Cognitive status of multiple sclerosis patients is associated with neocortical neuronal injury: A voxel-based sodium MRI study

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TARGET AUDIENCE: Clinicians and physicists interested in multiple sclerosis (MS) patient care and/or MS research and physicists interested in X-nuclei MRI development and *in vivo* applications.

PURPOSE: Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system in young adults. Cognitive dysfunction occurs in almost half of MS patients[1] and is related to cortical lesions and atrophy[2]. The key role of sodium accumulation leading to neuronal injury in MS has recently been highlighted[3-6], in particular in grey matter of secondary progressive MS patients, known to suffer more frequently from cognitive impairment[6]. Using in vivo sodium MRI, we aimed to i) quantify brain sodium accumulations in MS patients with cognitive impairment and ii) characterize the spatial topography of grey matter sodium abnormalities, reflecting neuronal injury, in cognitive MS patients.

METHODS: MR scans were performed on a 3T Verio system holding multi-nuclear options (Siemens, Erlangen, Germany) in two groups of MS patients (n=37 "non-cognitive" MS and n=21 "cognitive" MS, classified by the Brief Repeatable Battery, with a disease duration ≤ 10 years) and n=31 age and sex-matched healthy controls. ^{23}Na MRI was acquired using a double-tuned ^{23}Na-^{1}H volume head coil (Rapid Biomedical, Rimpar, Germany) and a 3D density-adapted radial projection reconstruction pulse sequence[7] (TE=200µs, TR=120ms, 17000 projections and 369 samples per projection, 3.6mm^3 isotropic resolution, acquisition time = 34min) with two tubes filled with 50 mM of sodium placed in the FOV to serve for external references (Fig. 1). High-resolution proton MRI 3D-MPRAGE (TR=2300ms, TE=3ms, TI=900ms, 160 slices, 1mm^3 isotropic resolution) and T_2-weighted sequence (TR=9940ms, TE=90ms, 49 slices, 3-mm thickness, in-plane resolution 1x1mm) were obtained using a 32-element ^{1}H head coil (Siemens). The optimized post-processing pipeline is described in Fig. 2 and allowed to obtain total sodium concentration (TSC) from grey matter and white matter (for all subjects) and T2 lesions (for patients) and maps of spatial distribution of sodium accumulation and of atrophy in patients resulting from the statistical mapping analyses (SPM8, ANOVA, p=0,005, k=10).

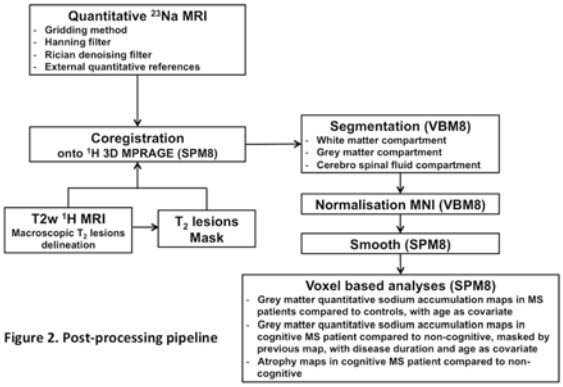

Figure 2. Post-processing pipeline

RESULTS: TSC was significantly increased in grey matter, normal appearing white matter and WM T2 lesions of cognitive MS patients compared to non-cognitive MS patients and controls (Fig. 3). TSC was increased only in WM T2 lesions for non-cognitive MS patients compared to white matter of controls (Fig. 3).

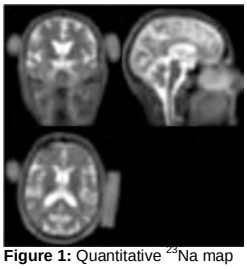

Figure 1: Quantitative ^{23}Na map

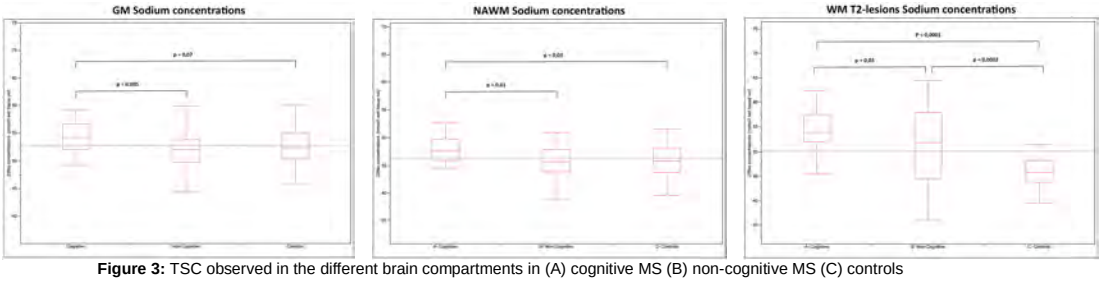

Figure 3: TSC observed in the different brain compartments in (A) cognitive MS (B) non-cognitive MS (C) controls

Statistical mapping analysis showed increased TSC circumscribed to the cingulate cortex, precuneus, temporal gyrus (superior, middle and inferior), dorsolateral prefrontal cortex, orbitofrontal cortex, pallidum and cerebellum (Fig. 4). These accumulations were independent of atrophy (no overlap).

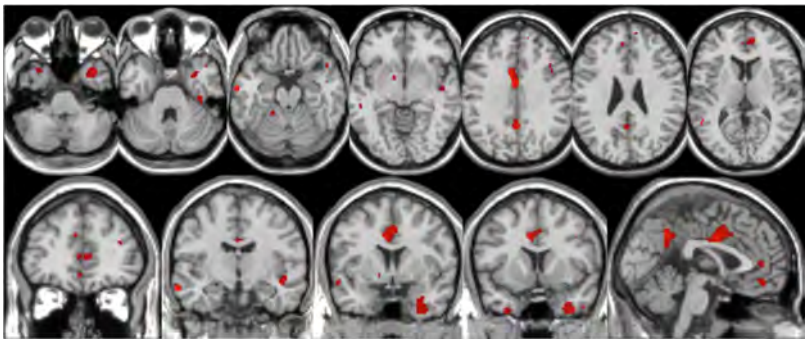

Figure 4: Spatial distribution of abnormal sodium accumulation in cognitive MS patients compared to non-cognitive MS patients (ANOVA, Cog > non-Cog; p=0.005, masked by contrast MS patients > Controls p=0.005).

DISCUSSION: This study evidences that sodium accumulation, at early stages of the disease, affects patients with cognitive impairment. Sodium accumulations were localised in the temporal gyri involved in visual object and known face recognition, word meaning during reading and sound processing. These accumulations were also localised in prefrontal cortices, involved in executive functions, such as working memory, cognitive flexibility, planning, inhibition, and abstract reasoning. These results are consistent with previous works, which demonstrated that cognitive deficits in MS affect mainly executive functions, visuo-spatial memory, attention and information processing speed[1]. Finally, sodium accumulations were localised in the cingulate cortex and the precuneus, brain structures involved in various functions. These widely connected cortical areas are known to be sensitive to the consequences of disseminated white matter MS lesions.

CONCLUSION: In cognitive MS, sodium accumulation, which is an indicator of neuronal injury, affects the neocortex (involved in higher functions). Furthermore, sodium MRI is able to depict neuronal injury, very early in the disease, before the occurrence of atrophy.

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