WHOLE BRAIN MULTI-METABOLITE STATISTICAL MAPPING ANALYSES TO CHARACTERIZE METABOLIC DISORDERS IN MULTIPLE SCLEROSIS USING COMBINATION OF TWO TILTED 3D-EPSI ACQUISITIONS.

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Target Audience: Basic scientists and clinicians involved in brain spectroscopy, metabolic tissue characterization and neurodegenerative disease.

Aims: Proton spectroscopy is a specific and sensitive technique permitting the in vivo characterization of metabolic disorders in multiple sclerosis (MS) (1). The spatial spread of metabolic disorders encountered in MS requires a large cerebral coverage, but whole brain MRSI sampling is not a trivial issue, suffering both from long acquisition time and large susceptibility artifacts over the large volume of interest. Fast 3D-MRSI techniques have been successfully proposed (2, 3, 4) to increase the cerebral MRSI coverage in a time compatible with clinical examination. To improve the S/N ratio and limit the effect of susceptibility artifacts, it has been recently proposed to combine metabolite maps reconstructed from two 3D-MRSI acquisitions obtained in two different orientations at ACPC and ACPC+15° (Fig.1) to obtain real whole brain MRSI sampling (5,6). We here used this technique to build spatially normalized metabolic templates of N-acetyl aspartate, glutamate+glutamine, creatine, choline and myo-inositol from data of 15 healthy volunteers, before applying similar processing to data from 8 Relapsing-Remitting (RR) MS patients. Statistical mapping analyses comparing whole brain metabolite maps between patients and controls were performed in order to characterize metabolic disorders in these MS patients.

Figure 1: The two tilted orientations of 3D EPSI brain acquisitions (ACPC (red) ACPC15° (orange)

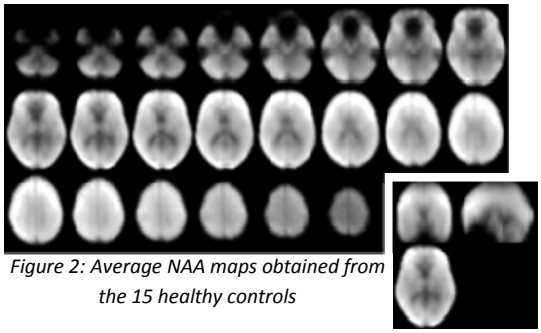

Figure 2: Average NAA maps obtained from the 15 healthy controls

Materials and methods: 15 controls (26.9 years ± 5.5) and 8 RR-MS patients (35 years ± 10.6; mean disease duration: 6.5 years ± 1.9; median Expanded Disability Status Scale (EDSS): 1.75, range: 0-4) matched for age and sex were examined. Written informed consent was obtained from all subjects. Imaging was performed on a 3 Tesla Magnetom Verio (Siemens, Erlangen, Germany) using a 32-channel head coil, with axial 3D T1 MPRAGE imaging used for anatomical reference, (TE=3.4ms; TR=2150ms; TI=1100ms; Flip angle=8°; FOV=240mm; Voxel= 1mm^3 isotropic; partitions= 176), and axial 3D EPSI (TE=20ms; TR=1710ms; FOV=280mm; Voxel=1cm^3 isotropic; TD=198ms; Flip angle=73°). After MIDAS reconstruction including B0 map correction, lipid suppression with masks, T1 segmentation and spectral fitting; metabolic maps of controls were spatially normalized using the EPI template of SPM8. A new metabolic template was built based on the average of normalized maps of each control. Then, each subject map (controls and patients) was spatially normalized using this new template before combination using weighted average of the normalized maps derived from each of the two orientations. Statistical mapping analyses (SPM 8, two samples t-test, $p<0.005$, FDR corrected $p<0.05$ at the cluster level, age and gender as covariates) were performed to evidence in MS patients the topography of metabolic abnormalities of N-acetyl aspartate (NAA), glutamate + glutamine (Glx), creatine (tCr), choline (Cho) and myo-inositol (m-Ins). White matter lesion and brain atrophy maps of patients were also obtained.

Results: Using the procedure described, 5 metabolite templates were reconstructed from controls (example of NAA in Fig 2), and 5 spatially normalized metabolite maps were obtained for each subject. Statistical mapping analyses comparing metabolite levels of MS patients relative to controls showed the spatial distribution of metabolic disorders, with i) decreases of NAA and GLX inside thalamus, frontal cortex, cingulate, parahippocampal gyrus and fornix, ii) decreases of Cho and significant atrophy inside the thalamus, the cingular gyrus and the fronto-temporal white and grey matter regions and iii) increases of m-Ins and tCr inside white matter T2 lesions and the normal appearing white matter inside the frontal and temporal occipital regions (Fig.3).

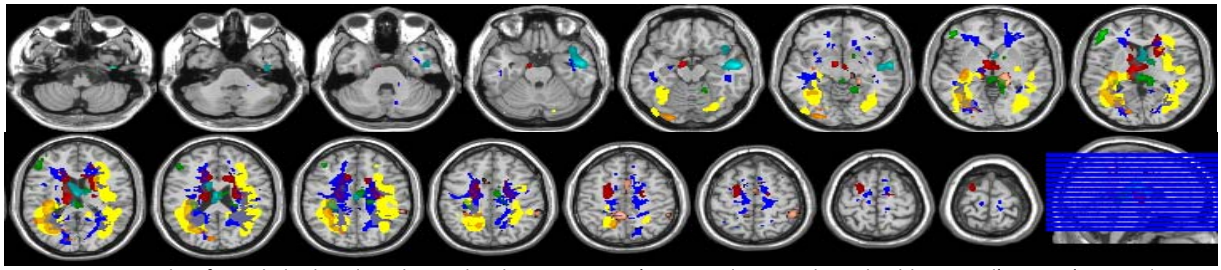

Figure 3: Topography of metabolic disorders observed in the 8 MS patient's group relative to the 15 healthy control's group (unpaired T-test; p<0.005, FDR corrected p<0.05 at the cluster level) showing common local decreases of NAA (red), GLX (green), Cho (cyan), and increases of m-Ins (yellow) and tCr (orange). Atrophy (salmon) and T2-lesions (blue) probabilistic maps were also reported.

Discussion/Conclusions: This preliminary transversal study allowed, for the first time, the acquisition of a truly whole brain metabolic characterization from the vertex to the cerebellum with sufficient quality to evidence pixel-wise metabolic disorder patterns present in a group of patients with RRMS relative to matched controls. We observed here in MS patients, in line with previous regional MRS/MRSI approaches, decreases in NAA and GLX levels in the limbic, motor and prefrontal networks (8,9), reported to be associated to neuronal mitochondrial dysfunction and neuro-astrocytic decoupling (7). Increases of tCr and m-Ins in T2 lesions and also in the normal appearing white matter may reflect increases in cellular density and glial/microglial activity also present in MS (10, 11). Co-localization of decreases in Cho levels and atrophy inside the thalami and the cingular gyrus could reflect cellular loss in these regions known to be affected early in the progression of MS (12, 13). In contrast to most of the previous MRS data from literature (14), using the pixel-wise approach we did not observe significant increases in Cho. This could be potentially explained by i) the diffuse aspect of demyelination, ii) remyelination processes in these early RR MS patients and iii) the limited number of patients included in this preliminary study. To conclude, our data support the promising contribution of statistical mapping analyses as applied to double tilted whole brain 3D ^{1}H-EPSI acquisitions to non-invasively elucidate metabolic disorders linked to pathophysiological processes associated with multiple sclerosis in admissible clinical examination times.

References: (1) Bertholdo, D. et al. Neuroimaging Clin. N. Am. 2013 (2) Ebel, A. et al. Magn. Reson. Med. 2001 (3) Sabati. M. et al. Magnetic Resonance Imaging. 2013 (4) Sabati. M. et al. Journal of Magnetic Resonance Imaging. 2014 (5) Lecocq, A. et al. ISMRM 2013 (6) Lecocq, A. et al. JMRI 2014 (in press) (7) Witte, M. et al. Trends Mol. Med. 2014 (8) Wylezinska et al. Neurology. 2003 (9) Giorgio, A., De Stefano, N. Neurol Sci. 2010 (10) Kirov, I. et al. Neurology 2013 (11) Lassmann, H. Exp. Neurol. 2013 (12) Hulst, H. et al. Neurology 2013 (13) Achiron, A. et al. Brain Struct. Funct. 2013 (14) Hattingen, E. et al. NMR Biomed. 2011.