_{\text{B1}\text{SNR}}$ | 0.014                    | 0.005           | 30.44                   | 10.87        |
| $g_{\text{SNR}}$ vs. $g_{\text{UN}}$                 | 0.014                    | 0.005           | 30.44                   | 10.87        |
| AVF\textsubscript{B1\textsuperscript{MR}} vs. AVF\textsubscript{B1\textsuperscript{NO}} | -0.031                   | 0.012           | -40.79                  | 15.79        |
| AVF\textsubscript{B1\textsuperscript{MR}} vs. AVF\textsubscript{B1\textsuperscript{SNR}} | 0.011                    | 0.004           | 14.47                   | 5.26         |
| AVF\textsubscript{B1\textsuperscript{SNR}} vs. AVF\textsubscript{B1\textsuperscript{NO}} | 0.018                    | 0.006           | -48.65                  | 16.22        |
| EWM MVF\textsubscript{B1\textsuperscript{MR}} vs. MVF\textsubscript{B1\textsuperscript{NO}} | 0.053                    | 0.022           | 143.24                  | 59.46        |
| EWM MVF\textsubscript{B1\textsuperscript{SNR}} vs. MVF\textsubscript{B1\textsuperscript{NO}} | 0.033                    | 0.048           | 36.48                   | 52.75        |
| EWM MVF\textsubscript{B1\textsuperscript{SNR}} vs. MVF\textsubscript{B1\textsuperscript{NO}} | -0.012                   | 0.022           | -13.08                  | 23.96        |

List of the bias ($\overline{\epsilon}$B1) and error ($\epsilon$B1) values as defined in Figure 9, along with their relative value with respect to the dynamic range $\Delta DR$: $\overline{\epsilon}$DR = $\overline{\epsilon}$B1/100, $\epsilon$DR = $\epsilon$B1/10.$\overline{\epsilon}$B1 and $\epsilon$B1 are calculated for MVF\textsubscript{MR}, AVF\textsubscript{MR}, and \g\textsubscript{MR} in the MNI space after applying tissue-weighted smoothing (Tabelow et al., 2019), yielding: CoV\textsubscript{B1\textsuperscript{MR}}, CoV\textsubscript{UN\textsuperscript{MR}}, and CoV\textsubscript{NO\textsuperscript{MR}}, where MR \in {\text{gMR, AVFMR, and MVFMR}}. For tissue-weighted smoothing, a full width at half maximum Gaussian smoothing kernel of 6 mm was used. Bland-Altman analysis (see section “Test-Retest Analysis of the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction”) was used to compare CoV\textsubscript{B1\textsuperscript{MR}} and CoV\textsubscript{NO\textsuperscript{MR}} against CoV\textsubscript{B1\textsuperscript{MR}} based on the reference method, yielding bias ($\overline{\epsilon}$CoV) and error (\epsilon CoV) values. A higher variability across the brain is expected to increase $\overline{\epsilon}$CoV whereas a higher local variability is expected to increase \epsilon CoV.
Test-Retest Analysis of the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction

The relative error ($\epsilon_{\text{test}}^i$) and bias ($\delta_{\text{DR}}^i$) values of the test-retest analysis are summarized in Table 3 and shown as Bland-Altman plots in Figure 7. The test-retest analysis revealed a $\delta_{\text{DR}}^i$ below an absolute value of 8.4% for each metric ($g_{\text{MR}}^i$, $\text{AVF}_{\text{MR}}^i$, and $\text{MVF}_{\text{MR}}^i$), where the $\text{AVF}_{\text{MR}}^i$ showed the lowest $\delta_{\text{DR}}^i$ with 0.79% (Figure 7 and Table 3). The $\epsilon_{\text{test}}^i$ was below 22.2% for each metric, where the $\text{AVF}_{\text{MR}}^i$ showed the lowest $\epsilon_{\text{test}}^i$ with 20.5% (Figure 7 and Table 3).

Influence of $B_1+$ Correction on the Group-Averaged MR G-ratio, Axon, and Myelin Volume Fraction

The relative error ($\epsilon_{\text{B1+}}^i$) and bias ($\delta_{\text{B1+}}^i$) values of the $B_1+$ correction analysis are summarized in Table 4 and shown as Bland-Altman plots in Figures 8, 9. For $g_{\text{MR}}$, compared to the no-correction case, UNICORT showed both lower $\epsilon_{\text{B1+}}^i$ (UNICORT vs. no correction: 10.9% vs. 37.0%) and $\delta_{\text{B1+}}^i$ (30.4% vs. −89.1%). For both $\text{AVF}_{\text{MR}}$ and $\text{MVF}_{\text{MR}}$, UNICORT yielded lower $\epsilon_{\text{B1+}}^i$ (UNICORT vs. no correction; $\text{AVF}_{\text{MR}}$: 5.3% vs. 15.8%; 16.2% vs. 59.5%) and lower $\delta_{\text{B1+}}^i$ ($\text{AVF}_{\text{MR}}$: 14.5% vs. −40.8%; $\text{MVF}_{\text{MR}}$: 48.6% vs. 143.2%). Altogether, the UNICORT correction reduced the bias and error in the MR g-ratio and its constituents by roughly a factor of three. The lower $\epsilon_{\text{B1+}}^i$ and $\delta_{\text{B1+}}^i$ associated with UNICORT was also reflected by the fact that values of $g_{\text{MR}}$, $\text{AVF}_{\text{MR}}$, and $\text{MVF}_{\text{MR}}$ (Figure 8, lower panel) lie closer to the unit slope line than values of $g_{\text{NO}}$, $\text{AVF}_{\text{NO}}$, and $\text{MVF}_{\text{NO}}$ (Figure 8, upper panel). When computing $\delta_{\text{DR}}^i$ and $\epsilon_{\text{B1+}}^i$ of $g_{\text{MR}}$ in the whole-WM ROIs (see Supplementary Figure 1), $\delta_{\text{DR}}^i$ was consistently lower for both the no-correction case (whole-WM ROIs vs. high-SNR ROIs: 36.5% vs. 143.2%) and UNICORT (13.1% vs. 48.6%), whereas $\epsilon_{\text{B1+}}^i$ was similar (no-correction: 52.8% vs. 59.5%; UNICORT: 24.0% vs. 16.2%).

Group Variability in MR G-ratio, Axon, and Myelin Volume Fraction

$g_{\text{MR}}$ showed on average smaller CoV than $\text{AVF}_{\text{MR}}$ and $\text{MVF}_{\text{MR}}$ (Figure 10). In all maps, the CoV was the highest in the deep brain areas. The relative error ($\frac{\delta_{\text{B1+}}^i}{\text{CoV}_{\text{B1+}}} + 100$) and bias ($\frac{\epsilon_{\text{B1+}}}{\text{CoV}_{\text{B1+}}} + 100$) values of CoV with respect to the $B_1+$ reference measurement...
are summarized in Table 5 and the error and bias are also displayed as Bland-Altman density plot in Figure 11. For g_{MR}, compared to the no correction case, UNICORT showed similar $\epsilon^{CoV}$ (UNICORT vs. no correction: 0.6% vs. 0.6%) but lower $\delta^{CoV}$ (−0.1% vs. −0.4%). UNICORT yielded higher $\epsilon^{CoV}$ (UNICORT vs. no correction: 1.0% vs. 0.8%) and lower $\delta^{CoV}$ (−0.2% vs. −0.4%) for AVF_{MR}, and higher $\epsilon^{CoV}$ (1.2% vs. 0.4%) and higher $\delta^{CoV}$ (−0.5% vs. −0.1%) for MVF_{MR}. The lower $\delta^{CoV}$ of g_{MR} and AVF_{MR} associated with UNICORT reveals itself as a slight shift of the points toward the unit slope line in the scatter density plot (Figure 12).

**DISCUSSION**

In this study, we showed that omitting the correction of the magnetization transfer saturation map (MT_{sat}) for residual B_{1}+ effects introduces large error and bias in the MR g-ratio and the constituents (myelin and axon volume fractions, or in short MVF_{MR} and AVF_{MR}). We also demonstrated that this error and bias can be reduced by roughly a factor of three using the data-driven UNICORT B_{1}+ correction (implemented in the hMRI toolbox, see text footnote 1) when a B_{1}+ field measurement is unavailable.

**The Effect of Omitting the B_{1}+ Field Measurement**

MT_{sat} have been often used as a proxy for the MVF_{MR} in g-ratio weighted imaging (Mohammadi et al., 2015;...
Campbell et al., 2018; Ellerbrock and Mohammadi, 2018; Hori et al., 2018; Kamagata et al., 2019), because they are directly linked to the macromolecular pool with an intrinsic correction for underlying longitudinal relaxation time and $B_1^+$ field inhomogeneities effects (Helms et al., 2008). Despite the latter intrinsic correction for $B_1^+$ field inhomogeneities, we found that the residual $B_1^+$ effects on MT$_{sat}$ map were still observable. In particular, the bias and error of the MR g-ratio ($g_{MR}$) was about $-89$ and $37\%$ higher, respectively, when omitting the $B_1^+$ correction. We found the same trend for MVF$_{MR}$ and AVF$_{MR}$; while the error and bias were even larger for MVF$_{MR}$ when $B_1^+$ correction was omitted, it was smaller but still substantial for the AVF$_{MR}$. We found that omitting $B_1^+$ leads to a substantially higher (more than 10-fold) bias in the MR g-ratio and its constituents when compared to a test-retest analysis of our data (Figure 7 and Table 3). Also, the error due to omitting the $B_1^+$ correction was twice as large as the error observed in the test-retest analysis for the MR g-ratio and the MVF, whereas for AVF the errors were similar. We expect that the high error will be of particular relevance for group studies because it can be regarded as an error that evolves when replacing the reference method with the alternative method. For comparison, age-related changes assessed by g-ratio weighted imaging (Cercignani et al., 2017; Berman et al., 2018) have been reported to vary between 30 and 100% (in absolute values: $g_{MR}0.02–0.04$ (Figure 5 in Cercignani et al., 2017). Consequently, the reported effect size of age-related changes would have become potentially undetectable if the $B_1^+$ field correction has been omitted in the study of Cercignani et al. (2017). The $B_1^+$ effect is particularly relevant for the MR g-ratio method by Cercignani et al. (2017) that combined quantitative MT (Gloor et al., 2008) with NODDI, because the qMT method does not possess an intrinsic correction for $B_1^+$ field inhomogeneities as opposed to the MT$_{sat}$ methods used here. Note that we reported, for better intuition, the bias and error relative to the dynamic range of the parameters across the investigated white matter (WM) ROIs (the dynamic range of $g_{MR}$ is $\Delta_{DR} = 0.046$; the absolute bias and error can be found in Table 4).

To reduce this source of bias and error, we propose a data-driven approach to correct for $B_1^+$ field inhomogeneities when no $B_1^+$ field measurement is available. To this end, we used UNICORT to estimate the $B_1^+$ field (Weiskopf et al., 2011). We found that using the UNICORT-estimated $B_1^+$ field to correct residual $B_1^+$ field inhomogeneities in MT$_{sat}$ reduces at the group
level the bias and error in the MR g-ratio and its constituents by roughly a factor of three. However, the UNICORT estimated $B_1+$ inhomogeneity can be erroneous with the error varying across subjects. To assess this variability, we estimated coefficient-of-variance (CoV) maps of $g_{MR}$, AVF$_{MR}$, and MVF$_{MR}$ for all three methods. In general, an increased CoV can be found at tissue boundaries (e.g., cerebral spinal fluid to WM) due to slight misregistration between the maps of axonal and myelin markers and/or imperfect normalization (Figure 10). Additionally, we found a strong increase in the bias and error of the CoV of MVF maps (increase in bias: 11% and in error: 18%) when UNICORT $B_1+$ correction was used as compared to no correction. The CoV of $g_{MR}$ and AVF$_{MR}$ did not show a consistent trend: while the bias decreased, the error increased for both parameters. In other words, the UNICORT $B_1+$ correction leads to higher accuracy in the g-ratio and its constituents but comes at the cost of a lower precision in MVF.

**G-ratio, Myelin, and Axonal Volume Fraction Across the White Matter**

Our $g_{MR}^{B_1}$ and AVF$_{MR}^{B_1}$ across the white matter were within the range of the reported values of previous studies ($g_{MR}^{B_1}$: 0.64–0.76; AVF$_{MR}^{B_1}$: 0.26–0.43 in Cercignani et al., 2017; Berman et al., 2018). The range of MVF$_{MR}^{B_1}$ was in the upper half of previously reported values (0.17–0.42 in Cercignani et al., 2017). Our slightly higher MVF$_{MR}$ values might be due to differences in the calibration approach: while we calculated the reference MVF$_{REF}$ from previously published ex-vivo histology data (Graf von Keyserlingk and Schramm, 1984), Cercignani et al. (2017) used a reference from previously published ex-vivo histology g-ratio data in the corpus callosum and Berman et al. (2018), did not perform any calibration assuming that macromolecular tissue volume and MVF$_{MR}$ are equal. An error in the calibration constant can lead to a bias in the MVF estimates which in turn leads to an error and bias in the MR g-ratio (Campbell et al., 2018).

**Confounding Factors**

As this study calculates the in-vivo MR g-ratio, there is no histological data available from the participants of this study, which could be used for calibration or as a gold standard reference. For calibration of MT$_{sat}$ to MVF$_{MR}$, we estimated the histological MVF (MVF$_{hist}$) from published ex-vivo data within the human medulla oblongata (Graf von Keyserlingk and Schramm, 1984). Since the reference MVF$_{hist}$ and the
calibrated MT\textsubscript{sat} map were taken from different subjects, this might introduce a systematic bias in the MR g-ratio. However, since we found a relatively good agreement between our g\textsubscript{MR}, AVF\textsubscript{MR}, and MVF\textsubscript{MR} values with previously reported values obtained by a different calibration approach (Cercignani et al., 2017; Berman et al., 2018), we expect that it had a small effect on the results. Moreover, we focused on the effect of omitting B\textsubscript{1}+ correction, which will lead to additional inaccuracies in g-ratio weighted imaging, independent of the quality of the calibration.

Although, not reported in previous NODDI-based g-ratio mapping studies (Stikov et al., 2015; Cercignani et al., 2017; Jung et al., 2017; Mancini et al., 2017; Ellerbrock and Mohammadi, 2018; Hori et al., 2018), we found that the intra-cellular volume fraction (ν\textsubscript{icvf}) determined with NODDI tends to be biased at small signal-to-noise ratios (SNR < 39), resulting in a ceiling effect, i.e., ν\textsubscript{icvf} \approx 1. To avoid a corresponding bias in g\textsubscript{MR} (and AVF\textsubscript{MR}), we restricted the analysis to regions with sufficiently high SNR (Figure 3). To investigate whether our findings generalize to low-SNR regions as well, we performed an additional Bland-Altman analysis of MVF\textsubscript{MR} in whole-WM ROIs. To this end, a larger set of ROIs was used covering the entire white matter. Although the bias was smaller for the whole-WM as compared to the high-SNR ROI analysis, we found the same trend: the error and bias were reduced when using UNICORT B\textsubscript{1}+ correction relative to no correction. Note that the smaller bias for the whole-WM analysis is most probably an artifact of the calibration procedure. Since the ROI used for calibration was not part of the high-SNR ROIs but was part of the whole-WM ROIs, we think it could have reduced the bias in the whole-WM ROI analysis as compared to the high-SNR analysis.

We note that the presented results were based on a customized B\textsubscript{1}+ mapping method (Lutti et al., 2010). Using vendor specific protocols for B\textsubscript{1}+ and MT\textsubscript{sat} mapping may influence the results (Leutritz et al., 2020). Moreover, the calibration factor in Equation (1) may have to be recalibrated for different MT-pulses.

Future studies should investigate the effect of B\textsubscript{1}+ correction on MR g-ratio mapping when using alternative biomarkers to estimate AVF\textsubscript{MR} and MVF\textsubscript{MR} (e.g., Ellerbrock and Mohammadi, 2018). Moreover, there are alternative B\textsubscript{1}+ mapping approaches available which might vary in precision (Lutti et al., 2010) and therefore can affect the MR g-ratio values. However, the differences in the precision of these methods are in the order of few percentage and thus much smaller than the effect of omitting the B\textsubscript{1}+ field or using the data-driven UNICORT B\textsubscript{1}+ estimate (Weiskopf et al., 2011).

**CONCLUSION**

In this study, we assessed the effect of B\textsubscript{1}+ correction on the accuracy of MR g-ratio as well as axonal and myelin volume fraction based on MT\textsubscript{sat} and NODDI. Our results demonstrate that B\textsubscript{1}+ correction via a measured B\textsubscript{1}+ field map is the method of choice. If the B\textsubscript{1}+ field map cannot be acquired, we propose the retrospective, data-driven UNICORT B\textsubscript{1}+ correction to estimate and correct for B\textsubscript{1}+ field inhomogeneities, which reduces the error and bias by a factor of three. UNICORT is implemented in the free and open-source hMRI toolbox (see text footnote 1).

**DATA AVAILABILITY STATEMENT**

The datasets presented in this article are not readily available because the data that support the findings of this study are available on request from the corresponding author. The data have not been made freely available on the internet due to privacy or ethical restrictions. Requests to access the datasets should be directed to corresponding author.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the Ärztekammer Hamburg. The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

SM and TE contributed to the conception and design of the study, performed statistical analysis and MRI processing, and wrote the first draft of the manuscript. All authors contributed substantially to revising the manuscript critically for intellectual content and have approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.674719/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the
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