

Total sodium brain concentrations in compartments of patient with Multiple Sclerosis. A preliminary in vivo ²³Na MRI study

W. Zaaroui¹, S. Konstandin², A. M. Nagel³, T. Wichmann⁴, D. Berthel⁴, S. Confort-Gouny¹, P. J. Cozzone¹, B. Audoin^{1,5}, J. Pelletier^{1,5}, L. R. Schad², and J-P. Ranjeva¹

¹CRMBM UMR CNRS 6612, Marseille, France, Metropolitan, ²Computer Assisted Clinical Medicine, Heidelberg University, Mannheim, Germany, ³Department of Medical Physics in Radiology, Heidelberg, Germany, ⁴Rapid Biomedical GmbH, Rimpfing, Germany, ⁵Pôle de Neurosciences Cliniques, Service de Neurologie, Hôpital de La Timone, Marseille, France, Metropolitan

Background: Recent histological data suggest that sodium (²³Na) plays an important role in axonal degeneration as encountered in several neurological diseases such as multiple sclerosis (MS) or Alzheimer disease. Indeed, mitochondrial dysfunction induces an intra-axonal accumulation of sodium leading to an accumulation of calcium that stimulates several toxic Ca-dependent enzymes causing structural and functional axonal injury (Stys, J Neurol Sci 2005; Waxman, Nat Clin Pract Neurol 2008). Sodium MRI is the only non invasive technique that can assess *in vivo* the variations of brain total sodium (tNa) concentrations.

Objective: This preliminary study aimed to determine the sensitivity of ²³Na MRI at 3 Tesla to assess the differences in tNa signals between MS patient and healthy controls in the various brain compartments (i.e. white matter (WM) and grey matter (GM)).

Methods: MR explorations were performed on a 3T Verio system holding multi-nuclear options (Siemens, Erlangen Germany) using a single-tuned 8-channel ²³Na head receive array coil with integrated transmit birdcage (Rapid Biomedical, Rimpfing, Germany). The sodium MRI acquisition consisted in a density-adapted three-dimensional radial projection reconstruction pulse sequence (DA-3DPR) (Nagel et al. Magn Reson Med 2009) with the following parameters: TE=0.55ms, TR=33ms, 13000 projections and 384 samples per projection, readout time per spoke = 20ms, 3 averages, FA=65°, nominal resolution of 4.5x4.5x4.5mm³, acquisition time = 23min06sec. Reconstruction of the 3D radial acquisition was performed offline using a home-made procedure developed on Matlab (Nagel et al. MRM 2009). High resolution 3D proton MRI (MPRAGE, TR=2300ms, TE=3ms, TI=900ms, FOV=256x256mm², matrix=256x256, 160 slices, 1x1x1mm³ of resolution) and T2-weighted sequences (TR=9940ms, TE=90ms, FOV=250x250mm², matrix=256x256, 49 slices, 3 mm thickness, 1x1x3mm³ of resolution) were obtained using a 32 elements head coil (Siemens). We explored one patient suffering from relapsing-remitting MS (23 yo, female) and 4 healthy controls (44 yo ± 11, 2 females, 2 males). tNa 3D MRI was normalized using the signal from an external reference (C_{Na}= 140mM). For the control subjects, tNa 3D MRI was coregistered onto the 3D proton MPRAGE volume (SPM8). The 3D proton MPRAGE volume was segmented in the native space (VBM8 toolbox) and masks from GM and WM were obtained by thresholding the corresponding density maps at 0.75. These masks were applied onto the coregistered 3D tNa volume. Histograms of GM and WM tNa were computed. For the MS patient, T2 lesions were delineated using a semi-automatic method (IDL) and 3D tNa MRI, proton T2 weighted images and T2 lesion mask were coregistered onto the ¹H 3D MPRAGE volume. Lesion inpainting was performed onto the ¹H 3D volume by affecting the normal appearing WM (NAWM) mean value onto the lesions. After segmentation of this inpainted 3D volume, the same procedure as for controls was applied to obtain GM and WM masks. The T2 lesion mask was also used to extract the tNa of lesions and also to remove contributions of lesions to the NAWM signal.

Results: As illustrated in figure 1, tNa signals of T2 lesions (21.2±5.6a.u.) and of NAWM (20.6±6.5a.u.) in the MS patient were higher than in the WM of the healthy controls. An elevated tNa in the GM (24.8±8.4 a.u.) compartment was also evidenced in the MS patient (figure 2). Examples of ²³Na MR images acquired in the MS patient and in one control are presented in figure 3 (the red arrows indicate the presence of large T2 lesions). ²³Na maps of GM, NAWM and lesions from the MS patient are displayed in figure 4.

Discussion and Conclusion: This preliminary study demonstrates that the total sodium signal is abnormally elevated in MS lesions as evidenced in a recent paper (Inglese et al, Brain 2010). Furthermore, there is a clear trend of tNa increase in NAWM and GM in the patient compared to controls. This compartmental tNa increase may be related to diffuse pathological processes that have been evidenced in patients since the earliest stage of multiple sclerosis using quantitative proton MRI such as magnetization transfer imaging (Jure et al, JMRI 2010). Upcoming studies performed on a larger population of MS patients would benefit to validate these results and investigate the influence of the intra and extracellular sodium concentrations. Sodium MRI has the potential to bring relevant markers to better understand the neurodegenerative processes occurring in several neurological diseases.

