Quantitative 7T sodium magnetic resonance imaging of the human brain using a 32-channel phased-array head coil: Application to patients with secondary progressive multiple sclerosis

Tobias Wilferth | Angelika Mennecke | Lena V. Gast | Sebastian Lachner | Max Müller | Veit Rothhammer | Konstantin Huhn | Michael Uder | Arnd Doerfler | Armin M. Nagel | Manuel Schmidt

1Institute of Radiology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany
2Department of Neuroradiology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany
3Department of Neurology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany
4Division of Medical Physics in Radiology, German Cancer Research Centre (DKFZ), Heidelberg, Germany

Correspondence
Tobias Wilferth, Institute of Radiology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Maximiliansplatz 3, 91054, Erlangen, Germany. Email: tobias.wilferth@uk-erlangen.de

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Apparent tissue sodium concentrations (aTSCs) determined by $^{23}$Na brain magnetic resonance imaging (MRI) have the potential to serve as a biomarker in pathologies such as multiple sclerosis (MS). However, the quantification is hindered by the intrinsically low signal-to-noise ratio of $^{23}$Na MRI. The purpose of this study was to improve the accuracy and reliability of quantitative $^{23}$Na brain MRI by implementing a dedicated postprocessing pipeline and to evaluate the applicability of the developed approach for the examination of MS patients. $^{23}$Na brain MRI measurements of 13 healthy volunteers and 17 patients with secondary progressive multiple sclerosis (SPMS) were performed at 7 T using a dual-tuned $^{23}$Na/$^1$H birdcage coil with a receive-only 32-channel phased array. The aTSC values were determined for normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) in healthy subjects and SPMS patients. Signal intensities were normalized using the mean cerebrospinal fluid (CSF) sodium concentration determined in 37 separate patients receiving a spinal tap for routine diagnostic purposes. Five volunteers underwent MRI examinations three times in a row to assess repeatability. Coefficients of variation (CoVs) were used to quantify the repeatability of the proposed method. aTSC values were compared regarding brain regions and subject cohort using the paired-samples Wilcoxon rank-sum test. Laboratory CSF sodium concentration did not differ significantly between patients without and with MS ($p = 0.42$). The proposed quantification workflow for $^{23}$Na MRI was highly repeatable with CoVs averaged over all five volunteers of 1.9% ± 0.9% for NAWM and 2.2% ± 1.6% for NAGM. Average NAWM aTSC was significantly higher in patients with SPMS compared with...
the control group \( (p = 0.009) \). Average NAGM aTSC did not differ significantly between healthy volunteers and MS patients \( (p = 0.98) \). The proposed post-processing pipeline shows high repeatability and the results can serve as a baseline for further studies establishing \(^{23}\text{Na} \) brain MRI as a biomarker in diseases such as MS.

**KEYWORDS**
7 T, brain MRI, multiple sclerosis, \(^{23}\text{Na} \) MRI, tissue sodium concentration, ultrahigh field strength

## 1 | INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system that is characterized by demyelination and neuro-axonal damage.\(^7\) Over the long term, degenerative processes lead to sustained or progressive disability. As experimental studies have suggested that intracellular sodium accumulation and the resulting metabolic changes may play a key role in the pathogenesis of neuronal injury,\(^2\) and because of the general importance of \( \text{Na}^+/\text{K}^- \)-ATPase as a major energy consumer in the central nervous system,\(^3\) several studies on sodium magnetic resonance imaging (\(^{23}\text{Na} \) MRI) of MS patients have been performed in the last years.\(^4\) Compared with healthy brains, an increased tissue sodium concentration (TSC) has been found not only in MS lesions, but also in normal appearing white matter (NAWM) and in normal appearing gray matter (NAGM) of MS patients for all three subtypes of MS (relapsing–remitting MS,\(^5,6\) secondary progressive MS,\(^7,8\) [SPMS], and primary progressive MS).\(^7,8\) Furthermore, increased TSC is correlated with the metrics of the course of disease, for example, grade of disability.\(^6,7,9\) As the TSC represents a volume-weighted average of intracellular and extracellular sodium, it is sensitive to changes in both spaces and an increase can be related to a neuronal energy deficit, which results in intra-axonal accumulation of sodium ions,\(^2,10-12\) as well as to neuronal degeneration with extension of the extra-axonal space and altered tissue microstructure. It was shown that \(^{23}\text{Na} \) MRI intensity changes between different types of MS and healthy controls also depend on the \(^{23}\text{Na} \) MR imaging technique used and the resulting contrast.\(^13\) Overall, there is increasing evidence that \(^{23}\text{Na} \) MRI can provide potential biomarkers for neurodegeneration and neuroinflammation in MS.\(^4\)

However, despite the progress in \(^{23}\text{Na} \) brain MRI during recent years,\(^14,15\) many studies are still limited by the inherent physical properties of \(^{23}\text{Na} \) MRI. Due to the intrinsically reduced NMR sensitivity and the low in vivo concentrations compared with proton (\(^{1}\text{H} \) MRI, large voxel volumes and long acquisition times are necessary to achieve a sufficient signal-to-noise ratio (SNR). Consequently, the low resolution and strong partial volume effects (PVE) restrict the accuracy of TSC quantification, especially of small MS lesions,\(^16\) but also of gray matter (GM) and white matter (WM), due to imprecise differentiation of brain compartments. In addition, because of the fast biexponential relaxation behavior of spin-3/2-nuclei, ultrashort echo-time sequences, which use radial acquisition-based k-space sampling, are commonly applied for quantitative \(^{23}\text{Na} \) MRI.\(^17\) However, these sequences have a broad point spread function (PSF), which further contributes to PVE.

Regarding the signal calibration for quantification, external references with known \(^{23}\text{Na} \) concentrations are mostly used.\(^18\) As dedicated head coils with integrated receive phased arrays to enable improved spatial resolution by increasing SNR\(^19,20\) often prohibit external references due to restricted space, using internal references such as the cerebrospinal fluid (CSF)\(^21\) or vitreous humor\(^22\) for quantification would be desirable. However, currently, these are rarely employed and further validation is necessary.

The aim of this work is to improve the accuracy of TSC quantification in brain tissue in general, and in particular in MS patients, by establishing a dedicated measurement setup and postprocessing workflow to address the aforementioned limitations. Healthy volunteers and patients suffering from SPMS were examined with high-resolution \(^{23}\text{Na} \) MRI using a 32-channel receive phased-array head coil at 7 T. The acquired data were corrected for T1/T2 relaxation and PVE as well as receive coil sensitivity profiles. Furthermore, concentration calibration using the CSF compartment as an individual reference signal was validated by determining the sodium concentration in laboratory CSF analysis in cohorts of patients with and without MS receiving a spinal tap for routine diagnostic checkup. As suggested by Stobbe and Beaulieu,\(^23\) the term apparent tissue sodium concentration (aTSC) was used for the determined concentration values to account for the not exactly known signal loss resultant from residual quadrupolar interactions in the brain. After validating the repeatability in volunteer MRI measurements, the method was used to examine the aTSCs of NAWM and NAGM in healthy volunteers and SPMS patients. Moreover, for the SPMS patients, the aTSC values of the lesions were evaluated.

## 2 | METHODS

### 2.1 | Image acquisition

All measurements were carried out at a 7-T whole-body MR system (MAGNETOM Terra, Siemens Healthcare, Erlangen, Germany).
$^{23}$Na MRI was performed using a dual-tuned $^{23}$Na/$^1$H head coil (RAPID Biomedical, Rimpar, Germany) that consists of a $^{23}$Na/$^1$H quadrature transceiver birdcage coil and an additionally integrated 32-channel receive phased-array head coil for $^{23}$Na MRI. Before the acquisition of the $^{23}$Na MRI data, a $B_0$-shim based on $^1$H MRI using the standard brain $B_0$-shim provided by the vendor and a global $^{23}$Na flip angle (FA) calibration were conducted. $^{23}$Na MRI datasets were acquired using a density-adapted 3D radial readout scheme with the following sequence parameters: TR = 120 ms, nominal FA = 86°–90° (depending on patient-specific SAR limitations), RF pulse length (TP) = 0.55 ms, TE = 0.35 ms, $T_{RE} = 10$ ms, nominal spatial resolution $\Delta x^3 = 2.5 \times 2.5 \times 2.5$ mm$^3$ (defined by $\Delta x = 1/2 \ k_{max}$, with $k_{max}$ the maximum k-space position), $T_{AQ} = 14$ min. Additionally, a noise-only scan (TR = 30 ms, nominal FA = 0°, $T_{AQ} = 1$ min, all other parameters identical to the image acquisition) was conducted to calculate the noise correlation matrix that was required for adaptive combined (ADC) reconstruction of the multichannel data.

For anatomical information, high-resolution $^1$H 3D $T_1$-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) (TR = 2500 ms, TE = 2.92 ms, TI = 1100 ms, nominal spatial resolution $\Delta x^3 = 0.65 \times 0.65 \times 0.65$ mm$^3$, nominal FA = 7°, $T_{AQ} = 7$ min 59 s) and fluid-attenuated inversion recovery (FLAIR) (TR = 9000 ms, TE = 269 ms, TI = 2600 ms, nominal spatial resolution $\Delta x^3 = 0.8 \times 0.8 \times 0.8$ mm$^3$, $T_{AQ} = 7$ min 14 s) sequences were carried out using a 1Tx/32Rx $^1$H head coil (Nova Medical, Wilmington, MA, USA). The coil change was necessary, as the $^1$H birdcage of the dual-tuned $^{23}$Na/$^1$H head RF coil does not provide sufficient diagnostic image quality for segmentation of anatomical images.

### 2.2 Sodium image reconstruction

The acquired $^{23}$Na MRI raw datasets were reconstructed offline using a custom-written MATLAB script (MATLAB, MathWorks, Natick, MA, USA). A Hamming filter was used to increase SNR and to reduce Gibbs’ ringing artifacts and a density compensation was applied before performing a nonuniform Fast Fourier Transform (NUFFT) with a grid oversampling factor of 2. The k-space data were zero-filled to the 0.65 mm isotropic voxel size of the MPRAGE data to improve the accuracy of the partial volume correction (PVC). The 32 channels were combined using the ADC algorithm (blocksize = 10, interpolation factor = 2).

After image reconstruction, the inhomogeneous receive profile of the $^{23}$Na 32-channel receive phased-array head coil was corrected using a universal sensitivity map, which was obtained by averaging eight individually calculated receive profiles, as described by Lachner et al. The complete postprocessing of the acquired data is summarized in Figure 1 and the single steps are described in more detail in the following.

### 2.3 Relaxation correction

As the brain compartments have different relaxation behavior, a very short TE ($> T_{2}\ast$) and a long TR ($> 5 \ T_1$) would be necessary to obtain quantitative measurements without relaxation bias. However, regarding SNR and acceptable measurement times, the choice of such sequence parameters is not feasible for in vivo measurements. Therefore, a relaxation correction was performed, generally assuming a homogeneous FA, a biexponential transverse relaxation with the theoretical fraction of fast ($T_{2}\ast$) to slow ($T_{2s}\ast$) relaxing components of 60%/40% for a single homogeneous compartment, and a monoexponential longitudinal relaxation. The signal was corrected by multiplying the uncorrected signal intensity by the following correction factor:

$$
\begin{align*}
C_{\text{relaxation}, T_2} &= 1/ \left( 0.6 \exp \left( -\frac{\text{TE}}{T_{2f}} \right) + 0.4 \exp \left( -\frac{\text{TE}}{T_{2s}} \right) \right) \\
C_{\text{relaxation}, T_1} &= \left( 1 - \cos(\text{FA}) \exp \left( -\frac{\text{TR}}{T_1} \right) / \left( 1 - \exp \left( -\frac{\text{TR}}{T_1} \right) \right) \right) \cdot C_{\text{relaxation}} = C_{\text{relaxation}, T_2} / C_{\text{relaxation}, T_1}
\end{align*}
$$

In GM and WM, the relaxation behavior was modeled by a biexponential transverse relaxation with the relaxation times $T_{2f}\ast = 4.2$ ms and $T_{2s}\ast = 34.4$ ms and a monoexponential longitudinal relaxation with $T_1 = 37.1$ ms. In CSF, for both transverse and longitudinal relaxation, a monoexponential behavior was assumed ($T_{2f}\ast = T_{2s}\ast = T_1 = 54.4$ ms; $T_1 = 64$ ms). The dependence of the correction factor on the chosen parameters and an estimation of the error when these parameters vary between subjects or in pathologies can be found in Figure S1.

As the exact relaxation parameters of MS lesions are not known and are furthermore expected to depend at least partially on the specific lesion, two different relaxation models were examined. As the pathology of MS is characterized by degeneration processes that are connected to enlargement of the extra-axonal space, a loss of structure is expected in the environment of sodium ions in MS lesions, which results in longer relaxation times. Furthermore, a recent study gave hints for a more fluid-like lesion environment compared with healthy WM. Therefore, the relaxation parameters of healthy WM were assumed as lower bound (model 1: $T_{2f}\ast = 4.2$ ms, $T_{2s}\ast = 34.4$ ms, $T_1 = 37.1$ ms) and the relaxation parameters of CSF as upper bound (model 2: $T_{2s}\ast = 54.4$ ms, $T_1 = 64$ ms) for the relaxation behavior of MS lesions.
To improve the accuracy in quantification, PVE were corrected using the geometric transfer matrix (GTM) method as described by Niesporek et al.,\textsuperscript{30} which is based on binary masks and provides region-wise partial volume corrected average signal intensities for every compartment.

The lesion mask was created using the FLAIR image and the AI-based segmentation software mdbrain (mediaire GmbH, Berlin, Germany). All regions identified as lesions by the software using a lesion size threshold of 5 μl according to the MAGNIMS guidelines to avoid false positive inflammatory T2-weighted lesions\textsuperscript{37} were included in the analysis. Finally, the corrected average signal intensities were normalized to the cerebrospinal fluid (CSF) sodium concentration determined by spinal tap to obtain mean aTSC values for the white matter (WM), gray matter (GM), and lesion compartment. The aTSC values were derived under the assumption that each region (e.g., WM, GM, or lesion compartment) exhibits constant sodium signal intensities. USM, universal coil sensitivity map

**2.4 Segmentation of anatomical images and PVC**

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**FIGURE 1** Postprocessing workflow for the determination of apparent tissue sodium concentration (aTSC) values for the different brain compartments. Tissue masks were created from segmentation of high-resolution anatomical 1H magnetization-prepared rapid acquisition gradient echo (MPRAGE) and fluid-attenuated inversion recovery (FLAIR) datasets. These masks were then used for binary mask-based partial volume correction (PVC) of the coil profile-corrected 23Na MRI dataset. For simulation of the point spread function for PVC and for relaxation correction, literature relaxation parameters were used. Finally, the corrected average signal intensities were normalized to the cerebrospinal fluid (CSF) sodium concentration determined by spinal tap to obtain mean aTSC values for the white matter (WM), gray matter (GM), and lesion compartment. The aTSC values were derived under the assumption that each region (e.g., WM, GM, or lesion compartment) exhibits constant sodium signal intensities. USM, universal coil sensitivity map.
processes that would otherwise distort the concentration values of NAWM/NAGM. However, as the mostly neglectable small lesion loads in the healthy control group do not allow for a proper examination, the resulting aTSC values were not further evaluated. Finally, the $^{23}$Na MRI dataset was coregistered to the MPRAGE dataset to match the masks.

The region-spread function (RSF) for each compartment that describes the signal smearing was then calculated by convolution of the binary tissue masks with the PSF of the compartment. The same relaxation behavior as for the relaxation correction was assumed for simulation of the PSF for each compartment. Using the RSF, the GTM was calculated, which describes the signal contributions of each compartment arising from PSF smearing of the other examined compartments. Finally, a corrected average signal intensity was obtained for every tissue compartment.

### 2.5 Concentration determination

Because the dual-tuned $^{23}$Na/$^1$H head coil did not allow the use of external references for the determination of the aTSC, the CSF compartment was used as an internal reference. To validate CSF as an individual reference and to obtain a mean concentration value, its sodium concentration was determined by using laboratory CSF sodium values acquired from independently conducted, medically indicated spinal taps during clinical diagnostic routines for 23 patients without and for 14 patients with a confirmed MS diagnosis.

Frequently, signal intensities of tissues are determined within manually drawn regions of interest (ROIs). However, due to the low nominal spatial resolution in combination with strong PVE resulting from fast transverse relaxation, ROI positioning can have a strong effect on the calculated concentration values. By using the binary mask-based PVC, a corrected average $^{23}$Na signal intensity over almost the whole brain was calculated for each tissue compartment (as described in subsection 2.4). These average signal intensities were then normalized to the determined mean laboratory CSF concentration for the respective cohort to obtain aTSC values for NAWM and NAGM, as well as for lesions. Only the lower parts of the brain at the level below the midbrain (i.e., the rest of the brainstem and cerebellum), where the 1Tx/32Rx $^1$H head coil did not provide sufficient MPRAGE image quality for appropriate segmentation, were excluded from the evaluation.

### 2.6 In vivo MRI measurements

All in vivo MRI measurements were approved by the local ethical review board and all healthy volunteers as well as patients provided informed consent prior to the examination. Seventeen patients (three males, 14 females; age 51 ± 8 years, range 33–63 years) with a confirmed SPMS diagnosis respecting the revised McDonald criteria\cite{35} were enrolled in this study. For all patients, aTSC values of NAWM, NAGM, and lesions were determined.

To assess the variation in the determined $^{23}$Na concentrations, the measurement protocol was conducted three times in a row for five healthy volunteers with short breaks of about 5 min and repositioning in between. This ensured independent scans under nearly identical conditions. Furthermore, eight healthy volunteers were examined once, such that in total aTSC values of NAWM and NAGM were determined for 13 healthy subjects (six males, seven females; age 39 ± 11 years, range 22–52 years), who served as the control group for the MS patients.

### 2.7 Statistical analysis

A Wilcoxon rank-sum test was used to test for significant deviations in the mean CSF sodium concentration between patients with and without MS.

The results of the three consecutive measurements ($M_1, M_2, M_3$) of five volunteers were used to assess the variability of the aTSC determination for the different compartments. Bland–Altman plots were used for plotting the difference between the aTSC values of two measurements $M_i$ and $M_j$ ($i, j = 1, 2, 3; i < j$) of the same volunteer against the mean value of the same measurements. The coefficient of repeatability was calculated as 1.96 times the SD (limits of the 95% confidence interval) over all measurements of the differences between two measurements.\cite{38} Additionally, for each of the five volunteers the coefficient of variation (CoV) was determined as the ratio of the SD over the mean aTSC of the three measurements for NAWM and NAGM. These CoV values were furthermore used to calculate a mean CoV for all five volunteers and the corresponding SD. The differences between the mean aTSC values over the five volunteers for the measurements $M_1, M_2,$ and $M_3$ were analyzed using a one-way ANOVA for NAWM and NAGM.

Furthermore, the determined aTSC values of the healthy control group were tested for correlation with the CSF fraction of the examined brain volume by calculating the Pearson's correlation coefficient, as such correlations would provide a hint regarding insufficient correction of PVE.

The mean NAWM and NAGM concentration values of the MS patients and healthy volunteers were tested for significant differences using the paired-samples Wilcoxon rank-sum test. Additionally, the mean concentration values of lesions in MS patients were compared with the
NAWM values, again with the use of the paired-samples Wilcoxon rank-sum test. Bonferroni correction was used to account for multiple comparisons.

The means of the NAWM, NAGM, and lesion aTSC values for the two lesion models were tested for significant differences using the paired-samples Wilcoxon signed-rank test for both healthy controls and SPMS patients.

Results were considered statistically significant for \( p \) values less than 0.05. All statistical analysis was performed with MATLAB R2019b.

3  |  RESULTS

3.1  |  Laboratory CSF sodium concentration

The results of the laboratory CSF sodium concentration are shown in Figure 2. No significant differences were found between controls without MS (147.9 ± 2.0 mmol/l) and patients suffering from MS (147.2 ± 2.5 mmol/l) using the Wilcoxon rank-sum test (\( p = 0.42 \)). Therefore, the mean sodium CSF concentration of both groups (147.6 ± 2.2 mmol/l) was used for normalization of the \( ^{23} \text{Na} \) MR signal intensities for MS patients as well as healthy controls.

3.2  |  In vivo MRI measurements

Exemplary measurement results of one healthy volunteer (V1) and two MS patients with different brain atrophy and lesion loads (P4 and P11) are shown in Figure 3.

The receive coil profile correction using the universal sensitivity map clearly increased the \( ^{23} \text{Na} \) MR signal intensity of the lateral ventricles as they are located in the center of the FOV. Regions that were identified as lesions show visibly increased signal intensity in \( ^{23} \text{Na} \) images, especially in those with a larger volume.

The repeatability of the quantification approach is presented in Figure 4, using Bland-Altman plots. The results of the determined aTSC values for NAWM and NAGM, as well as the CoV values for all five volunteers, are also given in Table 1. The limits of agreement at the 95% confidence interval were equal for both lesion models with \(-2.9\) and \(+3.2\) mmol/l for NAWM (coefficient of repeatability 3.1 mmol/l) and \(-5.7\) and \(+6.5\) mmol/l for NAGM (coefficient of repeatability 6.1 mmol/l). The average CoVs over all five volunteers were \(1.9\% \pm 0.9\%\) for NAWM (the same for both lesion models), and \(2.2\% \pm 1.5\%\) and \(2.2\% \pm 1.6\%\) for NAGM using lesion models 1 and 2, respectively.

The differences in the NAWM and NAGM average aTSC values between the two lesion models could be neglected regarding the coefficients of repeatability for the same measurements.

One-way ANOVA did not reveal any significant differences between the mean aTSC over all five volunteers for the three measurements \( M_3 \), \( M_2 \), and \( M_1 \), neither for NAWM nor NAGM, independent of the underlying lesion relaxation model (NAWM: \( p = 0.99/0.98 \) for lesion model 1/model 2; NAGM: \( p = 0.94 \) for both lesion models).

All determined aTSC values for the different brain compartments, as well as the corresponding mean and SD values, can be found in Table 2 for the healthy volunteers and in Table 3 for the SPMS patients. Furthermore, the results are depicted in boxplots in Figure 5.

**Figure 2**  Boxplots of the cerebrospinal fluid (CSF) sodium concentration determined by spinal tap for patients without multiple sclerosis (MS) (no MS) and patients with MS (MS). No significant differences were found between the two groups.
The differences in the average aTSC values between the two lesion models were significant in all examined compartments \((p < 0.03)\), except for the NAWM of healthy volunteers \((p = 0.25)\). Nevertheless, for NAWM and NAGM, the differences were still negligible for concentration determination regarding the coefficients of repeatability determined in the five volunteer measurements and the intersubject variability in the SPMS cohort. By contrast, for lesions, the average aTSC was 22% higher for model 1 (lesion = WM) than for model 2 (lesion = CSF). This resulted from both the relaxation correction as well as PVC with varying proportions strongly depending on the specific anatomy of the patient due to different lesion loads, lesion volumes, and lesion locations, and therefore also a different influence of PVE.

Additionally, the results for the healthy control group were analyzed in more detail to obtain a better understanding of the quantification method using PVC and CSF as an internal reference. No significant correlation was found between the CSF fraction of the examined brain volume and the determined aTSC values, neither for NAWM \((\rho = 0.05/0.06, p = 0.86/0.87 \text{ for model 1/model 2})\), nor for NAGM \((\rho = -0.37/-0.36, p = 0.22/0.22 \text{ for model 1/model 2})\). The PVC had major influence on the resulting aTSC values, especially because the CSF compartment was used as an internal reference. Normalized to the CSF concentration, the mean aTSC value was corrected from 52% to 44% of the \(^{23}\text{Na} \) CSF signal intensity for NAWM and from 69% to 44% of the \(^{23}\text{Na} \) CSF signal intensity for NAGM. Also, the ratio of NAGM/NAWM was affected by the PVC and was corrected from 1.32 to 1.52.

The average NAWM aTSC was significantly higher in patients with SPMS than in the control group \((p = 0.007 \text{ for model 1} \text{ and } p = 0.009 \text{ for model 2})\). For NAGM, no significant differences were found between the aTSC values of healthy volunteers and patients \((p = 0.98 \text{ for model})\.

![Exemplary measurement data of one healthy volunteer (A) and two multiple sclerosis (MS) patients with different brain atrophy and lesion loads (B and C). For each subject, \(^{23}\text{Na} \) images with and without coil profile correction using a universal coil sensitivity map (USM), anatomical \(^1\text{H} \) magnetization-prepared rapid acquisition gradient echo (MPRAGE), and fluid-attenuated inversion recovery (FLAIR) images, as well as the created tissue masks for white matter (WM), gray matter (GM), MS lesions, and cerebrospinal fluid (CSF), are shown. Hyperintensities in the FLAIR image categorized as MS lesions also show increased signal intensities in \(^{23}\text{Na} \) images (red arrows).](image-url)
The average aTSC of MS lesions was significantly higher than the aTSC of NAWM of SPMS patients, as well as the aTSC of NAWM in the healthy control group \((p < 0.001\) for both cases). All results remain significant after Bonferroni correction for the three different comparisons (NAWM and NAGM of healthy volunteers vs. MS patients and lesions vs. NAWM of MS patients).

**DISCUSSION**

In this work, a \(^{23}\text{Na}\) MRI postprocessing workflow that combines different correction methods for improved determination of the aTSC of brain compartments was implemented and evaluated at a field strength of 7 T. Because of the significant increase in SNR compared with birdcage coils,\(^{19,20}\) the use of an additionally integrated 32-channel receive phased-array head coil enabled \(^{23}\text{Na}\) MRI with a high nominal spatial resolution of \((2.5 \text{ mm})^3\) isotropic in feasible scan times. The repeatability was assessed by three consecutive MRI measurements of five healthy volunteers. To evaluate the feasibility of the proposed quantification workflow, the method was applied to a healthy control group, as well as patients suffering from SPMS.

**4.1 | CSF as an internal reference for concentration normalization**

As the integrated \(^{23}\text{Na}\) 32-channel receive phased-array of the dual-tuned \(^{23}\text{Na}/^1\text{H}\) head coil prohibits the use of external references due to restricted space around the head, an internal reference had to be used. Besides the vitreous humor in the eyes,\(^{22}\) CSF can be used as an internal reference for concentration calibration.\(^{21}\) The determined sodium concentrations are in good agreement with the literature.\(^{39}\) As no significant differences were found between healthy controls and patients suffering from MS and as the SD of the determined CSF sodium concentration values was only 1.5% of the mean value, CSF can be considered as an appropriate internal reference for the examined patient cohort using the presented postprocessing workflow. As measurement fluctuations between subjects dominate intrasubject fluctuations caused by CSF sodium rhythms, the time of day of the MRI examination is not expected to have any relevant influence. In other pathologies such as migraine,\(^{40}\) however,
the CSF sodium concentration might differ from healthy volunteers, such that the use of different values would be required. It might also not be sufficient to consider only CSF signal from single slices or a specific ROI instead of the whole CSF compartment due to the reduced volume for averaging. Furthermore, the correction of influences from the imaging process such as coil profiles and PVE is crucial, as otherwise aTSC values of other compartments (WM, GM) would be clearly overestimated.

4.2 | aTSC quantification and repeatability in NAWM and NAGM of healthy volunteers

The mean aTSC values for NAWM and NAGM across all healthy volunteers for the current study are consistent with results described in the literature, which, however, present a wide range of values because of different acquisition schemes and quantification approaches. Compared only with the most recent studies at different field strengths, the values of NAWM coincide, while the values of NAGM are clearly higher. The latter might result from different aspects distinguishing our study from previous published studies. First, we used the CSF sodium concentration determined by spinal tap as an internal reference. With 147.6 mmol/l, the value was noticeably higher than all published values determined by MRI with the help of external references. Second, none of the cited studies used both PVC and relaxation correction. We showed that the PVC especially increased the GM aTSC in relation to WM aTSC. In combination with the also improved spatial resolution of our study, this might explain the higher aTSC values in GM, whose structures are mostly only the size of a few 23Na voxels. Additionally, the applied segmentation algorithm to generate the binary masks might particularly influence the measured concentrations in small regions such as GM.

Only a few systematic studies are available regarding the repeatability of 23Na MRI of the human brain, and none of them at a field strength of 7 T. The calculated intrasubject CoVs as well as the intersubject SD of the aTSC values in our study are comparable or even smaller than those from previous studies.

### TABLE 1 Overview of the results for the aTSCs of the NAWM and NAGM for the repeatability measurements of five healthy volunteers

| Volunteer | Sex | Age (years) | Measurement | aTSC NAWM (mmol/L) | aTSC NAGM (mmol/L) |
|-----------|-----|-------------|-------------|-------------------|-------------------|
|           |     |             | Model 1     | Model 2           | Model 1           | Model 2           |
| V1        | F   | 43          | M₁          | 42.5              | 42.5              | 62.8              | 62.8              |
|           |     |             | M₂          | 43.9              | 43.9              | 63.9              | 63.8              |
|           |     |             | M₃          | 44.1              | 44.1              | 63.7              | 63.6              |
|           |     |             | mean        | 43.5 ± 0.7        | 43.5 ± 0.7        | 63.5 ± 0.5        | 63.4 ± 0.4        |
|           |     |             | CoV         | 1.6%              | 1.6%              | 0.8%              | 0.7%              |
| V2        | M   | 41          | M₁          | 44.1              | 44.1              | 71.7              | 71.7              |
|           |     |             | M₂          | 41.4              | 41.3              | 65.2              | 65.2              |
|           |     |             | M₃          | 41.9              | 41.9              | 65.2              | 65.1              |
|           |     |             | mean        | 42.5 ± 1.2        | 42.4 ± 1.2        | 67.4 ± 3.1        | 67.3 ± 3.1        |
|           |     |             | CoV         | 2.8%              | 2.8%              | 4.6%              | 4.6%              |
| V3        | M   | 28          | M₁          | 43.2              | 43.2              | 67.2              | 67.1              |
|           |     |             | M₂          | 40.6              | 40.6              | 62.8              | 62.7              |
|           |     |             | M₃          | 40.7              | 40.7              | 64.9              | 64.9              |
|           |     |             | mean        | 41.5 ± 1.2        | 41.5 ± 1.2        | 65.0 ± 1.8        | 64.9 ± 1.8        |
|           |     |             | CoV         | 2.9%              | 2.9%              | 2.8%              | 2.8%              |
| V4        | F   | 22          | M₁          | 36.3              | 36.3              | 57.8              | 57.8              |
|           |     |             | M₂          | 37.4              | 37.4              | 57.8              | 57.8              |
|           |     |             | M₃          | 37.2              | 37.2              | 59.2              | 59.1              |
|           |     |             | mean        | 37.0 ± 0.5        | 37.0 ± 0.5        | 58.3 ± 0.7        | 58.2 ± 0.6        |
|           |     |             | CoV         | 1.3%              | 1.3%              | 1.1%              | 1.1%              |
| V5        | M   | 25          | M₁          | 47.7              | 47.7              | 75.9              | 75.8              |
|           |     |             | M₂          | 48.4              | 48.2              | 77.6              | 77.5              |
|           |     |             | M₃          | 48.9              | 48.8              | 79.3              | 79.3              |
|           |     |             | mean        | 48.3 ± 0.5        | 48.2 ± 0.4        | 77.6 ± 1.4        | 77.5 ± 1.4        |
|           |     |             | CoV         | 1.0%              | 0.9%              | 1.8%              | 1.8%              |

Abbreviations: aTSC, apparent tissue sodium concentration; CoV, coefficient of variation; NAGM, normal appearing gray matter; NAWM, normal appearing white matter.
In the current study, significantly higher (9%–10%, depending on the lesion model) aTSCs in the NAWM of MS patients were found compared with those for healthy controls. With measured elevations up to 39%, this was also the case in other previously published MRI MS studies. In the current study, significantly higher (9%–10%, depending on the lesion model) aTSCs in the NAWM of MS patients were found compared with those for healthy controls. With measured elevations up to 39%, this was also the case in other previously published MRI MS studies. In the current study, significantly higher (9%–10%, depending on the lesion model) aTSCs in the NAWM of MS patients were found compared with those for healthy controls. With measured elevations up to 39%, this was also the case in other previously published MRI MS studies.

### TABLE 2
Overview of the results for the aTSCs of the NAWM and NAGM for all healthy volunteers. For V1 to V5, the mean aTSC and SD of the three consecutive measurements are denoted.

| Volunteer | Sex | Age (years) | aTSC NAWM (mmol/L) | aTSC NAGM (mmol/L) |
|-----------|-----|-------------|--------------------|--------------------|
|           |     |             | Model 1            | Model 2            | Model 1            | Model 2            |
| V1        | F   | 43          | 43.5 ± 0.7         | 43.5 ± 0.7         | 63.5 ± 0.5         | 63.4 ± 0.4         |
| V2        | M   | 41          | 42.5 ± 1.1         | 42.4 ± 1.2         | 67.4 ± 3.0         | 67.4 ± 3.0         |
| V3        | M   | 28          | 41.5 ± 1.2         | 41.5 ± 1.2         | 65.0 ± 1.8         | 64.9 ± 1.8         |
| V4        | F   | 22          | 37.0 ± 0.4         | 37.0 ± 0.4         | 58.3 ± 0.7         | 58.3 ± 0.6         |
| V5        | M   | 25          | 48.3 ± 0.5         | 48.2 ± 0.4         | 77.6 ± 1.4         | 77.5 ± 1.4         |
| V6        | F   | 47          | 48.8              | 48.8              | 70.0              | 69.9              |
| V7        | M   | 49          | 43.7              | 43.6              | 58.2              | 58.2              |
| V8        | F   | 51          | 44.5              | 44.5              | 61.4              | 61.3              |
| V9        | M   | 51          | 41.6              | 41.6              | 55.1              | 55.0              |
| V10       | F   | 52          | 38.9              | 38.9              | 55.9              | 55.9              |
| V11       | F   | 34          | 35.5              | 35.5              | 52.8              | 52.8              |
| V12       | F   | 40          | 45.9              | 45.9              | 66.7              | 66.7              |
| V13       | M   | 25          | 40.5              | 40.5              | 66.6              | 66.6              |
| mean      |     | 39 ± 11     | 42.5 ± 3.8         | 42.5 ± 3.8         | 63.0 ± 6.7         | 62.9 ± 6.6         |

Abbreviations: aTSC, apparent tissue sodium concentration; NAGM, normal appearing gray matter; NAWM, normal appearing white matter.

### TABLE 3
Overview of the results for the aTSCs of the NAWM, NAGM and MS lesions for all MS patients.

| Patient | Sex | Age (years) | aTSC NAWM | aTSC NAGM | aTSC MS lesion |
|---------|-----|-------------|-----------|-----------|---------------|
|         |     |             | Model 1   | Model 2   | Model 1       | Model 2       |
| P1      | F   | 62          | 43.7      | 43.8      | 64.5          | 64.4          |
| P2      | F   | 52          | 49.1      | 49.2      | 72.7          | 72.6          |
| P3      | F   | 63          | 46.1      | 46.1      | 69.2          | 69.2          |
| P4      | F   | 55          | 45.0      | 45.6      | 61.6          | 61.4          |
| P5      | F   | 55          | 50.1      | 50.1      | 68.3          | 68.2          |
| P6      | M   | 41          | 43.8      | 43.8      | 51.8          | 51.7          |
| P7      | F   | 33          | 45.7      | 45.7      | 62.7          | 62.6          |
| P8      | F   | 56          | 58.7      | 59.0      | 80.9          | 80.8          |
| P9      | M   | 53          | 50.3      | 51.0      | 60.0          | 59.9          |
| P10     | M   | 52          | 42.7      | 43.2      | 62.6          | 62.5          |
| P11     | F   | 53          | 46.2      | 46.4      | 61.7          | 61.6          |
| P12     | F   | 46          | 45.4      | 45.7      | 62.7          | 62.4          |
| P13     | F   | 53          | 43.9      | 44.0      | 58.2          | 58.1          |
| P14     | F   | 52          | 47.0      | 47.1      | 65.5          | 65.4          |
| P15     | F   | 39          | 44.0      | 44.3      | 56.2          | 56.1          |
| P16     | F   | 50          | 44.1      | 44.3      | 59.7          | 59.5          |
| P17     | F   | 46          | 43.4      | 43.6      | 57.9          | 57.9          |
| mean    |     | 51 ± 8      | 46.4 ± 3.8 | 46.6 ± 3.8 | 63.3 ± 6.6 | 63.2 ± 6.8 | 100.8 ± 13.5 | 82.7 ± 10.9 |

Abbreviations: aTSC, apparent tissue sodium concentration; MS, multiple sclerosis; NAGM, normal appearing gray matter; NAWM, normal appearing white matter.

### 4.3 aTSC in NAWM, NAGM, and MS lesions of SPMS patients

In the current study, significantly higher (9%–10%, depending on the lesion model) aTSCs in the NAWM of MS patients were found compared with those for healthy controls. With measured elevations up to 39%, this was also the case in other previously published MRI MS studies.
particular SPMS studies,\textsuperscript{7,9} which all used sequence parameters similar to the parameters used in this study, particularly nominal FAs around 90°. By contrast, in a study using very short RF pulses with lower nominal FAs, no significant elevation in NAWM TSC was detected.\textsuperscript{13} This could be explained by the loss of myelin in MS patients and the resulting changes in the molecular environment of the sodium ions in NAWM. The degradation of WM results in a more homogeneous environment with a reduced residual quadrupole splitting and lengthened relaxation times. As a result, sodium ions are more visible for MRI not optimized for minimal residual quadrupole signal loss (high nominal FAs with accordingly longer RF pulses).\textsuperscript{13,23} Regarding these results, the measured aTSC increase is not expected to result from a higher amount of sodium, but from increased T2 relaxation times related to myelin damage, which facilitate the detection by $^{23}$Na MRI. Nevertheless, future studies on $^{23}$Na MRI should further evaluate the origin of signal intensity changes between MS patients and healthy controls, in particular the influence of altered relaxation behavior and real increases in sodium concentration, for example, due to extended extracellular space.

In our study, aTSC values were corrected for PVE and, furthermore, no correlation was found between the determined NAWM aTSC values and the fraction of CSF in the examined volume. Therefore, increased CSF volume as a result of brain atrophy in MS patients, which was also mentioned as an explanation for WM TSC elevation in MS patients,\textsuperscript{13} is not expected to have a relevant impact on NAWM aTSC values.

For NAGM, no significant differences between MS patients and the healthy control group were detected. Results of previous studies regarding NAGM TSC values in MS patients are controversial and often depend on the evaluated area and the MS subtype, but many studies also detected higher TSC,\textsuperscript{5–7} especially in patients with SPMS.\textsuperscript{7–9} In this study, only the mean value over the whole GM was evaluated, which may explain the different results compared with studies that explicitly examined deep GM or cortical GM. Furthermore, especially for cortical GM with its proximity to CSF, biases due to stronger brain atrophy are possible when PVE are not considered sufficiently and may also lead to higher aTSC values in MS patients compared with healthy controls. By addressing this effect by higher spatial resolution and PVC, the accuracy in this study might be improved.

Depending on the lesion model, the mean lesion aTSC in this study was between 77% and 117% higher than in the NAWM of MS patients and was between 95% and 137% higher than in the WM of healthy controls. This is clearly higher than values reported in the literature,\textsuperscript{5–9,13} which are between 12%\textsuperscript{8} and 41%\textsuperscript{7} for the NAWM of MS patients and 17%\textsuperscript{9} and 82%\textsuperscript{5} for the WM of healthy controls. However, in these works, PSF smearing was not explicitly corrected. Stobbe and Beaulieu\textsuperscript{16} have shown that for typical lesion sizes, $^{23}$Na MR signal intensity is usually clearly underestimated by up to 95% for small lesions. For similar lesion models as used in this work, they estimated an average TSC increase in MS lesions of between 60% and 160%, which is in very good accordance with our study.

### 4.4 Influence of different relaxation models of MS lesions on quantification

The relaxation properties of MS lesions are not exactly known and moreover depend on the individual lesion.\textsuperscript{34,35} In this work, two different relaxation models of MS lesions that represent the lower (MS lesion = WM) and upper bound (MS lesion = CSF) of expected values were evaluated. For the NAWM and NAGM of both healthy controls and MS patients, no relevant differences were present in the determined aTSC values using either model. This suggests that for quantification of average aTSC values for these compartments, the exact relaxation properties of MS lesions are irrelevant due to their low fraction of the total examined volume. As expected, with 22% higher aTSC values for model 1 compared with model 2, the assumed lesion relaxation model had a strong influence on $^{23}$Na quantification in MS lesions. This resulted from both the relaxation...
correction as well as PVC, with varying proportions strongly depending on the specific anatomy of the patient due to different lesion loads and lesion locations, and therefore also a different influence of PVE. Improved analysis could be achieved by not only considering upper and lower bounds, but also by trying to determine mean relaxation times. However, this might be challenging, because even recently published and time-efficient \(^{23}\)Na relaxometry techniques such as MR fingerprinting do not reach the necessary spatial resolutions in feasible scan times.

### 4.5 Limitations

One limitation of the presented method is that only mean values over the whole examined compartments, WM, GM, and lesions are available, and the topography of alteration in aTSC inside these compartments, as was shown in other studies, is not possible. However, the segmented compartments of the brain used for PVC could be subclassified in future studies, allowing the determination of mean aTSC values in more detailed brain structures.

Regarding the PVC, the main limitation is the modeling of the relaxation behavior for the different compartments. In this work, the theoretical fraction 60%/40% of fast to slow relaxing components for transverse relaxation of a homogenous molecular system was assumed, as corresponding relaxation times were adopted from the literature. However, brain tissue, and in particular WM, are highly heterogeneous tissues, for which the theoretical fraction does not hold any more. This is a point that should be considered in further studies determining \(^{23}\)Na relaxation times, but nevertheless the PVC is expected to give reliable results, as shown in previous works.

In addition to the coil profile correction, PVC, and relaxation correction applied in this study, further correction might be included in future studies. Examples are interleaved \(^1\)H motion correction and gradient trajectory correction, which could both be implemented without affecting the current postprocessing pipeline. Even although no image artifacts were visible in images of this study, this might become important at higher field strengths and higher spatial resolutions.

An intrinsic limitation of \(^{23}\)Na MRI is the long scan times. As the \(^1\)H birdcage of the dual-tuned \(^{23}\)Na/\(^1\)H head RF coil does not provide sufficient image quality for anatomical images, a coil change was necessary, which further elongated the measurement time. In this context, dedicated coils, which serve for both \(^{23}\)Na MRI and diagnostic \(^1\)H MRI, are desirable.

Furthermore, due to very long scan times that were not feasible for patients, repeatability was only evaluated in healthy subjects and therefore no examination of lesions was possible in this context. Also, comparing measurements among different sites and scanners is a crucial future step to further evaluate the robustness of the proposed method.

### 5 CONCLUSION

Our study presented a measurement and postprocessing setup for quantitative \(^{23}\)Na MRI of the human brain at 7 T that was applied to healthy subjects and MS patients. In combination with the proposed postprocessing pipeline, CSF was shown to be a stable internal reference for healthy controls as well as patients with MS. Our method showed high repeatability. The results can serve as a baseline for further studies establishing \(^{23}\)Na brain MRI as a biomarker in diseases such as MS.

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### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

### ORCID

Angelika Mennecke https://orcid.org/0000-0001-6795-5627

Lena V. Gast https://orcid.org/0000-0002-4599-1122

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