Mapping magnetization transfer saturation (MT\textsubscript{sat}) in human brain at 7T: Protocol optimization under specific absorption rate constraints

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\textbf{Purpose:} To optimize a whole-brain magnetization transfer saturation (MT\textsubscript{sat}) protocol at 7T, focusing on maximizing obtainable MT\textsubscript{sat} under the constraints of specific absorption rate (SAR) and transmit field inhomogeneity, while avoiding bias and keeping scan time short.

\textbf{Theory and Methods:} MT\textsubscript{sat} is a semi-quantitative metric, obtained by spoiled gradient-echo MRI in the imaging steady-state. Optimization was based on an established 7T dual flip angle protocol, and focused on MT pulse, readout flip angle, repetition time (TR), offset frequency (Δ), and correction of residual effects from transmit field inhomogeneities by separate flip angle mapping.

\textbf{Results:} A 100% SAR level was reached at a 180° MT pulse flip angle, using a compact sinc main lobe (4 ms duration) and minimum TR = 26.5 ms. The use of Δ = +2.0 kHz caused no discernible direct saturation, while Δ = −2.0 kHz resulted in 45% higher MT\textsubscript{sat} in white matter (WM) compared to Δ = +2.0 kHz. A 4° readout flip angle eliminated bias while yielding a good signal-to-noise ratio. Increased TR yielded only a little increase in MT\textsubscript{sat}, and TR = 26.5 ms (scan time 04:58 min) was thus selected. Post hoc transmit field correction clearly improved homogeneity, especially in WM.

\textbf{Conclusions:} The range of MT\textsubscript{sat} is limited at 7T, and this can partly be overcome by the exploitation of the asymmetry of the macromolecular lineshape through the sign of Δ. To reduce scan time, a compact MT pulse with a sufficiently narrow frequency response should be used. TR and readout flip angle should be kept short/small. Transmit field correction through separate flip angle mapping is required.

\textbf{KEYWORDS}
7T, human brain, magnetization transfer, MT\textsubscript{sat}, spoiled gradient echo, ultra-high field

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INTRODUCTION

Magnetization transfer (MT) is a unique contrast mechanism enabling detection and quantification of otherwise MR-invisible macromolecules.\(^1,2\) MT is highly correlated with myelination\(^3\) and thus used to study white matter (WM) diseases, most notably multiple sclerosis.\(^4,5\) Contrast is induced by applying high-energy, off-resonance radiofrequency (RF) pulses, targeting the broad absorption line of the rotationally restricted protons bound to macromolecules. This magnetic saturation is then transferred to the free water, where it manifests as a tissue-specific decrease in signal amplitude.

At 7T, the application of MT pulses is curtailed by safety limits of the specific absorption rate (SAR) which increases quadratically with field strength. This limits the achievable signal reduction and the range of any derived metrics. In addition, the more pronounced RF inhomogeneities at 7T may impose a spatial bias. Further, because of the increased Larmor frequency at 7T, it must be avoided that chemical exchange saturation transfer (CEST) resonances overlap with the saturation profile of the off-resonance RF pulse.\(^6\) Due to these challenges, MT-mapping is still relatively uncommon in an ultra-high field (≥7T) in vivo setting, although it has been performed using either a two-pool model\(^7-10\) or through measurement of the Z-spectrum and subsequent multiple-pool analysis at 7T\(^11\) and 9.4T.\(^12\) Nevertheless, the signal reduction by MT-weighting benefits from higher field strength due to the longer T\(_1\).\(^1,2,13\) Further, the shift of the macromolecular absorption line with regard to the free water resonance will also increase at higher field strengths.\(^14\) This warrants further investigation of the feasibility of in vivo MT at 7T.

From the MT-weighted (MT-w) signal, semi-quantitative metrics can be derived to describe the MT effect. The MT saturation (MT\(_{\text{sat}}\)) represents the fraction of free water saturated by a single MT pulse during repetition time (TR)\(^15\) and care must thus be taken to minimize contributions that confound MT when implementing it. MT\(_{\text{sat}}\) is obtained from an empirical signal equation of an MT-w spoiled gradient echo, which is supplemented by two spoiled gradient-echo acquisitions with T\(_1\)- and proton density (PD)-weighting (forming a dual flip angle [DFA] experiment). Because of this, MT\(_{\text{sat}}\) is unbiased by T\(_1\) relaxation (for a small flip angle [FA] and TR << T\(_1\)) unlike the conventional magnetization transfer ratio (MTR) where T\(_1\) relaxation will counteract MT and reduce contrast. Also unlike MTR, the quadratic dependence of MT on the transmit field\(^16\) cancels out in the algebraic derivation of MT\(_{\text{sat}}\), thus inherently compensating for FA inhomogeneities to a large extent. MT\(_{\text{sat}}\) thus provides a time-efficient alternative to fully quantitative techniques but with increased specificity and contrast compared to MTR. MT\(_{\text{sat}}\) is mostly used in a multi-parameter mapping (MPM) context,\(^17,18\) for which dedicated processing tools have been developed.\(^19\)

Thus far, MT\(_{\text{sat}}\) has mainly been implemented at 3T where it has been used in a variety of clinical studies. These include research on spinal cord injury,\(^20,21\) effects of aging\(^22-24\) as well as multiple sclerosis to assess the g-ratio\(^25,26\) and to discriminate between disability levels.\(^27\)

In this study, the steps of optimizing MT-weighting in the context of an MPM protocol for whole-brain imaging are described, explicitly addressing the 7T specific issues of increased SAR and compromised transmit field homogeneity. The developed MT-w sequence was added to an established 7T DFA protocol\(^28\) to obtain MT\(_{\text{sat}}\). The choices of MT pulse shape, TR, readout FA and offset frequency are discussed based on separate experiments. Correction for residual effects of transmit field inhomogeneities was also addressed, and efforts were made to maintain a clinically feasible scan time (~5 min) with sub-millimeter resolution. Last, the repeatability of the suggested protocol was tested on a single subject.

THEORY

2.1 MT\(_{\text{sat}}\)

A 3D spoiled gradient-echo MT-w sequence can be described by a simple signal equation to the introduction of MT\(_{\text{sat}}\), the fractional decrease in longitudinal magnetization of free water, M\(_z\), due to a single saturation event within TR.\(^15\) For small FAs\(^29\) and for T\(_1\) >> TR, the imaging steady-state signal from an MT-w spoiled gradient echo, S\(_{\text{MT-w}}\), is approximated:

\[
S_{\text{MT}} = S_0 \alpha \left( \frac{R_1 \TR}{R_1 \TR + \delta_{\text{MT}} + \alpha^2/2} \right)
\]  

(1)

where \(\delta_{\text{MT}}\) denotes MT\(_{\text{sat}}\), \(\alpha\) is the readout FA in radians, \(R_1 = 1/T_1\) and \(S_0\) is the signal amplitude under fully relaxed conditions, ie, TR >> T\(_1\). Using maps of \(R_1\) and \(S_0\) obtained from a DFA experiment, \(\delta_{\text{MT}}\) is calculated from \(S_{\text{MT-w}}\):

\[
\delta_{\text{MT}} = \left[ S_0 \alpha / S_{\text{MT-w}} - 1 \right] R_1 \TR - \alpha^2/2.
\]  

(2)

The influence of transmit field inhomogeneities are introduced into Equation (2) through the substitution \(f_T \alpha_{\text{nom}} = \alpha\), where \(f_T\) is the transmit field bias and \(\alpha_{\text{nom}}\) is the nominal FA (set in the user interface). Using this substitution in the equations for \(S_0\) and \(R_1\) in a DFA experiment, one obtains \(S_0 = S_{0,\text{app}} / f_T\) and \(R_1 = R_{1,\text{app}} f_T^2\), where \(S_{0,\text{app}}\) and \(R_{1,\text{app}}\) are the corresponding estimates obtained with nominal FAs.\(^29\)

Equation (2) can be re-written in a similar way:

\[
\delta_{\text{MT}} = \left[ f_T \alpha_{\text{nom}} \cdot S_{0,\text{app}} / f_T - 1 \right] f_T^2 R_{1,\text{app}} TR - \left( f_T \alpha_{\text{nom}} \right)^2 / 2 = f_T^2 \delta_{\text{MT-app}}.
\]  

(3)
The longitudinal magnetization of the macromolecular pool, $M_{z,b}$, is reduced by the MT pulse, $\omega_1 = \gamma B_1$ of duration $t_{\text{sat}}$. This is described by differential absorption:

$$M_{z,b}(0) - M_{z,b}(t_{\text{sat}}) = -\pi g_b \left(2\pi \Delta T_{2,b}\right) \int_0^{t_{\text{sat}}} M_{z,b}(t) \omega_1^2(t) \, dt \tag{4}$$

where $g_b \left(2\pi \Delta T_{2,b}\right)$ is the super-Lorentzian macromolecular absorption lineshape, $\Delta$ is the MT pulse offset frequency and $T_{2,b}$ is the transverse relaxation time of the macromolecular pool. Direct saturation of $M$ can also be described by Equation (4), except with a Lorentzian lineshape governed by $T_2$. If no other confounding contrast mechanism is present and the decrease of $M_{z,b}(t)$ during $t_{\text{sat}}$ can be ignored, the ensuing transfer renders $\delta_{\text{MT}}$ to the macromolecular pool size fraction, $F_b$:

$$\delta_{\text{MT}} \propto -\pi g_b \left(2\pi \Delta T_{2,b}\right) F_b \int_0^{t_{\text{sat}}} \omega_1^2(t) \, dt. \tag{5}$$

Hence, $\delta_{\text{MT}}$ will depend not only on macromolecular content, but also on lineshape and transmit field inhomogeneities as well as the apparent transfer rate. However, the square of $\omega_1$ is mirrored by $\delta_{\text{MT}} = f_T^2 \delta_{\text{MT,app}}$ in Equation (3). This means that by using $\delta_{\text{MT,app}}$ one gets a reflection of the macromolecular content, which is inherently compensated for transmit field inhomogeneities, motivating the use of nominal FAs for calculation of $M_{z,b}^\text{sat}$:

$$\delta_{\text{MT,app}} = [S_{\text{app},\text{norm}}/S_{\text{MT}} - 1] R_{1,\text{app}} TR - \alpha_{\text{norm}}^2/2. \tag{6}$$

$M_{z,b}^\text{sat}$ henceforth refers to the metric calculated using nominal FAs (Equation (6)).

### 2.2 RF energy and pulse shape

The power integral $\int_0^{t_{\text{sat}}} \omega_1^2(t) \, dt$ is often used as a surrogate parameter in SAR models. As described above, this integral also governs the energy and induced $\delta_{\text{MT}}$ (Equation (5)) of the MT pulse through the differential absorption law (Equation (4)). The power integral can be expressed as:

$$\int_0^{t_{\text{sat}}} \omega_1^2(t) \, dt = \omega_1^2(1) \frac{1}{t_{\text{sat}}} \int_0^1 \omega_1^2(t') \, dt' \tag{7}$$

where $\omega_1(1)$ is the maximum amplitude of the RF pulse and the rightmost normalized integral depends solely on the normalized RF shape $\omega_1(1)$.

By using $\omega_{1,\text{max},\text{sat}} = \omega_{1,\text{max}} t_{\text{sat}}$, $\int_0^1 \omega_1(1) \, dt'$, the power integral is expressed in terms of $\omega_{\text{sat}}$ and $t_{\text{sat}}$, which can be controlled experimentally:

$$\int_0^{t_{\text{sat}}} \omega_1^2(t) \, dt = Q \omega_{\text{sat}}^2/t_{\text{sat}} \tag{8}$$

where the shape factor:

$$Q = \frac{\int_0^1 \omega_1^2(t') \, dt'}{\left(\int_0^1 \omega_1(t') \, dt'\right)^2} \geq 1, \tag{9}$$

carries the influence of the pulse shape. Note that $Q = 1$ for a rectangular pulse.

### 2.3 Noise propagation into the MT sat map

The signal in Equation (1) can be expressed in analogy to the Ernst equation by using $R_{1,\text{MT}} = Р_1 + \delta_{\text{MT}}/T R$. For a fixed TR and MT pulse, noise propagation from $S_{\text{MT}}$ into $\delta_{\text{MT,app}}$ is minimized for an optimal readout FA:

$$\alpha_{\text{opt}} = \sqrt{2R_{1,\text{MT}} TR/\sqrt{3}} = \alpha_{\text{MT, max}}/\sqrt{3} \tag{10}$$

where $\alpha_{\text{MT, max}}$ yields the highest signal in the MT-w acquisition and can be obtained by a variable FA experiment and a linear fit to the signals. The full derivation is given in Supporting Information, which is available online. As in the DFA experiment, a global optimization of $\alpha_{\text{MT, max}}$ is not possible.

### 2.4 Residual effects of transmit field inhomogeneities

From the $f_T^2$-dependence in Equation (3) and the $\omega_1^2(t)$-dependence in Equation (5), it is clear that $\delta_{\text{MT,app}}$ should be compensated for FA inhomogeneities. However, the decrease in $M_{z,b}$ under the duration of the MT pulse ($t_{\text{sat}}$) will render induced saturation and hence MT smaller than what would be expected from differential absorption (Equation (4)). Thus, $\delta_{\text{MT,app}}$ will be somewhat overcompensated by the inherent $f_T^2$-correction, leading to an underestimation when $f_T > 1$ and an overestimation when $f_T < 1$. This $f_T$ dependence of $\delta_{\text{MT,app}}$ can be described empirically by a linear dependence:

$$\delta_{\text{MT,app}}(f_T) = A \alpha_{\text{sat,nom}}^2 \left(1 - B \alpha_{\text{sat,nom}} f_T\right) \tag{11}$$

where $A$ and $B$ are phenomenological parameters specific to the MT pulse shape and duration. Equation (11) explicitly contains the nominal FA of the MT pulse, hence $A$ and $B$ can be obtained by varying $\alpha_{\text{sat,nom}}$ and performing a linear regression of $\delta_{\text{MT,app}}(f_T)/\alpha_{\text{sat,nom}}^2$ versus $\alpha_{\text{sat}}$. Given that the final transmit field-corrected estimate is
\[ \delta_{\text{MT,corr}} = \delta_{\text{MT,app}} (f_T = 1) = A \alpha_{\text{sat,nom}}^2 (1 - B \alpha_{\text{sat,nom}}), \]
the correction takes the form:

\[ \delta_{\text{MT,corr}} = \delta_{\text{MT,app}} (1 - B \alpha_{\text{sat,nom}}) / (1 - B \alpha_{\text{sat,nom}} f_T) \quad (12) \]

where the product \( B \alpha_{\text{sat,nom}} = C \) forms a pulse-specific parameter, which is used for post hoc transmit field correction of \( \text{MT}_{\text{sat}} \).

## 3 | METHODS

Experiments were performed on an actively shielded 7T MR system (Achieva, Philips Healthcare, Best, NL) with a head coil of 32 receive and 2 transmit channels with fixed phase setting (Nova Medical, Wilmington, MA). Eight healthy adult subjects (six females, 19 to 37 y old) were scanned after giving informed written consent as approved by the regional Ethical Review Board.

To map \( \text{MT}_{\text{sat}} \), an MT-w sequence was run in conjunction with a DFA experiment, thus forming an MPM protocol. For all three series, a non-selective 3D RF-spoiled multi-echo gradient-echo sequence was used with in-plane phase encoding anterior-posterior. Isotropic voxels of \((0.9 \, \text{mm})^3\) were defined within \( \text{FOV}_{\text{FH,AP,RL}} = 230 \times 230 \times 200 \, \text{mm}^3 \) (with some variation to match head size). Eight equidistant echoes were added 8.4 ms to the TR of the DFA acquisitions. If \( \alpha_{\text{sat,nom}} = 220^\circ \) was to be used, the TR would be increased by an additional 13 ms due to SAR limitations. To ensure the shortest possible scan time, \( \alpha_{\text{sat,nom}} \) was reduced to \( 180^\circ \) (the maximum value compatible with \( \text{TR} = 26.5 \, \text{ms} \)), resulting in a scan time of \( 4:58 \, \text{min} \). This decrease in scan duration will come at the expense of induced MT (see Equation (8)).

To illustrate the choice of pulse shape, four MT pulses with different shapes were compared for identical \( \alpha_{\text{sat}} = 180^\circ \) and energy (ensuring same \( \text{MT}_{\text{sat}} \), and same SAR). The compared pulse shapes were (a) a five-lobe sinc \( (Q = 5.26, t_{\text{sat}} = 15.8 \, \text{ms}, B_{1,\text{rms}} = 1.70 \, \mu\text{T}) \), which is the default MT pulse shape on the system (b) the implemented sinc main lobe \( (Q = 1.61, t_{\text{sat}} = 4.8 \, \text{ms}, B_{1,\text{rms}} = 3.10 \, \mu\text{T}) \), and last, for reference, (d) a rectangular pulse \( (Q = 1.00, t_{\text{sat}} = 3.0 \, \text{ms}, B_{1,\text{rms}} = 3.91 \, \mu\text{T}) \). The frequency response profiles were simulated by numerically solving the Bloch equations, ignoring relaxation effects, using the RF Pulse Wizard tool as provided with a copy of Ref. 45.

## 3.1 | Shape of MT pulse

The choice of MT pulse was motivated by previous 3T implementations where a Gaussian with \( t_{\text{sat}} = 4 \, \text{ms} \) and \( \alpha_{\text{sat,nom}} = 220^\circ \) was used. This MT pulse yields a good compromise between frequency response and short \( t_{\text{sat}} \). Since a Gaussian was not available on the system, a similar Gaussian-filtered sinc main lobe was used.

The 4 ms sinc main lobe pulse and a consecutive spoiler added 8.4 ms to the TR of the DFA acquisitions. If \( \alpha_{\text{sat,nom}} = 220^\circ \) were to be used, the TR would be increased by an additional 13 ms due to SAR limitations. To ensure the shortest possible scan time, \( \alpha_{\text{sat,nom}} \) was reduced to \( 180^\circ \) (the maximum value compatible with \( \text{TR} = 26.5 \, \text{ms} \)), resulting in a scan time of \( 4:58 \, \text{min} \). This decrease in scan duration will come at the expense of induced MT (see Equation (8)).

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## 3.2 | Readout FA

To empirically adjust the readout FA, \( \alpha_{\text{nom}} \) was varied through \( 2^\circ, 4^\circ, 6^\circ, 8^\circ \) in one volunteer (34-year-old female, \( \alpha_{\text{sat,nom}} = 180^\circ, t_{\text{sat}} = 4 \, \text{ms}, \Delta = +2.0 \, \text{kHz} \)). TR was slightly increased to 27 ms for all series to accommodate the slight increase in SAR for \( \alpha_{\text{nom}} = 8^\circ \).
The nominal $\alpha_{E,MT}$ was determined through pixelwise linear fitting of the four FAs in the brain parenchyma (segmented WM+GM).\textsuperscript{46} Thereafter, the median was used to calculate the nominal $\alpha_{opt}$ in Equation (10). The behavior of $MT_{sat}$ in WM, GM, and CSF was studied to identify the occurrence of bias.

### 3.3 | TR

To corroborate the choice of the shortest possible TR = 26.5 ms at $t_{sat} = 4$ ms, TR was varied through 26.5, 31.1, 35.6, 40.3 and 45.0 ms on one volunteer (24-yr-old male, $\alpha_{sat,nom} = 180^\circ$, $t_{sat} = 4$ ms, $\Delta = -2.0$ kHz). It was of interest to assess whether $MT_{sat}$ increased at higher TR, and if so, how much. Resulting acquisition times were 04:58, 05:49, 06:40, 07:33, and 08:26 min, where 08:26 min was deemed to be the maximum acceptable.

### 3.4 | Offset frequency

With RF pulses and timings established, the offset frequency of the MT pulse needs to be determined. On one hand, a strong increase in saturation and thus in $MT_{sat}$ is expected at smaller offsets due to the super-Lorentzian lineshape of the macromolecules.\textsuperscript{47,48} On the other hand, care must be taken to limit direct saturation and CEST. Thus, $\Delta$ was varied through 0.75, 1.0, 1.5, and 2.0 kHz on one subject (19-yr-old female, $\alpha_{sat,nom} = 180^\circ$, $t_{sat} = 4$ ms). Settings of $\Delta < 0.75$ kHz were not employed to avoid direct saturation by the sidebands at 0.48 kHz indicated by the simulations (see the Results section 4.1).

The $T_{2,b}$ has been shown to be quite similar in WM and GM.\textsuperscript{48,49} Hence, it was assumed that WM and GM have comparable absorption lineshapes. The MT-related component of $MT_{sat}$ should therefore vary proportionally with $\Delta$. The difference in average $MT_{sat}$ between WM and GM at the largest $\Delta = 2.0$ kHz (where direct saturation and CEST were assumed negligible) was calculated across all axial slices containing brain pixels. Any disproportionate increase of $MT_{sat}$ $\Delta MT_{sat}$ in GM relative WM at lower $\Delta$ was attributed to either direct saturation in tissue or CEST.

### 3.5 | Negative offset frequency

The lineshape of the macromolecules is shifted with respect to the free water resonance by $-2.34 \pm 0.17$ ppm ($-697$ Hz at 7T) in WM.\textsuperscript{14} To examine how much $MT_{sat}$ can be gained by this asymmetry, the MT pulse was applied with either a positive or a negative offset frequency ($\Delta = \pm 2.0$ kHz) in one subject (19-yr-old female, $\alpha_{sat,nom} = 180^\circ$, $t_{sat} = 4$ ms). To take $B_0$ inhomogeneity into account, the free water frequency offset, $f_0$, was also measured. A linear function of $MT_{sat}$ as a function of $f_0$ (in kHz) was fitted in segmented WM in a slice covering an area above the sinuses. Resulting slopes using $\Delta = \pm 2.0$ kHz were then compared.

### 3.6 | Residual effects of transmit field inhomogeneities

To determine the correction factor $C$ for the chosen MT pulse, the nominal FA of the MT pulse was varied within a range of $\alpha_{sat,nom} = 45^\circ-180^\circ$ ($B_{1, rms} = 0.87-3.37$ $\mu$T) in four subjects (three female, 23 to 28 y old). This variation of $\alpha_{sat,nom}$ mimics a variation of $f_1$ down to 25% as typically observed in the cerebellum at 7T.\textsuperscript{36}

The variation of $\alpha_{sat,nom}$ was performed as follows: Subject #1: $\alpha_{sat,nom} = 60-180^\circ$ in steps of 30°. Subject #2: $\alpha_{sat,nom} = 120^\circ-180^\circ$ in steps of 20°. Subject #3 $\alpha_{sat,nom} = 60^\circ-180^\circ$ in steps of 20° with extra measurements at 45°, 90°, 135°. Subject #4: $\alpha_{sat,nom} = 80-180^\circ$ in steps of 10° with an extra measurement at 135°. For subjects #1-#3, each series were acquired twice to increase robustness, resulting in 10, 8, 20, and 12 $MT_{sat}$ maps for the respective subjects. All $MT_{sat}$ maps for a subject were based on a single pair of DFA-derived $T_1$- and $S_0$ maps. In Equation (11), $\delta_{MT,app}$ was divided by $(\alpha_{sat,nom})^2$ to obtain $C$ in four ROIs by linear fitting. The ROIs were manually defined symmetrically (left-right) in frontal WM (average across all ROIs and subjects was $n_{pixels} = 794 \pm 220$) and in the caudate head (average across all ROIs and subjects was $n_{pixels} = 644 \pm 286$), where the latter represented GM. When performing the fit, each $\delta_{MT,app}/(\alpha_{sat,nom})^2$ data point was weighted by the inverse of the ROI standard deviation for the particular $\alpha_{sat,nom}$ used (ie, points acquired with $\alpha_{sat,nom} = 45^\circ$ were weighted less than points acquired with $\alpha_{sat,nom} = 180^\circ$). This was done to reduce the influence of noise on the fitting as SNR correlates strongly with $\alpha_{sat}$. Out of these $4 \times 4 = 16$ estimates of $C$, averages for GM (8 ROIs) and WM (8 ROIs) were calculated, as well as a total average, $C_{mean}$, of all ROIs, to be used for post hoc correction across the entire brain.

### 3.7 | Repeatability

After sequence parameters and $f_1$-correction had been established, the MPM protocol was repeated three times on a single subject to measure repeatability. By all combinations of $T_1$-w, PD-w, and MT-w images, this resulted in $3 \times 3 \times 3 = 27$ $MT_{sat}$ maps. Maps of the relative deviation from the mean of all 27 maps were calculated as well as the SD.
RESULTS

4.1 Shape of MT pulse

The FWHMs in the frequency responses (Figure 1, panel C) were very similar for all of the four MT pulses, yielding \( \Delta_{1/2} = 0.28, 0.30, 0.29, 0.27 \) kHz for the five-lobe sinc, sinc main lobe, Gaussian and rectangular pulse at their respective pulse durations. The sinc main lobe still showed small sidebands (1.6%) at \( \pm 0.48 \) kHz (21.6% for the rectangular pulse) which imposes a lower limit on \( \Delta \) to avoid direct saturation. The time-inefficient nature of the five-lobe sinc is demonstrated by the square of the \( B_1 \) amplitude (Figure 1, panel B) where very little saturation is created by the sidelobes. The increase in \( t_{\text{sat}} \) by 11.8 ms compared to the sinc main lobe would increase acquisition time by ~45%. If a fixed TR = 26.5 ms and \( t_{\text{sat}} = 4 \) ms was imposed, the frequency response of the five-lobe sinc was very wide (\( \Delta_{1/2} = 1.31 \) kHz at \( \alpha_{\text{sat}} = 91^\circ \) and 100% SAR). These features confirmed that the appropriate shape of the MT pulse is a shaped single lobe (here a Gauss-filtered sinc main lobe).

4.2 Readout FA

The \( M_{\text{sat}} \) maps obtained with different readout FAs were highly consistent (Figure 2). Like at 3T,\(^{15} \) a systematic positive shift of \( M_{\text{sat}} \) with increasing \( \alpha_{\text{nom}} \) is observed where \( M_{\text{sat}} \) in WM increased by 0.12 p.u. at \( \alpha_{\text{nom}} = 8^\circ \) compared to at \( \alpha_{\text{nom}} = 2^\circ \).

The nominal value of \( \alpha_{\text{MT,max}} \) in the brain parenchyma, spatially correlated to \( f_T \),\(^{28} \) had a median of 12.4°, which would require \( \alpha_{\text{nom}} \approx 7^\circ \) for optimal noise progression. In the CSF, progressive saturation at higher \( \alpha_{\text{nom}} \) due to long \( T_1 \) leads to lower SNR and a consecutive positive shift due to Rician noise distribution.

A nominal readout FA of \( \alpha_{\text{nom}} = 4^\circ \) was deemed a suitable compromise between yielding good SNR in the brain parenchyma, limiting the observed bias (average \( M_{\text{sat}} \) in WM of 1.28 ± 0.15 p.u. vs. 1.38 ± 0.17 p.u. for \( \alpha_{\text{nom}} = 8^\circ \)), and preserving a distinct CSF mode in the histograms. This value was thus chosen for the final protocol.

4.3 TR

Increasing TR resulted in only a minor increase of \( M_{\text{sat}} \) at TR = 40.3, 45.0 ms in WM (Figure 3). Thus, the shortest possible TR = 26.5 ms allowed by the pulse sequence timing at \( t_{\text{sat}} = 4 \) ms was chosen for the protocol.

4.4 Offset frequency

As expected, \( M_{\text{sat}} \) increased strongly as \( \Delta \) was decreased (Figure 4). However, the modes of GM and WM appeared

**FIGURE 1** Comparison of MT pulse shapes. Four MT pulses with \( \alpha_{\text{sat}} = 180^\circ \) and identical energy (A), their squared counterparts (B), and respective frequency response profiles (C). Pulse duration, \( t_{\text{sat}} = 15.8/4.0/4.8/3.0 \) ms and \( B_1 \) amplitude \( B_{1,\text{rms}} = 1.70/3.37/3.10/3.91 \) μT (\( B_{1,\text{max}} = 4.3/5.1/5.5/3.9 \) μT) for a five-lobe sinc (blue), main lobe sinc (orange), Gaussian with 2% cutoff (yellow), and rectangular shape (dashed black), respectively. The sinc main lobe shows small sidebands of 1.6% saturation at \( \pm 0.48 \) kHz (red arrows).
increasingly shifted to higher MT\textsubscript{sat} resulting in a proportionally larger increase in GM relative WM. The proportion of MT\textsubscript{sat} in GM relative WM was 0.47/0.50/0.57/0.62 at $\Delta = 2.0/1.5/1.0/0.75$ kHz. This indicates some confounding saturation effect added on top of MT. This shift in observed $\Delta MT_{\text{sat}}$, followed the increase in CSF very well (Figure 5), indicating that direct saturation of the free water contributes to the increasing MT\textsubscript{sat} in tissue. The absolute value of $\Delta$ was thus set to 2.0 kHz to limit contributions from non-MT sources, predominantly direct saturation, like at 3T.\textsuperscript{43,44}
At an offset frequency of $\Delta = -2.0$ kHz, a larger MT$_{sat}$ was observed compared to $\Delta = +2.0$ kHz (Figure 6). Average MT$_{sat}$ increased by 45% in WM ($1.14 \pm 0.16$ vs $1.65 \pm 0.20$ p.u) and by 35% in GM ($0.49 \pm 0.17$ vs $0.66 \pm 0.16$ p.u.). This observation is in accordance with the shift of the macro-molecular absorption line to lower frequencies.

Residual $B_0$ inhomogeneities shift $f_0$ to higher frequencies in most of the brain (82%/71% of WM/GM pixels). In these pixels, a negative $\Delta$ will increase the distance to free water ($\Delta f_0$) and to resonances underlying relayed Nuclear Overhauser Effects (rNOE), and thus reduce contributions from these effects. This is reflected by a negative correlation of MT$_{sat}$ to $f_0$ ($-1.0$ p.u. per kHz) for $\Delta = -2.0$ kHz in WM in an axial slice close to the sinuses (Figure 7). For $\Delta = +2.0$ kHz, a positive correlation (+0.6 p.u. per kHz) is observed when the distance to free water and CEST resonances decreases at higher $f_0$. To maximize MT$_{sat}$, the MT pulse was applied at $\Delta = -2.0$ kHz in the finalized protocol.

### 4.5 Negative offset frequency

The average $C$ across all ROIs was $C_{\text{mean}} = 0.34 \pm 0.11$. There was no significant difference ($P = .25$ for a two-tailed student’s t-test) between average $C$ in WM/GM ROIs ($0.31 \pm 0.09/0.37 \pm 0.09$). The average coefficient of determination was $r^2 = 0.20 \pm 0.12$ across all fits. Figure 8 shows scatter plots of $\delta_{\text{MT,app}}/(\alpha_{\text{sat,nom}})^2$ versus $\alpha_{\text{sat}}$ for an example subject, the fitted line, and corresponding $C$ estimate for each of the 4 ROIs. A figure of all four subjects is provided in Supporting Information Figure S1.

MT$_{sat}$ maps, before and after correction, of one subject (28-year-old male) acquired with the finalized protocol (Supporting Information Table S1) are shown in Figure 9. Substructures within the basal ganglia are clearly delineated and cortical boundaries are well defined. Before correction, however, locations of increased MT$_{sat}$ coincide with those of low transmit field amplitude. This bias was alleviated after the correction which also distinctly narrowed the WM mode in the histogram. MT$_{sat}$ appeared to be somewhat blurrier in peripheral cortical areas where $f_T < ~0.6$. In areas with $f_T < ~0.3$, MT$_{sat}$ was indistinguishable from noise, indicating the limit of the method at 7T.
regions of the cerebellum and temporal lobes. These regions suffer from low transmit field amplitude as well as being more susceptible to physiologic noise caused by breathing.\textsuperscript{50}

\section*{DISCUSSION}

At 7T, limits imposed by SAR and an inhomogeneous transmit field (approximately $0.3 \leq f_T \leq 1.5$, see Figure 9) are exacerbated. Nevertheless, we obtained $MT_{\text{sat}}$ maps of a quality comparable to 3T,\textsuperscript{15,31,43,44} although limitations were observed in areas of low transmit field amplitude (local $\alpha_{\text{sat}} < \sim 100^\circ$, $f_T < \sim 0.6$) where $MT_{\text{sat}}$ could be somewhat noisier. At very low transmit field amplitude (local $\alpha_{\text{sat}} < \sim 60^\circ$, $f_T < \sim 0.3$), reliable estimates for $MT_{\text{sat}}$ could not be obtained. In addition to decreasing SNR due to lower $\alpha_{\text{sat}}$, $R_1$ and $S_0$ cannot be reliably determined at very low $f_T$ by the underlying DFA experiment when the higher local FA decreases below the Ernst angle.\textsuperscript{28} It could therefore be beneficial to use multi-channel transmit RF technology and/or dielectric pads\textsuperscript{51} to improve transmit field homogeneity. The threshold value of $\alpha_{\text{sat}}$ (here $\sim 60^\circ$) depends on $MT$ pulse shape and duration.

To identify systematic variation, we relied on previous experience at 3T and by empirically studying how $MT_{\text{sat}}$ in different tissues changed depending on parameter settings. This was done either through qualitative features such as spatial symmetry or separation of tissue-specific modes in the histograms or quantitatively through the comparison of averages derived from automatic tissue segmentation. A previous report\textsuperscript{52} was complemented by aspects of TR, offset frequency sign, transmit field correction and repeatability.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Direct saturation. Scatter plot showing the shift of $MT_{\text{sat}}$ ($\Delta MT_{\text{sat}}$) in tissue (segmented WM and GM) most likely predominantly due to direct saturation for different $\Delta$ (denoted by different colors). At $\Delta = 2.0$ kHz (purple) negligible direct saturation in tissue was assumed. Circles denote the average value in each axial slice while diamonds denote the average across the whole volume. These values are plotted against average $MT_{\text{sat}}$ in ventricular CSF ($MT_{\text{sat,CSF}}$), used as a reference for direct saturation. A linear fit of the axial slice averages, with forced intercept through zero, is shown in black. The deviation at $\Delta = +1.0$ kHz (+3.5 ppm) is possibly due to CEST with the APT resonance.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Negative offset frequency. Top row: $MT_{\text{sat}}$ maps with $\Delta = \pm 2.0$ kHz and corresponding histograms (right). Bottom row: Bar graph showing mean/SD in segmented ventricular CSF, GM, and WM. $MT_{\text{sat}}$ increases substantially at $\Delta = -2.0$ kHz, especially in WM (~45%).}
\end{figure}
5.1 Shape of MT pulse

The implemented sinc main lobe is very similar to the default at General Electric MRI systems with a bell shape similar to a Gaussian. The sinc main lobe compares favorably to the pure Gaussian due to higher normalized energy ($Q = 1.33$ versus $Q = 1.61$), while still providing sufficiently narrow frequency response. The frequency response of either pulse...
was very similar, but the Gaussian will lack the small side-bands of the sinc main lobe. Previous work has shown no difference in MT$_{sat}$ for pulses with identical energy\textsuperscript{,15} and a sinc main lobe should thus be expected to behave very similar to a Gaussian. Last, it should be noted that MT$_{sat}$ is defined for an instantaneous saturation event which further motivates the choice of a short, time-efficient (low $Q$) pulse, facilitating short TR and acquisition time.

### 5.2 | Readout FA

A small positive shift of MT$_{sat}$ with increasing $\alpha_{nom}$ has previously been described at 3T.\textsuperscript{15} This effect originates from omitted non-linear terms in the approximate signal equation (Equation (1)), accounted for through a positive bias in MT$_{sat}$. Regarding the physical interpretation of MT$_{sat}$, it should be noted that the readout by $\alpha$ may disturb the MT dynamics during TR. By choosing $\alpha_{nom}$ smaller than the optimal 7\textdegree\textsuperscript{,5} regarding SNR, the bias was limited in areas of high $f_T$ without sacrificing too much precision. The reduced bias was traded off against decreased SNR in regions of low $f_T$. When targeting a specific structure, noise progression can be optimized to match the local $f_T$.\textsuperscript{31}

### 5.3 | TR

MT$_{sat}$ should increase with TR as this allows more time for MT to reestablish the equilibrium disturbed by the MT pulse.\textsuperscript{53} A similar small increase of MT$_{sat}$ in the TR range 18 ms $\leq$ TR $\leq$ 65 ms has been observed at 3T.\textsuperscript{15} In this work, the effect was weaker (Figure 3) which may be due to MT$_{sat}$ being smaller than at 3T. An increase in TR could thus only facilitate an increase in MT$_{sat}$ via increased energy of the MT pulse, which would be beneficial for low $f_T$ areas. Modification of the MT pulse would require repeating the optimization procedure, especially the calibration of the transmit field correction (Methods 3.6). We instead opted for a shorter measurement, with TR = 26.5 ms which is only slightly longer than the TR = 23.7 ms used at 3T.\textsuperscript{43,44}

### 5.4 | Offset frequency

Since fitted macromolecular absorption lines have been found to be similar in GM and WM, we expected a proportional increase of MT$_{sat}$ with decreasing frequency offset, in the absence of confounding contributions. In previous work at 1.5 T, T$_{2,b}$ has been estimated to 11.8 $\pm$ 1.3 $\mu$s and

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**Figure 9** Before and after correcting MT$_{sat}$ for residual effects of transmit field inhomogeneities. MT$_{sat}$ map acquired with the finalized protocol before (A) and after (B) correction of residual transmit field effects ($C = 0.34$) and the FA map used for correction (C). Corresponding histograms are also included (D). In the right periphery (white arrows), SNR is lower due to lower transmit field amplitude ($f_T < ~0.6$). In the right temporal lobe and cerebellum (blue arrows), transmit field amplitude is even lower ($f_T < ~0.3$) and MT$_{sat}$ becomes indistinguishable from noise. Overall, the transmit field correction works well and the homogeneity in WM is improved, as seen in the maps (red arrows) as well as by manifestation of a narrowing of the WM mode in the histogram (red arrows).
12.3 ± 1.6 μs in WM and 11.1 μs in cortical GM. Another study, also at 1.5 T, reported 10.4 ± 0.5 μs in WM and 9.2 ± 0.4 μs in GM. The gradual shift of MT sat at lower Δ is interpreted as being predominantly due to direct saturation in tissue. This interpretation was supported by linear regression of MT sat onto a reference experiment (Δ = +2.0 kHz), as previously applied to harmonize between scanners. This experiment showed that ΔMT sat correlated strongly with MT sat in CSF (Figure 5). The higher ΔMT sat at Δ = +1.0 kHz (3.4 ppm) is likely due to overlap with the APT frequency at +3.5 ppm and ensuing CEST. It should also be noted that hydroxyl and amine exchange at +2.5 ppm could influence MT sat at Δ = +0.75 kHz, although no obvious overestimation above the line was observed. As Δ = +2.0 kHz corresponds to 6.7 ppm at 7T, we assumed the virtual absence of exchanging resonances as confirmed in rat cortex. Our interpretation of direct saturation cannot be explained by the simulated profile (Figure 1C), probably because relaxation effects were ignored. Direct saturation is linked to short T2 of the free pool as observed in myelin water and iron-rich structures which decreases at higher field strength. However, the geometric mean T2s of different structures are proportionally shorter at 7T relative to those observed at 3T. Hence, we do not observe tissue-type specific effects.

Arguably, Δ = 2.0 kHz could still be affected by direct saturation. Since ΔMT sat changes gradually with offset frequency, it is not possible to prove the absence of direct saturation. We did not increase Δ beyond 2.0 kHz to avoid further diminishing the already rather weak MT sat and accepted any minor remaining bias. If a wider absolute MT sat difference between tissue types is desired, this could be achieved by decreasing Δ. This would involve some trade-off against a higher degree of direct saturation and various other effects, which would impair specificity to traditional MT.

### 5.5 Negative offset frequency

It is customary to apply the MT pulse at a positive Δ. However, it has been shown that the super-Lorentzian absorption line of the macromolecules is shifted toward lower frequencies relative free water resonance. The shift in Hz between peak macromolecular response and free water resonance scales with B0. We exploited this asymmetry to considerably increase MT sat (Figure 6), without creating more direct saturation or increasing SAR. The rNOE exchange is present on the negative side of the water resonance and it is possible that some contaminating saturation occurred because of this, even at the rather large offset of Δ = –2.0 kHz (–6.7 ppm). However, based on previously published experimental results from rat cortex in vivo, these effects are expected to be small compared to our MT sat values. In this study, eight consecutive 180° saturation pulses, comparable to our MT pulse (B1, rms = 2 μT, t sat = 13.8 ms) were applied and the observed saturation due to rNOE amounted to <0.5% at −6.7 ppm. Furthermore, the overall increase in MT sat at Δ = –2.0 kHz cannot be explained by B0 offset (represented by f0), which mostly shifted Δ–f0 toward lower values (ie, Δ = –2.0 kHz away from water). The majority of the observed increase in MT sat is thus interpreted to be caused by a shifted absorption lineshape. The observed B0-dependence (Figure 7) could be a combined effect of changing the

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**FIGURE 10** Repeatability experiment. The MPM protocol was repeated three times resulting in 27 MT sat maps. For each MT sat map, the pixel-wise relative deviation from the mean is shown (A) as well as the resulting standard deviation (B). The notations (T1-w #1 etc.) refer to which acquisitions were used for a particular MT sat map.
saturation of macromolecules, CEST as well as direct saturation of free water. The specific influence of rNOE could possibly explain the somewhat stronger correlation for $\Delta = -2.0$ kHz compared to $\Delta = +2.0$ kHz. This difference is in the same order of magnitude as the additional saturation from rNOE exchange based on the experimental results on the rat cortex. Large shifts occur mainly above the nasal sinuses and even in these pixels, strong deviations in MT$_{sat}$ were not observed. In 94% of pixels, $|f_0|$ was below 100 Hz (0.34 ppm). We thus conclude that an MT pulse with FWHM = 300 Hz (1 ppm) applied at $-2.0$ kHz ($-6.7$ ppm) yield a satisfactory safety margin of 2.45 ppm to the closest expected rNOE resonance at $-3.75$ ppm.

5.6 | Residual effects of transmit field inhomogeneities

The inherent correction of MT$_{sat}$ was insufficient at 7T due to the strong transmit field inhomogeneities. The post hoc correction clearly improved the homogeneity of MT$_{sat}$, especially in WM (Figure 9). In view of the relatively large variation in $C$ observed across the 16 ROIs, we ignored underlying differences in $B$ between GM and WM to perform a global post hoc correction.

This post hoc correction is implemented in the hMRI toolbox, albeit with a different weighting factor ($C = 0.40$ as derived at 3T for a Gaussian MT pulse of $\alpha_{sat, nom} = 220^\circ$). This control variable should be changed based on MT pulse when using the toolbox. For $\alpha_{sat, nom} = 180^\circ$, this correction factor would be scaled to $C = 180^\circ/220^\circ\cdot0.40 = 0.33$ (ignoring small differences in pulse shape and negative frequency offset) which is close to $C = 0.34 \pm 0.11$ determined experimentally in this study. This correction implicitly assumes the absence of confounding contributions to MT$_{sat}$.

5.7 | Repeatability

The high SD in the cerebellum and temporal lobes illustrates the limitation of the method imposed by low transmit field amplitude as well as physiological noise affecting $B_0$. The latter, caused by chest movement due to breathing, could potentially be remedied using data-driven post-correction methods of the raw k-space data.

5.8 | Limitations

Due to the recursive nature of the optimization procedure, parameter settings in some experiments did not reflect the final protocol (Supporting Information Table S1). For instance, the positive frequency offset in experiment 3.4 (Figure 4) demonstrates APT resonance but does not access the upfield rNOE exchange. However, the purpose of this experiment was to minimize direct saturation as a confounding mechanism of saturation. This was then followed by an upfield-downfield comparison. Minor confounding effects are likely to remain, making the semi-quantitative MT$_{sat}$ metric proportional to, albeit not identical to, the bound pool size ratio, $F_b$, modeled by fully quantitative approaches. In the MPM approach, this is traded in against speed and high resolution. In areas of very low transmit field ($f_T < -0.3$), however, MT$_{sat}$ could not be determined using this fast protocol.

6 | CONCLUSIONS

This study resulted in the following recommendations for setting up an MT$_{sat}$ protocol at 7T: (a) Short MT pulse with a compact shape and sufficiently narrow frequency response. (b) Small readout FA without punishing SNR too much. (c) Minimum TR (as decided by pulse sequence timing) to maintain short scan time. (d) Absolute offset frequency of 2.0 kHz to reduce confounding direct saturation, CEST, and rNOE exchange. (e) Negative sign of the offset frequency to induce more MT. This is a consequence of the shifted lineshape and benefits from higher $B_0$. (f) Separate FA-mapping for post hoc correction.

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CONFLICT OF INTEREST

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REFERENCES

1. Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. Magn Reson Med. 1989;10:135-144.
2. Henkelman RM, Stanisz GJ, Graham SJ. Magnetization transfer in MRE: a review. NMR Biomed. 2001;14:57-64.
3. Stikov N, Perry LM, Mezer A, et al. Bound pool fractions complement diffusion measures to describe white matter micro and macrostructure. *Neuroimage*. 2011;54:1112-1121.

4. Mehta RC, Pike GB, Ennemann DR. Improved detection of enhancing and nonenhancing lesions of multiple sclerosis with magnetization transfer. *AJNR Am J Neuroradiol*. 1995;16:1771-1778.

5. Ropele S, Fazekas F. Magnetization transfer MR imaging in multiple sclerosis. *Neuroimaging Clin N Am*. 2009;19:27-36.

6. van Zijl PCM, Lam WW, Jiadi Xu, Knutsson L, Stanisz GJ. Magnetization transfer contrast and chemical exchange saturation transfer MRI. Features and analysis of the field-dependent saturation spectrum. *Neuroimage*. 2018;168:222-241.

7. Dorchter RD, Moore J, Li K, et al. Quantitative magnetization transfer imaging of human brain at 7 T. *Neuroimage*. 2013;64:640-649.

8. McKeithan LJ, Lyttle BD, Box BA, et al. 7T quantitative magnetization transfer (qMT) of cortical gray matter in multiple sclerosis correlates with cognitive impairment. *Neuroimage*. 2019;203:116190.

9. Privooulos N, Jacobs HIL, Ivanov D, Uludağ K, Verhey FRJ, Poser BA. High-resolution in vivo imaging of human locus coeruleus by magnetization transfer MRI at 3T and 7T. *Neuroimage*. 2018;168:427-436.

10. Oh S-H, Shin W, Lee J, Lowe M. Variable density magnetization transfer (vdMT) imaging for 7 T MR imaging. *Neuroimage*. 2018;168:242-249.

11. Mougin OE, Coxon RC, Pittot A, Gowland PA. Magnetization transfer phenomenon in the human brain at 7 T. *Neuroimage*. 2010;49:272-281.

12. Zais M, Zu Z, Xu J, et al. A combined analytical solution for chemical exchange saturation transfer and semi-solid magnetization transfer. *NMR Biomed*. 2015;28:217-230.

13. Pohmann R, Shahj A, Balla DZ. Contrast at high field: relaxation times, magnetization transfer and phase in the rat brain at 16.4 T. *Magn Reson Med*. 2011;66:1572-1581.

14. Hua J, Jones CK, Blakeley J, Smith SA, van Zijl PCM, Zhou J. Quantitative description of the asymmetry in magnetization transfer effects around the water resonance in the human brain. *Magn Reson Med*. 2007;58:786-793.

15. Helms G, Dathe H, Kallenberg K, Dechent P. High-resolution maps of magnetization transfer with inherent correction for RF inhomogeneity and T1 relaxation obtained from 3D FLASH MRI. *Magn Reson Med*. 2008;60:1396-1407.

16. Henkelman RM, Huang X, Xiang QS, Stanisz GJ, Swanson SD, Bronskill MJ. Quantitative interpretation of magnetization transfer. *Magn Reson Med*. 1993;29:759-766.

17. Leutritz T, Seif M, Helms G, et al. Multiparameter mapping of relaxation (R1, R2*), proton density and magnetization transfer saturation at 3 T: a multicenter dual-vendor reproducibility and repeatability study. *Hum Brain Mapp*. 2020;41:4232-4247.

18. Weiskopf N, Suckling J, Williams G, et al. Quantitative multiparameter mapping of R1, PD*, MT, and R2* at 3T: a multi-center validation. *Front Neurosci*. 2013;7:95.

19. Tabelow K, Balteau E, Ashburner J, et al. hMRI — A toolbox for quantitative MRI in neuroscience and clinical research. *Neuroimage*. 2019;194:191-210.

20. Grabher P, Callaghan MF, Ashburner J, et al. Tracking sensory system atrophy and outcome prediction in spinal cord injury. *Ann Neurol*. 2015;78:751-761.

21. Freund P, Weiskopf N, Ashburner J, et al. MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. *Lancet Neurol*. 2013;12:873-881.

22. Filo S, Shtangel O, Salamon N, et al. Disentangling molecular alterations from water-content changes in the aging human brain using quantitative MRI. *Nat Commun*. 2019;10:3403.

23. Agustus JL, Golden HL, Callaghan MF, et al. Melody processing characterizes functional neuroanatomy in the aging brain. *Front Neurosci*. 2018;12:815.

24. Callaghan MF, Freund P, Draganiski B, et al. Widespread age-related differences in the human brain microstructure revealed by quantitative magnetic resonance imaging. *Neurobiol Aging*. 2014;35:1862-1872.

25. Kamagata K, Zalesky A, Yokoyama K, et al. MR g-ratio-weighted connectome analysis in patients with multiple sclerosis. *Sci Rep*. 2019;9:13522.

26. Campbell JSW, Leppert IR, Narayanan S, et al. Promise and pitfalls of g-ratio estimation with MRI. *Neuroimage*. 2018;182:80-96.

27. Lema A, Bishop C, Malik O, et al. A comparison of magnetization transfer transfer methods to assess brain and cervical cord microstructure in multiple sclerosis. *J Neuroimaging*. 2017;27:221-226.

28. Olsson H, Andersen M, Latt J, Wirestam R, Helms G. Reducing bias in dual flip angle T1-mapping in human brain at 7T. *Magn Reson Med*. 2020;84:1347-1358.

29. Helms G, Dathe H, Dechent P. Quantitative FLASH MRI at 3T using a rational approximation of the Ernst equation. *Magn Reson Med*. 2008;59:667-672.

30. Helms G, Dathe H, Dechent P. Modeling the influence of TR and excitation flip angle on the magnetization transfer ratio (MTR) in human brain obtained from 3D spoiled gradient echo MRI. *Magn Reson Med*. 2010;64:178-185.

31. Gringel T, Schulz-Schaeffer W, Eloquent F, Frolich A, Dechent P, Helms G. Optimized high-resolution mapping of magnetization transfer (MT) at 3 Tesla for direct visualization of substructures of the human thalamus in clinically feasible measurement time. *J Magn Reson Imaging*. 2009;29:1285-1292.

32. Helms G. Correction for residual effects of B1+ inhomogeneity on MT saturation in FLASH-based multi-parameter mapping of the brain. In: proceedings of the 23rd Annual Meeting of ISMRM, Toronto, Ontario, 2015, p. 3360.

33. Al-Abasse Y, Helms G. Influence of pulse length and shape on variable flip angle T1 mapping of human brain. In: proceedings of the 24th Annual Meeting of ISMRM, Singapore, 2016, p. 614.

34. Nehrkoe K, Bornert P. DREAM-a novel approach for robust, ultrafast, multislice B1 mapping. *Magn Reson Med*. 2012;68:1517-1526.

35. Nehrkoe K, Versluis MJ, Webb A, Bornert P. Volumetric B1+ mapping of the brain at 7T using DREAM. *Magn Reson Med*. 2014;71:246-256.

36. Olsson H, Andersen M, Helms G. Reducing bias in DREAM flip angle mapping in human brain at 7T by multiple preparation flip angles. *Magn Reson Imaging*. 2020;72:71-77.

37. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *Neuroimage*. 2012;62:782-790.

38. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5:143-156.

39. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17:825-841.
41. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp.* 2002;17:143-155.

42. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging.* 2001;20:45-57.

43. Draganski B, Ashburner J, Hutton C, et al. Regional specificity of MRI contrast parameter changes in normal ageing revealed by voxel-based quantification (VBQ). *Neuroimage.* 2011;55:1423-1434.

44. Helms G, Draganski B, Frackowiak R, Ashburner J, Weiskopf N. Improved segmentation of deep brain grey matter structures using magnetization transfer (MT) parameter maps. *Neuroimage.* 2009;47:194-198.

45. de Graaf RA. *In Vivo NMR Spectroscopy: Principles and Techniques.* Hoboken, NJ: John Wiley & Sons Ltd.; 2018. https://www.wiley.com/en-us/In+Vivo+NMR+Spectroscopy%3A+Princip les+%26+Techniques%2C+3rd+Edition-p-9781119382515. Accessed June 24, 2021.

46. Helms G, Dathe H, Weiskopf N, Dechent P. Identification of signal bias in the variable flip angle method by linear display of the algebraic Ernst equation. *Magn Reson Med.* 2011;66:669-677.

47. Morrison C, Stanisz G, Henkelman RM. Modeling magnetization transfer for biological-like systems using a semi-solid pool with a super-Lorentzian lineshape and dipolar reservoir. *J Magn Reson, Ser B.* 1995;108:103-113.

48. Sled JG, Pike GB. Quantitative imaging of magnetization transfer exchange and relaxation properties in vivo using MRI. *Magn Reson Med.* 2001;46:923-931.

49. Meineke J, Nielsen T. Data consistency-driven determination of B0-fluctuations in gradient-echo MRI. *Magn Reson Med.* 2019;81:3046-3055.

50. Tuetewisse WM, Brink WM, Webb AG. Quantitative assessment of the effects of high-permittivity pads in 7 Tesla MRI of the brain. *Magn Reson Med.* 2012;67:1285-1293.

51. Helms G, Piringer A. Simultaneous measurement of saturation and relaxation in human brain by repetitive magnetization transfer pulses. *NMR Biomed.* 2005;18:44-50.

52. Tao J, Seong-Gi K. Advantages of chemical exchange-sensitive spin-lock (CESL) over chemical exchange saturation transfer (CEST) for hydroxyl- and amine-water proton exchange studies. *NMR Biomed.* 2014;27:1313-1324.

53. Xu J, Yadav NN, Bar-Shir A, et al. Variable delay multi-pulse train for fast chemical exchange saturation transfer and relayed-nuclear overhauser enhancement MRI. *Magn Reson Med.* 2014;71:1798-1812.

54. Wiggerman V, MacKay AL, Rauscher A, Helms G. In vivo investigation of the multi-exponential T2 decay in human white matter at 7 T: implications for myelin water imaging at UHF. *NMR Biomed.* 2021;34. http://dx.doi.org/10.1002/nbm.4429.

55. Graham SJ, Henkelman RM. Understanding pulsed magnetization transfer. *J Magn Reson Imaging.* 1997;7:903-912.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.

**FIGURE S1** Residual effects of transmit field inhomogeneities of all subjects. Correction factor, C, derived through linear fitting (blue solid line) in ROIs placed in the caudate head (columns A, B) and frontal WM (columns C, D), representing GM and WM, respectively. Different rows show separate subjects. Headings denotes average f T and individual C for that ROI. The best fit obtained with the constraint C = Cmean = 0.34 is denoted by an orange dashed line

**TABLE S1** Sequence parameters and transmit field-correction factor, C, for the finalized protocol

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