Quantification of Extra- and Intra- cellular Brain Sodium Concentration in MS using 7.0 Tesla MRI

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BACKGROUND

Measurement of total sodium concentration (TSC) obtained using single quantum (SQ) sodium MRI is useful in the assessment of brain tissue injury in Multiple Sclerosis (MS) patients[1,2,3,4]. However, it does not allow discrimination of the extra-cellular (ESC) from the intra-cellular sodium concentration (ISC) that might be a marker delayed axonal damage[5]. Due to the low sensitivity of sodium MRI and the low brain ISC, ultra-high field MRI is particularly suited for the application of this method.

We have implemented a pulse sequence for the acquisition of triple quantum filtered (TQF)[6,7] and for the assessment of ISC and intracellular sodium volume fraction (ISVF), an indirect measure of ESC. Here we present preliminary findings of its application in MS patients at 7 Tesla (T).

OBJECTIVES

1) To compare TSC, ISC and ESC levels in MS patients vs healthy controls (CTRLs) using TQF sodium MRI at 7 Tesla (7T);
2) to investigate the associations between TSC, ISC and ESC and measures of lesion and brain volume;
3) to assess the clinical significance of ISC and ESC.

METHODS

Nineteen MS patients with a relapsing-remitting course (11F; mean age: 40.0±11.2 yrs; median EDSS: 2.0; range: 1.0-5-5; disease duration 9.1±7.4 yrs) and 17 CTRLs (8F; mean age: 46.16±11.65 yrs) underwent sodium MRI at 7T and proton MRI at 3T. The 7T MRI protocol included a modified GRE sequence with a new 12-step phase-cycling TQF scheme[6]. The 3T MRI protocol included DE-TSE and 3D T1W-MPRAGE. After creation of the TSC (mM), ISC (mM) and ISVF (%) maps[7], mean TSC, ISC and ISVF were measured with a histogram analysis over the entire gray and white matter (GM, WM) and with a regional voxel-based approach using SPM8. Between groups comparison was performed with an ANCOVA test controlling for age, gender and intra-cranial volume. The correlation between sodium MRI-derived parameters, proton MRI-derived measures and clinical scores were assessed using Spearman's rank correlation coefficient.

RESULTS

Compared to CTRLs (GM TSC:40.26±2.99mM; WM TSC: 27.87±2.55mM, GM ISVF:84.80±1.25% and WM ISVF: 89.38±1.40%), MS patients showed higher global GM and WM TSC (42.82±5.17mM and 31.38±4.03mM; $p<0.05$) and lower global GM and WM ISVF (84.20±1.57%; 87.91±1.52% $p<0.01$).

Global GM and WM ISC were higher in patients (13.96±1.44mM;14.29±1.35mM) than CTRLs (13.59±1.26mM; 13.84±1.26mM) but the difference was not statistically significant ($p>0.1$) (**Fig.1**). Among the clusters showing TSC increase at voxel level, ISC resulted significantly higher in thalamus, frontal middle gyrus, precentral gyrus and superior longitudinal fasciculus bilaterally, in the left insula and cortico-spinal tract and in the forceps minor ($p<0.05$, Ke=10) (**Fig.2**). Global GM ISVF showed a correlation trend with EDSS ($r=-0.47$, $p=0.054$) and global GM ISC showed a correlation with T2 lesion volume ($r=0.50$, $p<0.05$).

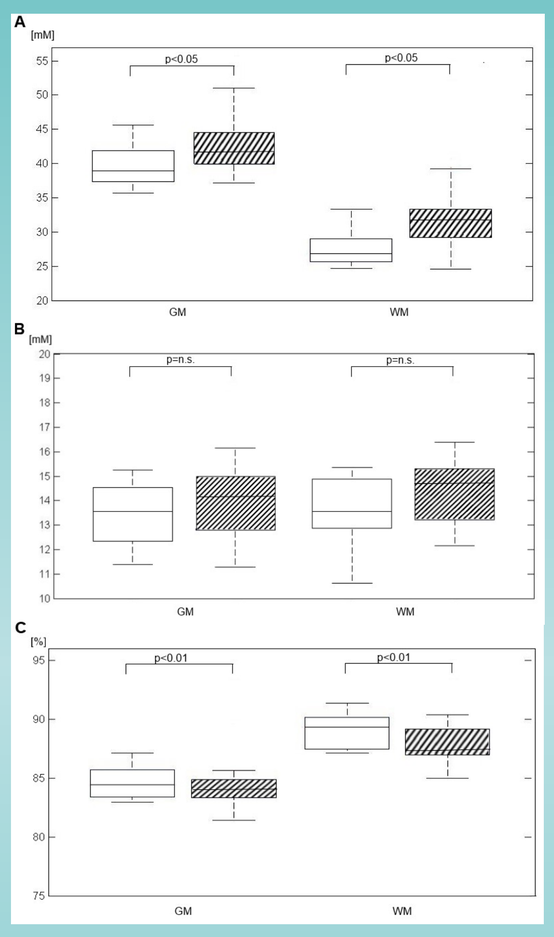

Figure 1. Box plots display the 25% to 75% values (boxes) ±95% values (whiskers), median values (horizontal lines within boxes) of mean TSC (A), ISC (B) and ISVF (C) value distribution in grey matter and white matter among healthy controls (empty box) and patients with relapsing-remitting multiple sclerosis (hatched box). Only significant p values are reported.

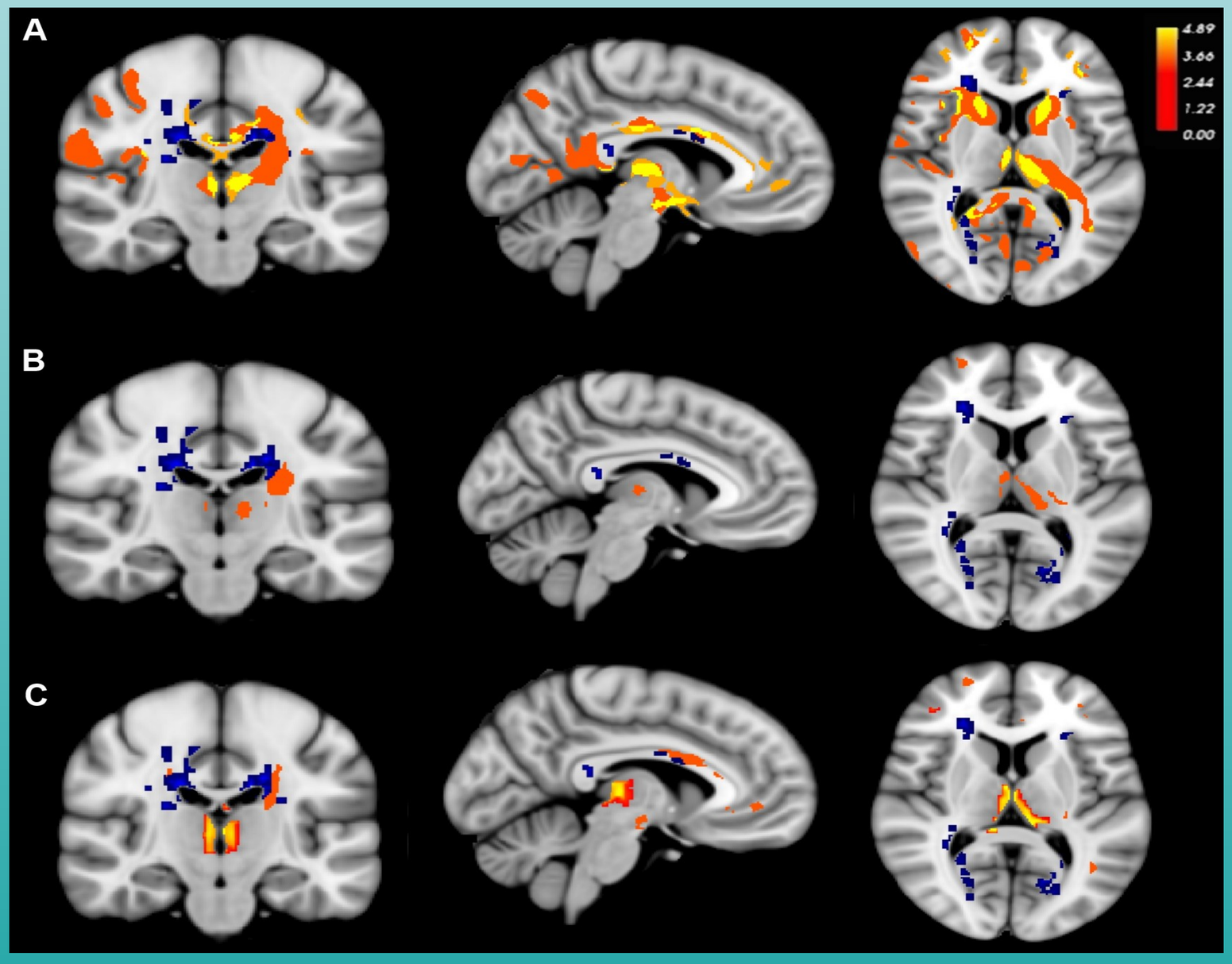

Figure 2. Statistical maps of abnormal increase in brain sodium concentrations in relapsing-remitting multiple sclerosis patients relative to healthy controls. Local increases of brain TSC (A), ISC (B), ISVF (C) are shown in red-yellow, superimposed on the lesion probability map (in blue). Comparisons were performed with SPM8 software (TSC maps: 2-group ANCOVA $p<0.001$, $k=20$ voxels, corrected for FWE at a p value of 0.05; ISC and ISVF maps on TSC clusters: 2-group ANOVA $p<0.05$, corrected for cluster extend of 10 voxels).

CONCLUSION

TSC increase within the CNS of MS patients may be related to an intracellular sodium accumulation, due to neuro-axonal metabolic dysfunction, as well as to an increased ESC, due to expansion of the extracellular space secondary to neuro-axonal loss. With the present study we confirm that TSC increases in GM and WM[1,2,3,4]. Our analysis of intra- and extracellular compartment shows a widespread and common pattern of TSC and ISVF alterations in WM and GM regions both at global and regional level. Assuming that TSC and ISVF increases are expression of neuro-axonal loss, their parallel increase could reflect the ongoing development of established disability, as suggested by ISVF correlation trend with EDSS. On the other hand, if ISC increase reflects neuro-axonal metabolic impairment, its regional increase may indicate dysfunctional areas in which compensatory mechanisms still prevail over structural alterations.

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