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Relationship of Sodium concentration and T2 relaxation in Multiple Sclerosis

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TARGET AUDIENCE Physicists and clinicians interested in the implications of relaxometry and sodium disruptions in Multiple Sclerosis (MS).
PURPOSE To investigate possible relationships between sodium concentration and ^{1}H T_2 relaxation changes in the normal appearing white matter (NAWM), normal appearing grey matter (NAGM) and lesions in MS patients.

INTRODUCTION: In healthy tissue intracellular and extracellular sodium are tightly regulated (10-15mM and 140mM respectively). Increases in total sodium concentration (TSC) are seen in MS and have been linked to disability and disease progression[1]. The reasons for this increase maybe two fold: 1) an increase of intracellular sodium as a consequence of demyelination and a subsequent redistribution of sodium channels[2], 2) an increase of extracellular sodium concentration as a consequence of an increase in extracellular space due to cell death. To understand the aetiology of TSC changes in MS a biomarker sensitive to myelination and cellular degradation may help. T_2 relaxometry using ^{1}H MRI has been shown to detect changes in normal appearing white (NAWM) and grey matter (NAGM) in MS relative to healthy controls. These changes are also thought to be due to demyelination and a reduction in the myelin water fraction of the tissue, resulting in higher T_2 values in MS patients[3,4]. Here we investigate the relationship between sodium concentration and T_2 relaxation in NAWM, NAGM and T_1 and T_2 lesions in relapsing remitting (RR), and secondary progressive (SP) MS.

METHODS: *Subjects:* 4 healthy controls (46±11 years, 2M, 2F), 5 RRMS (41±10 years, 2M, 3F) and 4 SPMS (57±10 years, 1M, 3F) patients gave written informed consent to participate in the study, which was approved by our local ethics committee.
Sodium Protocol: Subjects were scanned on a 3T Philips Achieva System (Philips Healthcare, Netherlands), using a fixed tuned sodium volume coil (Rapid Biomedical, Germany) and underwent 3D UTE sequence with 2D radial in plane readout[1], acquired with a resolution of 4x4x4 mm^3, FOV=240x240x200mm^3, TR=120 ms and TE= 0.27 ms. Two agar phantoms with 33 mM and 66 mM NaCl were placed either side of the head for calibration of TSC maps[1]. A ^{1}H PD-T_2w 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. For T_2 relaxation measurements a 2D fast spin multi-echo scan was acquired with TE=16 ms and seven echoes with 16ms echo spacing, TR=5230 ms, FOV=240 × 180 × 144 mm^3 and voxel size=1×1×2 mm^3. After registration, echoes were fitted with a least squares fit to find the T_2 in each voxel using in house software[5]. A 2D T_1w spin echo sequence was also acquired with the same field of view and voxel size, with TE=10 ms and TR= 625 ms, for T_1 lesion detection. For segmentation a 3D T1w turbo gradient echo structural scan was run with TE= 3.1 ms, TR= 6.9 ms, TI= 824 ms, FOV 256×256×180 mm^3 and voxel size 1x1x1 mm^3.
Segmentation and registration: Sodium and T_2 maps were both registered to the 3D T_1w 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 and T_2. Probabilistic tissue segmentation was performed using GIF[7]. Tissue volumes were calculated taking into account all the voxels with a probability higher than 25%, and the voxel volume was then added to the tissue class with maximum probability inside each voxel. These were used together with sodium concentration and T_2 relaxometry maps, to find the mean TSC and T_2 in WM, GM and the ventricles (CSF).
Lesion detection: For the SP and RR group T_2 lesions (T2-L) were identified using the fourth echo (TE= 64ms) of the multi-echo sequence, and T_1 hypointense (T1-L) regions were identified using the 2D T_1 weighted sequence. All visible lesions were outlined using a semiautomatic lesion segmentation tool in JIM 6.0 and these regions of interest were combined into masks to produce T2-L and T1-L masks, as well as masks for NAWM and NAGM in patients[5].

RESULTS: Figure 1 shows markedly different relationships in T_2 and corresponding TSC in controls, SP and RR groups. In controls the WM and GM values are very tightly clustered and a clear separation is seen between tissue and ventricular CSF. In the SP group this clustering is less tight, however NAWM, NAGM and lesions are still clearly separated from CSF. In this group the T_1 and T_2 lesions overlap the NAWM and NAGM clusters. In the RR group the spread of NAGM and NAWM values is much broader, with T_2 lesions showing much higher T_2 values (>200ms, Table 1) reducing the separation between lesions and ventricular CSF relative to SPMS patients.

	NAWM	NAGM	Ventricles	T2-L	T1-L
T_2 controls	90±2	112±8	948±254	-	-
T_2 SP	148±46	171±39	952±256	164.2±38	166±36
T_2 RR	115±17	140±11	1195±383	233±139	236±180
TSC controls	32±1	37.1±0.5	84±4	-	-
TSC SP	39±4	43±4	90±4	47±5	48±6
TSC RR	38±3	41±2	90±5	45±5	46±6

Table 1 - Mean and standard deviation of T_2 and TSC for each group (controls, SP and RR) in NAWM, NAGM, Ventricles (CSF), and T_1 and T_2 lesions

DISCUSSION: T_2 and TSC are tightly related in healthy tissue. T_2 values for WM, GM and CSF are in agreement with literature [4,8]. In SPMS the lack of clear separation between lesional and non-lesional tissue T_2 and TSC values suggests that lesions in SPMS are more comparable to non-lesional tissue rather than CSF. In addition, the cluster of points in the SPMS scatter is wider due to T_2 and TSC in NAWM and NAGM. This suggests that in SPMS the increases in TSC are related to demyelination, since this could lead to increases in T_2 and TSC, whilst still retaining T_2 values more comparable to normal appearing tissue than to CSF. The association between the two variables (TSC and T_2) is still apparent in SPMS. In contrast, the RR group has a much broader scatter of values, particularly for T2-L. Whilst T_1 lesions cluster together with normal appearing tissue, the T_2 of T2-L is less comparable to tissue and more comparable to CSF. This suggests a higher degree of tissue disruption resulting in increased extracellular space and/or inflammation and cell swelling, which would explain a larger increase in T_2 and a concomitant increase in TSC. The association between TSC and T_2 in RR is different to that of healthy controls and even the SP group, particularly for T2-L, where the changes in T_2 are greater than the TSC changes. This supports the presence of an increased proportion of extracellular fluid in T2-L at the RR stage of MS, leading to the increased TSC in T_2 lesions.

CONCLUSION: This pilot study shows T_2 and sodium appear to be correlated in WM and GM, and have the potential to identify pathophysiological differences in MS clinical subgroups. A larger cohort study is needed to definitively characterise the T2 relaxation and sodium abnormalities - and thereby elucidate the origin of the sodium increases - in different MS sub-groups and tissue compartments.

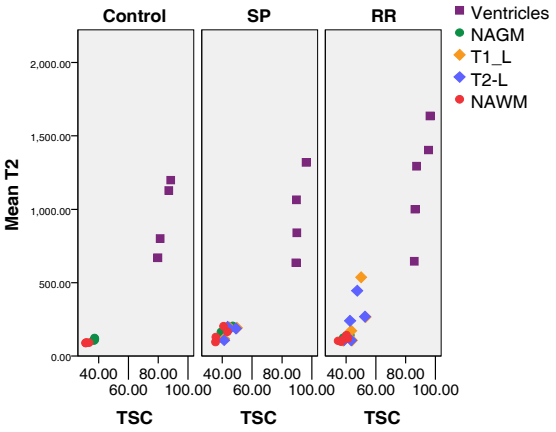

Figure 1 - Scatter plot of T_2 and TSC for NAWM, NAGM, ventricles (CSF), and T_1 and T_2 lesions for each subject.

References: *1) Paling et al Brain 2012, 2) Waxman, N Engl J Med 2006, 3) Webb, MRM, 2003, 4) MacKay, Magn Reson Imaging. 2006, 5) Paling, J Neurol Neurosurg Psychiatry, 2012 6) Modat, SPIE, 2014 7) Cardoso, MICCAI, 2012 8) Wansapura, J Magn Reson Imaging, 1999*
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