Quantification of sodium in healthy cervical cord using prior knowledge

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Target audience: Scientists and clinicians interested in the quantification of sodium using magnetic resonance spectroscopy (MRS).

Purpose: Evaluating the most accurate technique for fitting *in vivo* sodium MRS data.

Introduction Sodium MRI has the possibility to report on several pathologies affecting the spinal cord including spinal cord injury and multiple sclerosis. [23]Na MRI is challenging in the cord due to short T_2 relaxivities and partial volume effects. In tissue [23]Na T_2 relaxation is bi-exponential, resulting in a short T_2 fraction ($T_{2s} \sim 3\text{-}4ms$), which constitutes 60% of the signal, and a long T_2 fraction ($T_{2l} \sim 20\text{-}25ms$)[1].

Recently two ^{23}Na MRS protocols were presented, both based on the ISIS localization sequence, to overcome these challenges and measure sodium in the spinal cord: 1) using hypersecant (HS) inversion pulses (FAHS) and 2) a Fast UltraShort T_2 Sensitive (FUSS) sequence, using shorter sinc-gauss inversion pulses[2]. Both sequences result in a single resonance and similar SNR. However, the accuracy of the sodium concentrations found using these methods has not been explored. A single resonance is often fit to a single peak, however as the bi-exponential behavior of sodium in tissue is known this information can be factored into the analysis. Here we investigate different analysis techniques for ^{23}Na MRS and their effect on accuracy and variation within a group.

Methods

In vivo MRI: 6 healthy subjects were recruited (4 female, 2 male). Scanning was performed on a 3T Achieva TX system (Philips Healthcare, Best). A fixed tuned quadrature sodium transceive coil (Rapid, Germany) was used for [23]Na (33.8MHz). Using the Q-Body coil, ^{1}H images were taken in the sagittal and coronal planes for MRS planning. FUSS and FAHS spectra were acquired from an effective voxel size of 9x12x35mm³ centered on the C2-3 intervertebral disc, using inner volume saturation to suppress signal from CSF and bone, TR 300ms, BW 6000Hz, number of points 1024, TE=0.26ms, and n=800.

Quantification:

Immediately following the ^{23}Na MRS scan volunteers were removed, and replaced with an external concentration reference phantom (44.8mM NaCl), on which an identical scan was run[2]. All data were line broadened to 5Hz, zerofilled to 2048 and phased in JMRUI. The spectra were then fitted in each of the following 3 ways using the AMARES algorithm: a) a mono exponential fit with no prior knowledge (1 peak Mono fit) b) a bi-exponential fit (2 peaks), using prior knowledge for the amplitude ratios (60:40) and soft constraints on the linewidths (13-17Hz and 90-110Hz corresponding to T_{2l} and T_{2s} respectively) (Bi-fit) c) a combination fit, using the bi-exponential fit for *in vivo* data together with a mono-exponential fit for the reference phantom (Combo. Fit), Figure 1. Amplitudes were corrected for T_1 and T_2[1,2]. The sum of the peak amplitudes was used in the quantification for Bi-Fit data. Data was quantified using equation 1 where $S_{in\ vivo}$ and S_{ref} are the measured signal amplitudes respectively, [Na_{ref}] is the reference concentration and C_{load} is the correction factor for loading.

In vitro :

A 50ml phantom, made up of 4% agar and 40mM NaCl, was used for validation, which underwent an identical scan protocol. Prior constraints for the Bi-Fit were applied according to previously reported fractions for bound (T_{2s}) and unbound (T_{2l}) [23]Na in agar (50:50) and linewidths estimated corresponding to agar T_2 values ($T_{2s}=1.9ms$ and $T_{2l}=12.4ms$) measured at 7T[3].

$$[Na_{in\ vivo}] = \left(\frac{S_{in\ vivo}}{S_{ref}}\right)[Na_{ref}]C_{load} \quad ,(1)$$

Figure 1. Bottom- original spectrum, middle- example Bi-Fit, Top- example Mono-Fit

Analysis:

Quantification of sodium (mean±standard deviation (SD)) was compared for each fitting method using a paired t-test. T_2 relaxation times derived from spectral fitting were also recorded, for each fitting method.

	FUSS-Mono	FAHS -Mono	FUSS-Bi	FAHS-Bi	FUSS-Combo	FAHS-Combo
In vivo (mM)	28.5±6.0	26.6±5.6	34.3±10.7	36.0±7.8	55.69±12.9	57.5±10.6
Agar (mM)	47.6	59.0	41.3	34.5	58.6	61.4
T_{2l} (ms) in vivo	27.4±9.4	31.3±7.1	23.6±2.0	24.5±0.0	27.4±9.4	31.3±7.1
T_{2s} (ms) in vivo	na	na	3.1±0.3	2.9±0.0	3.1±0.3	2.9±0.0

Table 1 In vivo [23]Na concentration, T_{2s}, T_{2l} and agar concentration for each fitting method.

Results

In vitro- The agar data shows that FUSS Bi-Fit yields the most accurate quantification with only a 3% error in the calculated concentration (Table 1). Highest concentrations are found using Combo-Fit.

In vivo- Mean concentrations for each fitting method are shown in table 1. When using the same fitting method, FUSS and FAHS gave similar sodium concentrations (p>0.05 for all). Differences in sodium concentration do however, vary across fitting methods. *In vivo* the lowest concentrations are found using the Mono-Fit (p<0.05) and the highest with Combo-Fit (p<0.05). Coefficients of variation (CV) were 0.2 for *in vivo* sodium concentration across all fitting methods, with the exception of the FUSS Bi-Fit (CoV=0.3).

Figure 2. Sodium concentration using Bi-Fit with FUSS and FAHS for each volunteer.

Discussion

In vitro FUSS and FAHS Bi-fit give the most accurate concentrations *in vitro* supporting the bi-exponential nature of bound sodium. *In vitro* data from agar suggests that FUSS Bi-Fit is the most accurate fitting method, if this translates to *in vivo* an estimate of 23Na concentration in the spinal cord of 34±11mM can be made. This agrees well with the reported values in brain using [23]Na-MRI[4]. T_2 values derived using FUSS Bi-fit also support those measured in the brain for [23]Na ($T_{2s}=3.08ms$ and $T_{2l}=21.2ms$), however given the soft constraints on the linewidth this is somewhat expected[1]. The larger CV with FUSS Bi-Fit is however concerning, and the source of this variation needs further investigation. The larger variation in [23]Na concentration found using Bi-Fit can be seen in figure 2, at least two subjects appear to have an underestimation (1 and 4). Improvements, beyond natural between-subjects' variability, could perhaps include cardiac triggering the sequence and increasing the SNR through more averages. Alternatively, FAHS Bi-Fit gives a concentration similar to FUSS Bi-FIt (p>0.05) but with a smaller CV (0.2), and only a small deviation in the accuracy of the agar phantom concentration measurement. This may in part be due to the fact that the HS pulses in FAHS are less susceptible to the inherent B_0 inhomogeneity in the spinal cord, a factor that does not affect the phantom measurements. Mono-fit concentrations are high indicating the mono-exponential fit of the saline phantom maybe underestimating its amplitude, resulting in higher calculated concentrations (possibly due to using shim current values optimized for the agar scan).

Conclusion:

Sodium MRS data is fitted most accurately using a bi exponential fit. Using the sinc gauss inversion pulses (FUSS) together with Bi-Fit gives the most accurate results *in vitro*. Using Bi-Fit has the added advantage of the estimation of T_{2s} and T_{2l}. This method could be extended to estimate changes in the 60:40 ratio. Changes in the ratio could be related to an expansion in extracellular space (increased amount of T_{2l}) or an increase in intracellular sodium (increased amount of T_{2s}). Hence, we present a method with which to accurately quantify total sodium concentration in the spinal cord, whilst allowing changes in the proportion of bound and unbound sodium *in vivo* to be estimated.

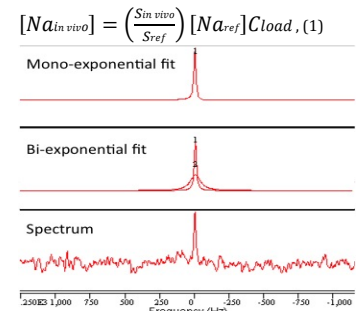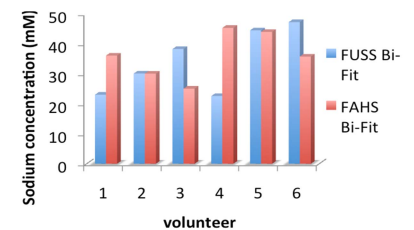1) Riemer et al, Proc. 20th ISMRM, 2012, 2) Solanky et al, Proc, 21st ISMRM, 2013 (351), 3) Madelin et al, Proc. 19th ISMRM (3505), 4) Inglese et al, Brain, 2010