Brain sodium accumulation and spreading correlate with disability in multiple sclerosis

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Objective: The key role of sodium accumulation leading to neuronal injury in multiple sclerosis has recently been highlighted [1, 2]. Using *in vivo* sodium MRI, we aimed here to *i)* quantify brain sodium accumulations and *ii)* characterize for the very first time spatial spreading of sodium abnormalities at different stages of relapsing remitting multiple sclerosis (RRMS).

Methods: MR explorations were performed on a 3T Verio system holding multi-nuclear options (Siemens, Erlangen, Germany) in two groups of RRMS patients (13 early RRMS, 13 advanced RRMS) and 15 healthy controls. ^{23}Na MRI was acquired using a double-tuned ^{23}Na-^{1}H volume head coil (Rapid Biomedical, Rimpar, Germany) and a density-adapted three-dimensional radial projection reconstruction pulse sequence (DA-3DPR) [3] (TE=200µs, TR=120ms, 17000 projections and 369 samples per projection, flip angle = 87°, acquisition time = 34 min, nominal spatial resolution of 4.5x4.5x4.5mm^3 after Hanning filtering) with two tubes filled with 50 mM of sodium placed in the field of view bilaterally close to the subject's head to serve as external references. High resolution proton MRI 3D-MPRAGE (TR=2300ms, TE=3ms, TI=900ms, FOV=256x256mm^2, matrix=256x256, 160 slices, 1x1x1mm^3 of resolution) and T_2-weighted sequence (TR=9940ms, TE=90ms, FOV=256x256mm², matrix=256x256, 49 slices, 3-mm thickness, 1x1x3mm^3 of resolution) were obtained using a 32-element ^{1}H head coil (Siemens).

The optimized post-processing pipeline included *(1)* reconstruction offline of the quantitative 3D radial sodium images (q^{23}Na MRI) (home-made procedure developed on Matlab [3]); *(2)* coregistration of the q^{23}Na MRI with the high resolved ^{1}H 3D-MPRAGE (Fig1). For the global brain compartments analysis, the post-processing steps included *(3A)* segmentation of the ^{1}H 3D-MPRAGE (VBM8) to obtain white matter (WM) and grey matter (GM) masks for all subjects and delineation of T_2 lesions onto the ^{1}H T_2w images (IDL) to obtain the T_2 lesions mask for each patient; *(4A)* application of masks to q^{23}Na MRI to obtain total sodium concentrations (TSC) from each brain compartment (WM, GM and T_2 lesions) (Fig2); *(5A)* statistical analysis (Wilcoxon rank test). For the statistical mapping analysis (SPM8), the post-processing steps included *(3B)* normalization and smoothing (8mm FWHM Gaussian kernel) of the coregistered q^{23}Na MRI and ^{1}H-MPRAGE; *(4B)* voxelwise statistical analysis on the q^{23}Na MRI to locate TSC abnormalities (3-group ANOVA).

Results: For the two groups of MS patients, TSC was increased inside demyelinating T_2 lesions, while increased TSC in normal appearing WM and GM was only observed in advanced RRMS (Fig3). In patients, increased TSC inside GM was correlated to disability (EDSS) (p=0.015), disease duration (p=0.030) and T_2 lesion load (p=0.001) but not to GM atrophy (p=0.366). Statistical mapping analysis showed increased TSC circumscribed to the cerebellum, the medial temporal lobes and the splenium of the corpus callosum in early RRMS while advanced RRMS showed a widespread abnormal accumulation of TSC inside the whole brain (caudate, thalami, insula, occipital, temporal and prefrontal cortices and the entire corpus callosum...) as illustrated in Fig4. Finally, EDSS was correlated to TSC increases inside motor and motor-planning regions (primary motor area, middle and superior frontal gyrus and cerebellum) stressing the functional role of sodium accumulation in MS.

Conclusions: Brain sodium accumulation dramatically spreads during the course of the disease especially in the normal appearing brain tissues concomitantly to progression of disability and independently from atrophy. Brain sodium MRI appears as a relevant tool to characterize and time the pathological cascade occurring between inflammation and neurodegeneration in MS.

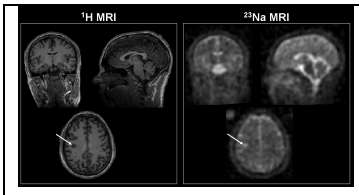

Fig1: q^{23}Na maps coregistered onto ^{1}H-MPRAGE

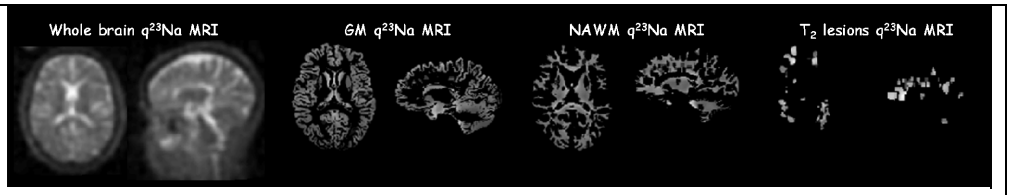

Fig2: Compartmentalized brain sodium maps from an advanced RRMS patient

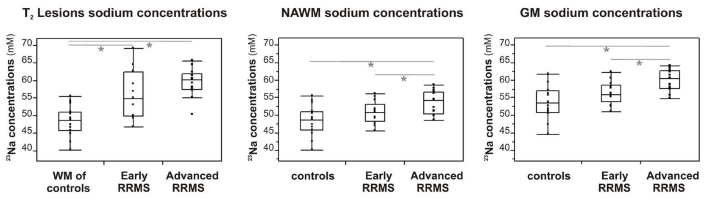

Fig3: TSC observed in the different brain compartments

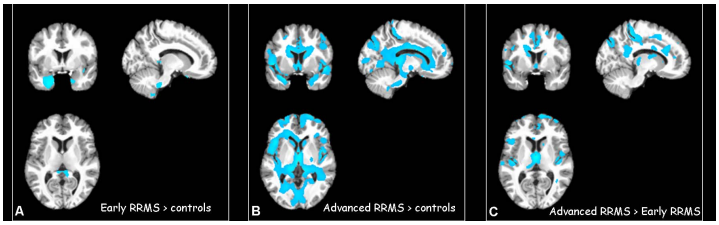

Fig4: Statistical mapping of abnormal TSC increase in early and advanced RRMS

References: (1) Waxman SG. Nat Clin Pract Neurol 2008;4(3):159-69. (2) Inglese M et al. Brain 2010;133(Pt 3):847-57. (3) Nagel AM et al. Magn Reson Med 2009;62(6):1565-73.