Combined Sodium NODDI: Towards quantitative *in vivo* intracellular and intraneurite sodium measures at 3T

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Purpose: Intracellular sodium (Na_{IC}) accumulation is thought to play a key role in a number of neurological and neurodegenerative conditions such as epilepsy, Multiple Sclerosis and Amyotrophic Lateral Sclerosis. Total sodium concentration (TSC), as measured by conventional sodium MRI, is a combination of bound and unbound sodium, which is commonly associated with Na_{IC} and extra-cellular (Na_{ISO}) sodium respectively. Whilst robust measures of TSC *in vivo* exist, separating Na_{IC} from Na_{ISO} remains challenging. Triple Quantum Filtering (TQF) methods have been shown to separate signal from the bound sodium (mostly located in the intracellular compartment) from free, or unbound sodium, in extracellular space. At 3T the poor SNR of TQF *in vivo* leads to long, low resolution (>8x8x8mm^3) scans, which are not easily tolerated by patients. We present here an alternative method combining TSC and ^{1}H diffusion weighted imaging to produce a model sensitive to bound (intracellular) sodium. The free (extracellular) sodium in tissue and CSF Na_{ISO} is assumed to be fixed at 140mM, which, combined together with measurements of the intracellular and extracellular volume fraction (VF_{IC} and VF_{ISO}) in each voxel, allows one to calculate the intracellular sodium concentration. Neurite Orientation Dispersion and Density Imaging (NODDI) uses diffusion weighted ^{1}H MRI to measure the intraneurite (i.e. restricted within axons), extraneurite (i.e. in soma) and extracellular (CSF) volume fractions in CNS[1]. TSC is a composite of sodium in the intracellular (intraneurite+extraneurite) and extracellular sodium in the voxel. Here we propose to combine sodium MRI and NODDI to obtain *in vivo* intracellular Na_{IC} and intraneurite Na_{IN} sodium concentrations at 3T.

Methods: *Intracellular and intraneurite sodium concentration:* The NODDI model can be used to calculate the compartmentalisation of tissue for each voxel yielding VF_{ISO} (extracellular volume fraction), VF_{IN} (intraneurite volume fraction) and V_{EN} (extraneurite volume fraction). Since the volume fractions for ^{1}H are the same as for sodium, TSC is simply a weighted sum of the sodium concentration within these compartments:

$$TSC = VF_{IN}\,Na_{IN} + VF_{EN}\,Na_{EN} + VF_{ISO}\,Na_{ISO} \quad \{1\}$$

We assume that Na_{ISO} remains constant at 140mM, as in quantitative TQF techniques[2]. Consequently Na_{IC} can be given by

$$Na_{IC} = TSC - 140mM\,VF_{ISO} \quad \{2\}$$

In pathology sodium changes are most likely to occur along the axons in the intraneurite space, where sodium channel disruption is more vulnerable [2], therefore elsewhere the sodium concentration (Na_{EN}) can be assumed to stay constant at normal intracellular levels of 12mM. Using these assumptions intraneurite sodium can be given by

$$Na_{IN} = (\,TSC - 140mM\,VF_{ISO} - 12mM\,VF_{EN}\,) / VF_{IN} \quad \{3\}$$

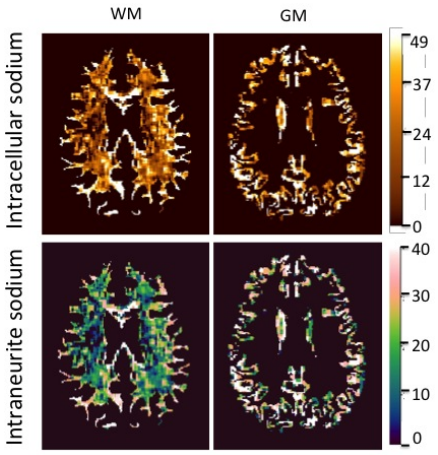

Figure 1. Combined Sodium NODDI maps of Na_{IC} and Na_{IN} sodium in mM, for WM and GM

Sodium Protocol: Four healthy controls were scanned (2M 2F, mean age 29±4 years) on a 3T Philips Achieva System (Philips Healthcare, Netherlands), using a fixed tuned sodium volume coil (Rapid Biomedical, Germany). Subjects underwent a 3D-Cones UTE sequence[4], with a resolution of 3x3x3 mm^3, FOV=240x240x240 mm^3, TR=120 ms, TE= 0.22 ms, total scan time 18 min. Two agar phantoms with 33 and 66 mM NaCl were placed either side of the head for calibration[4]. A ^{1}H PD-T2w scan was also acquired using the Q-Body coil for registration.

^{1}H Protocol: Subjects underwent ^{1}H MRI using a 32-channel head coil. The NODDI DWI protocol was collected with isotropic voxel size 2.5 mm^3, axial FOV=220x220 mm^2, 60 slices, SENSE=2, TE=73 ms, b-values 300/711/2000 s mm^{-2}, with 6/15/30 isotropically distributed directions and 10 interleaved non-diffusion weighted (b=0) images [5]. For segmentation a 3D T1w turbo gradient echo structural scan was run with TE= 3.1 ms, TR= 6.9ms, TI= 824 ms, FOV 256×256×180 mm^3 and voxel size 1x1x1 mm^3.

DWI analysis: NODDI data was corrected for motion and eddy current distortions using FSL5 [5]. NODDI fitting was performed with the NODDI Matlab Toolbox to produce maps of VF_{ISO}, VF_{IN} and V_{EN}[1].

Segmentation and registration: Sodium and NODDI maps were both registered to the PD-T2w scan, using the NiftyReg package [6]. A symmetric and inverse-consistent full affine registration was used and the maps were resampled with nearest neighbour interpolation to preserve biophysical quantities such as TSC. Probabilistic tissue segmentation was performed using GIF[7]. GM, WM and CSF masks were obtained using a tissue probability threshold of 25%, the tissue class that had the maximum probability inside each voxel was assigned to the whole voxel.

Results & Discussion:

Figure 1 shows *in vivo* Na_{IC} and Na_{IN} maps produced using the combined Sodium NODDI method. Mean Na_{IC} in WM was estimated as 10.6±0.9 mM, in close agreement with both literature values (10-15mM) and with studies using TQF to quantify bound sodium at 7T[2]. Mean Na_{IN} was estimated to be 14.2±1.6 mM in WM, quantification only obtained by virtue of the Sodium NODDI model. Concentrations in GM were higher, with mean Na_{IC} measured to be 19.0±1.6 mM and mean intraneurite concentration of 30.4±4.1 mM.. ROI analysis in the ventricles gives values close to zero (0.12±0.22 mM) for Na_{IN} in CSF demonstrating the effectiveness of this technique in preserving intracellular/bound sodium only. Standard deviations in this preliminary study are small for Na_{IC} (<10%) in comparison to TQF techniques which have SD>20% [2]; this suggests the proposed Sodium-NODDI technique could be more sensitive to small changes in Na_{IC} in WM. Further work on assessing and validating concentration in GM is needed with improvements perhaps in the Sodium NODDI acquisition protocol to allow better registration.

	WM	*GM*
Na_{IC} mM	10.6±0.9	19.0±1.6
Na_{IN} mM	14.2±1.6	30.4±4.1

Table 1 showing average and standard values for Na_{IC} and Na_{IN} over all subjects for WM and GM

Conclusion We have developed a novel technique combining *in vivo* Sodium MRI and NODDI for quantifying intracellular sodium, providing a clinically feasible technique. In addition our method has allowed estimation of the intraneurite sodium using MRI for the first time, providing further specification of sodium changes *in vivo,* which will be particularly important in locating changes in neurodegenerative or neuroinflammatory diseases.

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