Assessing the variability of $^{23}$Na MRI in skeletal muscle tissue: Reproducibility and repeatability of tissue sodium concentration measurements in the lower leg at 3 T

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The goal of this study was to evaluate the reproducibility and repeatability of tissue sodium concentration (TSC) measurements using $^{23}$Na MRI in skeletal muscle tissue. $^{23}$Na MRI was performed at 3 T on the right lower leg of eight healthy volunteers (aged 28 ± 4 years). The examinations were repeated at the same site after ~22 weeks to assess the variability over a medium-term period. Additionally, they were scanned at a second site shortly before or shortly after the first visit (within 3 weeks) to evaluate the inter-site reproducibility. Moreover, we analysed the effect of $B_0$ correction on the variability. Coefficients of variations (CVs) from mean TSC values as well as Bland–Altman plots were used to assess intra-site repeatability and inter-site reproducibility. In phantom measurements, the $B_0$ correction improved the quantitative accuracy. We observed differences of up to 4.9 mmol/L between the first and second visit and a difference of up to 3.7 mmol/L between the two different sites. The CV for the medium-term repeatability was 15% and the reproducibility CV was 9%. The Bland–Altman plots indicated high agreement between the visits in all muscle regions. The systematic bias of −0.68 mmol/L between site X and Y ($P = 0.03$) was slightly reduced to −0.64 mmol/L after $B_0$ correction ($P = 0.04$). This work shows that TSC measurements in healthy skeletal muscle tissue can be performed with good repeatability and reproducibility, which is of importance for future longitudinal or multicentre studies.

KEYWORDS
quantification, repeatability, reproducibility, skeletal muscle tissue, sodium MRI, total tissue sodium content

1 | INTRODUCTION

Noninvasive examinations of $^{23}$Na MRI-derived measures in skeletal muscle tissue are of great interest in clinical research due to their sensitivity to tissue viability and ion homeostasis. The most frequently proposed marker obtained by $^{23}$Na MRI is the tissue sodium concentration (TSC). The
TSC represents the volume fraction-weighted average of the intra- and extracellular sodium concentration. It is, therefore, sensitive to alterations in volume fractions or intra- and extracellular sodium concentrations. In healthy tissue, the sodium-potassium pump maintains a high sodium gradient over the cell membrane with an intracellular sodium concentration of ~15 mM and a 10-fold higher concentration in the extracellular space. In muscular disorders, mutations in genes encoding for ion channels or membrane-related proteins can lead to a disturbance of this carefully maintained gradient. $^{23}$Na MRI has previously exposed increases of sodium level in muscle tissue of patients with muscular channelopathies.1-4 On the other hand, mismatching of salt intake and renal excretion can lead to a disturbed homeostasis. For example, patients with hypertension exhibited an increased muscular sodium content that was detectable by $^{23}$Na MRI.5 In haemodialysis patients, $^{23}$Na MRI was used as a noninvasive method to monitor the tissue sodium removal of the dialyser.6 Another $^{23}$Na MRI study indicated that haemodialysis patients with type 2 diabetes have higher sodium content in muscle and skin tissue than control haemodialysis patients.7 Furthermore, a delayed muscle sodium recovery after exercise was reported in patients with type 2 diabetes, which can be explained by decreased sodium-potassium pump activity and alterations in the tissue microvasculature.8 Thus, $^{23}$Na MRI provides interesting quantitative markers that track pathological changes as well as response to treatment and exercise.

Due to the low in vivo concentration and small nuclear magnetic resonance sensitivity of sodium, $^{23}$Na MR imaging usually requires large voxel volumes and long acquisition times compared with $^1$H MRI (10–15 minutes in general). Furthermore, the sodium nucleus possesses very short relaxation times, which necessitates the use of dedicated ultrashort echo time (UTE) sequences to enable quantitative measurements.9 Although TSC has been measured in skeletal muscle tissue in several clinical studies,1,2,5,7,10,11 there are sparse data regarding the reproducibility and repeatability of TSC measurements. Research on the variability of $^{23}$Na MRI has been performed on brain and cartilage reporting a small variability between scan-rescan experiments.12-16 To date, no data exist that estimate the variability of quantitative $^{23}$Na MRI measurements in muscle during longitudinal studies or at different sites in multicentre studies.

The goal of this study was to test the reproducibility on two different scanners as well as the medium-term repeatability of sodium quantification in skeletal muscle tissue using a UTE sequence. We measured the TSC of the leg muscles two times during the course of several weeks to mimic the variability one could expect during longitudinal studies. Furthermore, we assessed the reproducibility of the TSC quantification approach on another site and evaluated the necessity of B0 corrections.

2 METHODS

2.1 Acquisition protocol

Imaging with the same protocol was performed on the right leg of eight healthy volunteers (five males and three females) with an average age of 28.1 ± 4.4 years. The institutional review boards of both institutions approved the study and all volunteers provided informed consent prior to the examination.

Two different MR systems were used: (1) a 3 T whole-body MR system (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) on site X, with a transmit/receive sodium RF birdcage knee coil (Stark Contrast, Erlangen, Germany) single-tuned at 32.6 MHz of length 16 cm and inner diameter 18 cm, and (2) a 3 T whole-body MR system (Magnetom Prisma, Siemens Healthineers) on site Y, with the same model of $^{23}$Na single-tuned knee coil as at site X.

The median interval between the visits at sites X and Y was 22 days (range: 7–25 days). Furthermore, each volunteer was scanned at site X a second time 25 ± 2 weeks later (range: 22–26 weeks). Prior to every acquisition, each volunteer rested in a supine position for 30 minutes to ensure uniform conditions for all examinations, since it is known that exercise—including even walking—can alter muscular sodium concentrations.9 We chose this resting time because there are signal decreases after exercise and postural changes, which were close to the baseline after ~30 minutes.8,17

2.2 MRI protocol

A global flip angle calibration (TE/TR 0.35/400 ms, rectangular excitation pulse of 0.5 ms duration, 12 measurements with linearly increasing nominal flip angle from 0 to 140°, sinusoidal fit) and a manual B0 shim using the $^1$H MRI-based B0-shimming routine of the manufacturer were performed. All $^{23}$Na images were acquired using a density-adapted 3D-radial readout scheme.18 The radial raw datasets were reconstructed offline with a custom-written MATLAB script (MathWorks, Natick, MA).

The spin density-weighted $^{23}$Na images were acquired with a comparatively long TR of 120 ms, one average, and a flip angle of 90°. A read-out duration of 10 ms was used. Two echoes were recorded at 0.3 and 14 ms with an isotropic field of view of 320 mm, which were reconstructed to a nominal spatial resolution of $3 \times 3 \times 15$ mm$^3$. The echo time was defined as the period between the middle of the rectangular excitation pulse (of 0.5 ms duration) and the beginning of the readout. Parameters for the radial readout were 8264 projections, a readout duration of 10 ms and a maximum gradient strength of 7.89 mT/m. The acquisition time was 10.46 minutes.
A $^1$H anatomical imaging protocol was added to facilitate image segmentation. The body coil was used for excitation and signal reception without repositioning the subject. A FLASH sequence was acquired with the following parameters: TR/TE 308/4.77 ms, 24 interleaved slices with field of view 288 × 288 mm$^2$, spatial resolution 1×1×5 mm$^3$ and an acquisition time of 0.55 minutes.

2.3 | Sodium quantification

All images were acquired with the same calibration tube phantoms as described in previous studies$^2$ (four cylinders filled with 20 and 40 mmol/L NaCl without and with 5% agarose gel), which were placed in a phantom holder next to the calf muscles and were included in the field of view. Magnitude images were reconstructed using a Hamming filter to reduce Gibb’s ringing artifacts.$^{19,20}$ Using the first echo image (TE 0.3 ms), sodium concentrations for the muscles were then measured using linear regression in MATLAB. Therefore, we computed the average signal intensities of two calibration phantoms (20 and 40 mmol/L NaCl in 5% agarose) and an ROI drawn in the background signal that was used as reference for 0 mmol/L sodium concentration. The resulting linear regression curve was used to extrapolate the sodium maps of the whole leg. TSC values were evaluated on the central slice of this map in three manually segmented muscles: tibialis anterior, soleus and gastrocnemius medialis.

If external reference samples are used for calibration, $B_0$ inhomogeneities due to high susceptibility differences can cause blurring artifacts and thus quantification errors, which can be mitigated by adequate correction methods. Furthermore, long readout periods during the radial readout scheme can be very sensitive to $B_0$ inhomogeneities. Thus, correction of the $B_0$ field inhomogeneity can improve the sharpness of anatomy and the apparent SNR.$^{21}$ Therefore, the resonance offset was calculated using the double-echo $^{23}$Na acquisition. The datasets were reconstructed as complex images and for each voxel the resonance offset was calculated according to

$$\delta = \frac{\Phi_2 - \Phi_1}{TE_2 - TE_1}$$

where $\Phi_1$ and $\Phi_2$ describe the phases of each voxel of the two images corresponding to echo times $TE_1$ and $TE_2$, respectively. The calculated $B_0$ maps were then used to calculate corrected TSC maps.$^{21,22}$ For this frequency-segmented approach, a separated k-space is calculated with the different off-resonance frequencies and transformed by Fourier transform into the image space. The corrected image is then obtained on a voxel-wise combination of these images.

2.4 | Phantom measurements

Additionally, phantom experiments were performed using a cylindrical phantom filled with 25 mmol/L NaCl. This phantom was scanned twice on site X and once at site Y, to give information about possible differences in TSC measurements due to hardware characteristics. The same protocol and data postprocessing as described above were applied. For $^{23}$Na signal calibration, a linear regression based on the signal from the calibration phantoms without agarose was performed.

2.5 | Data analysis

In vivo TSC values are presented as mean and standard deviation (SD) in mmol/L. A one-way ANOVA test was applied to compare the mean TSC of the different muscle groups. Individual comparisons between two muscles were performed with a paired-sample t-test with Bonferroni-corrected P-values (adjusted alpha = 0.05/3 = 0.0167) for multiple comparisons. The variability is expressed as the coefficient of variation (CV) defined as the ratio of the SD to the mean to assess the repeatability (between scan 1 and 2 at site X) and the reproducibility (between the first scans at sites X and Y). Bland-Altman plots were computed with the absolute difference between the two measurements plotted against the mean of the two measurements. Such plots measure a possible systematic difference between two datasets as well as the limits of agreement at the 95% confidence interval (CI). Furthermore, the coefficient of repeatability is calculated as 1.96 multiplied by the SD of the differences.$^{23}$

3 | RESULTS

The sodium concentrations of the phantom could be measured with good accuracy (Table 1). While there was only a difference of 2.4% between the first and second scan at site X, we observed a difference of 11.2% between sites X and Y. After $B_0$ correction, this discrepancy diminished to 4.5%.
Figure 1 presents exemplary $^{23}$Na images of one subject for the three different examinations, the corresponding B$_0$ and TSC maps (without and with B$_0$ correction). The calibration phantoms exhibited slight off-resonances that were higher in the phantoms in the middle of the phantom holder than in the outer part. Table 2 presents the off-resonances measured in the phantom experiment and in vivo measurements. There was a systematic off-resonance of an average of $-17$ Hz in the calibration phantoms that was observed across sites and scan time points. B$_0$ correction increased the measured TSC.

The mean TSC values were measured on the three muscle regions for each volunteer (Figure 2). We observed a significant difference in TSC in at least one muscle (ANOVA: $P < 0.0005$). The tibialis anterior muscle has lower TSC values than the gastrocnemius medialis ($P = 0.00006$) and the soleus muscle ($P = 0.004$).

**Table 1** Measured mean tissue sodium concentration (TSC) in mmol/L of the phantom (25 mmol/L NaCl) for each site and scan. Values are provided without (“uncorrected”) and with B$_0$ correction

|                      | Scan X.1  | Scan X.2  | Difference X.1 – X.2 | Scan Y   | Difference X.1 – Y |
|----------------------|-----------|-----------|----------------------|----------|-------------------|
| Uncorrected TSC      | Phantom   | 25.5 ± 1.1| 24.9 ± 1.1           | 2.4%     | 22.7 ± 1.1        | 11.2%              |
| B$_0$-corrected TSC  | Phantom   | 26.1 ± 1.1| 25.5 ± 1.1           | 2.3%     | 25.0 ± 1.0        | 4.5%               |

**Figure 1** $^{23}$Na images, tissue sodium concentration (TSC) and B$_0$ maps of one healthy volunteer at site X during the first (A) and second (B) visit and (C) at site Y. A phantom holder was placed just underneath the calf with four reference tubes from the left to the right: 40 mmol/L NaCl, 40 mmol/L NaCl with 5% agarose, 20 mmol/L NaCl, and 20 mmol/L NaCl with 5% agarose. The corresponding TSC maps and B$_0$-corrected TSC maps as well as B$_0$ maps are plotted next to the $^{23}$Na images. Off-resonances occurred in the calibration phantoms. The correction generally increases the calculated TSC in the leg muscles and reduces the difference between examinations.

**Table 2** Mean off-resonances in Hz for the phantom and in vivo measurements of the central slice for each site and scan. The in vivo values represent the mean off-resonances over the eight subjects. Calibration phantom 1 is the reference phantom containing 40 mmol/L NaCl in 5% agarose and calibration phantom 2 is the reference phantom with 20 mmol/L NaCl in 5% agarose.

|                        | Scan X.1  | Scan X.2  | Scan Y   |
|------------------------|-----------|-----------|----------|
| Off-resonances for phantom measurement | Calibration phantom 1 | $-14.2 ± 2.4$ | $-15.8 ± 2.5$ | $-19.3 ± 2.1$ |
|                        | Calibration phantom 2 | $-25.3 ± 4.8$ | $-25.5 ± 3.7$ | $-26.9 ± 3.6$ |
|                        | Phantom    | $5.6 ± 1.8$ | $3.5 ± 1.7$ | $0.5 ± 2.2$   |
| Off-resonances for in vivo measurement | Calibration phantom 1 | $-19.9 ± 9.4$ | $-22.8 ± 6.9$ | $-22.2 ± 11.1$ |
|                        | Calibration phantom 2 | $-12.5 ± 8.3$ | $-11.4 ± 7.9$ | $-7.2 ± 10.7$ |
|                        | Leg        | $0.4 ± 1.8$ | $-0.8 ± 2.6$ | $-1.3 ± 5.7$  |
The midterm repeatability of TSC measures are presented in Figure 3. We observed differences of up to 4.9 mmol/L in the muscles between the first and second visits. The Bland–Altman plot indicates high agreement between the visits in all muscle regions with a mean repeatability coefficient of 4.8 mmol/L. The limits of agreement at the 95% CI were −4.7 to +4.9 mmol/L and the CV over all three muscles was 15%.

The reproducibility of TSC measures before and after B0 correction is presented in Figure 4. A difference of up to 3.7 mmol/L between the two different sites was observed. The CVs before and after B0 correction were in a similar range (9.2% vs. 9.0%). The systematic bias of −0.68 mmol/L between sites X and Y (P = 0.03) was slightly reduced to −0.64 mmol/L after B0 correction (P = 0.04). At the 95% CI, the limits of reproducibility agreement between the two sites were −3.6 to +2.2 mmol/L. The mean TSC for each scan as well as the repeatability and reproducibility CV per muscles are given in Table 3. Correction of the B0 field inhomogeneity effects improved the SNR in both sites (Table 4). Furthermore, SNR was systematically higher at site X (9.1 at site X vs. 6.6 at site Y).

4 | DISCUSSION

In this study we assessed the midterm repeatability of the TSC quantification in skeletal muscle tissue at 3 T. This study is also the first to compare TSC quantification of skeletal muscle tissue at different sites. We also investigated the effect of B0 correction.

23Na MRI acquisitions using similar RF coils and reference phantoms were implemented at two different sites. TSC trends in healthy skeletal muscle were consistent at both sites with a lower TSC in the tibialis anterior muscle compared with the examined calf muscles. The mean values of TSC measured during this study are in the range of 12 to 21 mmol/L, which corresponds to that usually reported in the literature for healthy skeletal muscle tissue.24,25 The differences in TSC between muscle groups could be caused by differences in intracellular sodium concentrations.
**FIGURE 4** Reproducibility of tissue sodium concentration (TSC) without (A) and with (B) B0 correction. Here, the Bland–Altman graph plots the mean of the TSC from the scan 1 at site X and the scan at site Y against the differences of both scans. There is a significant offset between the two sites, which is reduced after B0 correction. Each colour represents a different muscle.

**TABLE 3** Mean mean tissue sodium concentration (TSC) in mmol/L per muscle for all subjects given for each site and scan. The mean and coefficient of variation are presented for the two reproducibility scans as well as for the two repeatability scans. The CVs are slightly reduced after B0 correction.

|                | Site X Scan 1 (X.1) | Scan 2 (X.2) | Mean of X.1 and X.2 | CV of X.1 and X.2 | Site Y Scan 1 (Y) | Mean of X.1 and Y | CV of X.1 and Y |
|----------------|--------------------|--------------|---------------------|-------------------|------------------|------------------|----------------|
| Uncorrected TSC| tib. ant.          | 14.2 ± 1.4   | 14.3 ± 1.0          | 14.2 ± 1.2        | 13.6 ± 1.2       | 13.9 ± 1.3       | 10.6           |
|                | soleus             | 18.0 ± 1.4   | 17.8 ± 1.9          | 17.9 ± 1.7        | 17.3 ± 1.0       | 17.7 ± 1.3       | 7.0            |
|                | gast. med.         | 16.9 ± 2.2   | 17.1 ± 2.8          | 17.0 ± 2.5        | 18.7             | 16.0 ± 1.3       | 16.5 ± 1.9     | 11.1          |
| B0 corrected TSC| tib. ant.          | 14.3 ± 1.3   | 14.4 ± 1.0          | 14.3 ± 1.2        | 13.7 ± 1.2       | 14.0 ± 1.3       | 10.5           |
|                | soleus             | 18.1 ± 1.4   | 18.0 ± 1.9          | 18.0 ± 1.7        | 17.5 ± 1.0       | 17.8 ± 1.3       | 6.7            |
|                | gast. med.         | 17.0 ± 2.2   | 17.3 ± 2.8          | 17.1 ± 2.5        | 18.3             | 16.2 ± 1.3       | 16.6 ± 1.9     | 10.8          |

**TABLE 4** Mean SNR per muscle at site X and site Y. Total SNR is the average over the three muscles. SNR is measured as 0.655 times the mean signal in the muscle divided by the standard deviation of the background noise.

| SNR                  | Site X Mean SD | Site Y Mean SD |
|----------------------|----------------|----------------|
| Uncorrected $^{23}$Na image |                |                |
| tib. ant.            | 8.7 ± 1.7      | 6.0 ± 0.9      |
| soleus               | 9.6 ± 1.2      | 7.0 ± 0.9      |
| gast. med.           | 9.1 ± 1.4      | 6.9 ± 1.0      |
| total                | 9.1 ± 1.5      | 6.6 ± 1.0      |
| B0 corrected $^{23}$Na image |            |                |
| tib. ant.            | 12.8 ± 2.4     | 8.8 ± 1.5      |
| soleus               | 14.9 ± 1.7     | 10.9 ± 1.9     |
| gast. med.           | 13.5 ± 1.7     | 10.2 ± 2.1     |
| total                | 13.7 ± 2.1     | 9.9 ± 2.0      |
or differences in intracellular volume fraction. Due to their variety of functions, leg muscles comprise different fibre types and varying amounts of intramuscular fat and vascularisation.\textsuperscript{26,27} For example, muscle cells in tibialis anterior can exhibit a larger diameter than those of soleus muscle.\textsuperscript{28}

The phantom measurements showed that $B_0$ correction could partially improve the quantitative accuracy and reproducibility between the two different sites. Thus we performed $B_0$ correction for the in vivo data. In previous work concerning quantitative cardiac $^{23}\text{Na}$ MRI, $B_0$ correction had only a negligible influence on the measured TSC.\textsuperscript{29} The larger influence of the $B_0$ correction on measured TSC values that was observed in our work might be caused by the relatively high off-resonance values of the reference tubes (mean off-resonance of up to 32 Hz). By contrast, Lott et al\textsuperscript{29} used blood as an internal reference, avoiding high susceptibility differences. Here, our $B_0$ inhomogeneity correction can minimise the distortion in the calibration vials to improve the efficacy of quantification as well as to increase the SNR in the muscles. Despite the relatively small frequency range of the $B_0$ field inhomogeneity for sodium imaging, our results have shown that higher apparent SNR can be achieved with appropriate correction.

We observed differences of up to 4.9 mmol/L in the muscles between the first and second visits. In addition, TSC measures showed good reproducibility (CV = 9%). The observed variability of TSC is similar to that in brain and cartilage, for which CVs of 2\% to 13\% were reported.\textsuperscript{12-14} Only recently, a high degree of reliability of $^{23}\text{Na}$ MRI was reported during a scan-rescan experiment (1 week apart) in skin and skeletal muscle on the same scanner.\textsuperscript{30} The authors used a gradient echo pulse sequence with TE = 12 ms and therefore only measured the long component of the fast bi-exponential decay.

In skeletal muscle tissue, in vivo measurements of TSC are not only sensitive to the underlying pathology (eg, channel leakage, leaky membrane, high blood pressure), but are also prone to prior exercise or change of position. The interstitial fluid displacement after postural change resulted in a decrease of 20\% of the $^{23}\text{Na}$ signal over 30 minutes.\textsuperscript{17} After exercise, changes in the $^{23}\text{Na}$ signal of 10\% to 30\% compared with baseline were reported in healthy volunteers depending on the prior exercise protocol.\textsuperscript{4,8,31} In this study, to reduce variations due to exercise or positional changes, all volunteers rested in a supine position for 30 minutes before the examination started and were asked to refrain from rigorous exercise 1 day prior to the examination.

Clinical studies previously reported significant alterations in the TSC in a variety of study populations. After haemodialysis, the TSC dropped significantly from 21.5 to 16.9 mmol/L in haemodialysis patients and from 27.8 to 19.5 mmol/L in patients with type 2 diabetes.\textsuperscript{7} Furthermore, Hyperkalemic periodic paralysis patients with permanent weakness exhibited higher mean TSC (40.7 ± 3.9 mmol/L) than patients without permanent muscle weakness (31.3 ± 4.8 mmol/L) and healthy volunteers (24.3 ± 3.4 mmol/L).\textsuperscript{32} In Duchenne muscular dystrophy patients, the TSC in the lower leg reached 26 ± 1.3 mmol/L in comparison with 16.5 ± 1.3 mmol/L in healthy controls.\textsuperscript{7} Although only a case report study, TSC measures were obtained from the lower leg of a Duchenne muscular dystrophy patient during a 6-month treatment with a mild diuretic substance.\textsuperscript{33} The authors reported a decrease of up to 23\% from 32 to 24.6 mmol/L in muscular sodium concentration, which is larger than the observed variability in our healthy cohort. Our results indicate that these effect sizes are also large enough to be visualised in multicentre studies.

This study has some limitations concerning the technical concept and study design. We investigated the effect of $B_0$ inhomogeneities as this did not require any additional scan time. Thereby, we were able to shrink the differences between the two sites. Our dual echo sodium approach was integrated in the spin density-weighted sodium sequence and the resulting $B_0$ maps were of sufficient quality, which was also shown in recent work regarding $^{23}\text{Na}$ MRI-based $B_0$ shimming.\textsuperscript{34} No $B_1$ correction was performed because we wanted to keep the measurement time short. However, we used birdcage coils from the same manufacturer. Thus, potential $B_1$ inhomogeneities should have a negligible influence on repeatability and reproducibility (Figures S1 and S2). In addition, our phantom measurements revealed that our setup already yields good quantitative accuracy without $B_1$ correction. However, this might be different in studies where different types of RF coils are used or the RF coils have lower $B_1$ homogeneity. Furthermore, possible differences in the gradient delay across sites could have led to additional blurring. Nevertheless, our variations between the different scans might be due to biological variation between visits, differences in the SNR, and small variations in $B_1$ between site X and site Y (Figures S1 and S2). We applied a UTE pulse sequence with a relatively long TR of 120 ms to minimise relaxation effects. If there is remaining $T_2^*$ or $T_1$ weighting this should not influence the repeatability and reproducibility since the impact is the same for all examinations. Regarding the study design, limitations include the small number of subjects as well as missing a short-term repeatability assessment. Furthermore, we were focusing on the midterm variability, which is of most interest for clinical studies that would monitor changes over a longer period, likely to be several months.

In conclusion, quantitative $^{23}\text{Na}$ MRI is a promising tool to measure longitudinal changes in patients. Here, we reported a good reliability and low CV of TSC in different muscles of the lower leg. The reported differences in the absolute TSC values are lower than previously reported alterations in the TSC in diseased skeletal muscle tissue. Thus, TSC measures might be sensitive enough for detecting changes in the sodium levels of muscle in longitudinal and multicentre $^{23}\text{Na}$ MRI studies.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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