ULTRA-FAST T2 MAPPING OF MULTIPLE SCLEROSIS PATHOLOGY IN EARLY DISEASE

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Background: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by recurrent inflammations of white and gray matter (WM, GM, 1-2). WM lesions show various extents of inflammation, macrophages, remyelination and oligodendrocyte loss (3) ; GM lesions are less inflammatory and characterized by myelin and axonal loss (2). Magnetic resonaceT2-based images are particularly useful, in the clinical routine of MS patients, due to their sensitivity to the effects of inflammation (i.e. micro-oedema and tissue degeneration). Recently, quantitative T2 relaxometry techniques have been applied to study the normal appearing white matter characteristics in advanced MS patients (4), showing that a quantitative approach might contribute detecting abnormal tissue in MS even in the absence of lesions. In this study, we applied an ultra-fast T2 relaxometry method (5) to a group of MS patients in the early stage of the disease and to a group of healthy controls. This new method relies on a nonlinear inverse reconstruction algorithm which directly estimates a T2 and spin-density map from a train of undersampled spin echoes and allows a whole brain scan in 3 minutes. The goal of the project was to assess the sensitivity of this ultra-fast technique to assess brain tissue alterations in early stages of the disease.

Methods: We enrolled 30 multiple sclerosis patients (age 34.8±9.2, mean±SD, 21:10 , female:male (F:M)) at early stage of the disease (duration from first symptoms, 33.3±21, mean± SD, interval 2-70 months) and 18 healthy controls (age=33±9.7, mean±SD, 10:8, F:M). All scans were performed in a 3T Trio machine (Siemens, Erlangen, Germany) equipped with a 32 channel coil. The protocol included: high-resolution MPRAGE (TR/TE = 2300/2.98 ms, voxel size = 1x1x1.2 mm^3, FoV = 256x240x160), MP2RAGE (TR/TE = 5000/3 ms, inversion time = 700 ms, FA = 4°, voxel size = 1x1x1.2 mm^3, FoV = 256x240x160) and T2 relaxometry (TR/TE = 5850/9-189 ms, voxel size = 1x1x4 mm^3, FoV = 30x192x160, 21 echoes, scan time: 3.15 min). T1 maps were derived from MP2RAGE volumes. MPRAGE and T2 maps were linearly registered to respectively MP2RAGE volumes and T1 maps using ELASTIX (6). T2 maps (Fig1) were interpolated using third order BSpline during registration to MPRAGEs because of their lower spatial resolution. Regions of interest (ROIs) were then automatically extracted from the MPRAGE images (Fig1) using an in-house software based on variational expectation-maximization tissue classification (7). The following ROIs were obtained: global white and cortical gray matter, thalamus and basal ganglia (caudate, putamen and globus pallidus), cerebellar WM and GM. Statistical analysis was performed using permutation-based Hotelling tests with age and gender as covariates as well as correction for family-wise error rate. The following H0 hypotheses were tested: (i) there are no global differences in WM and cGM between patients and controls; (ii) there are no differences in cerebellar GM and WM between patients and controls and (iii) there are no differences in the thalamus and basal ganglia between patients and controls. Spearman correlation was used to correlate ROIs that showed significant differences between patients and controls with disease duration from initial symptoms and from diagnosis (months). Last, a naive bayes classifier was performed to classify patients from controls.

Results: The results from the statistical analysis are reported in *Table 1*. We refuted the H0 (i) hypothesis for global WM seen that we found that WM T2 was significantly higher in patients than controls (*84.82±2.18 ms* vs *83.13±2.11 ms,* p=0.03). On the contrary we confirmed the H0 hypothesis (ii) and (iii) despite we observed a trend of higher T2 in cerebellar GM in patients than in controls (*103.17±3.65 ms* vs *100.85±3.55 ms,* p=0.07). No significant correlation was found between the patients T2 in WM and the duration of disease from the first symptoms (fig2) as well from diagnosis. Nevertheless, patients whose symptoms appeared less than 1 year before the study showed higher WM T2 value (*85.71±2.18 ms*) than patients with longer disease duration (*84.48±2.13 ms, p=ns*) and controls (*83.13±2.11 ms,* p=0.01). Patients with disease duration between 1year and 6 years showed less pronounced differences from control subjects (p=0.05). These results suggests the highest sensitivity of this technique towards recent inflammatory processes.

Conclusion: Ultra-fast T2 relaxometry provides a valuable instrument to quantify the impact of MS in early stages of the disease, particularly during the first year after symptoms appearance..Including this sequence in clinical protocol will allow implementing new classification methods that might complement staging of disease severity and follow-up.

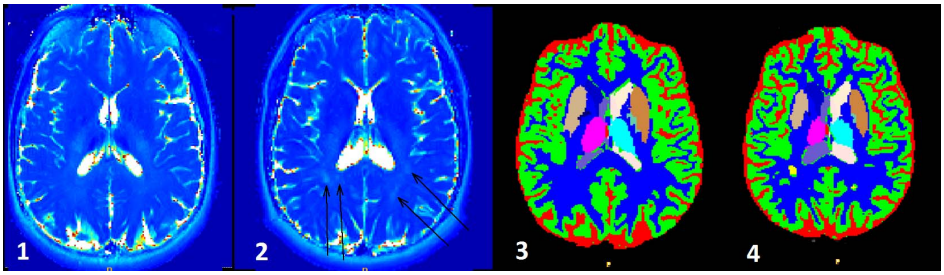

Figure1*.Representative Slice of T2 map of a control (1) and a patient (2), and their respective segmented maps (3,4). Lesions in (2) are pointed out by black arrows. Segmented slice: WM is in blue, GM matter in green and CSF in red. Others colors are used to identify the Thalamus, putamen pallidum, caudate.*

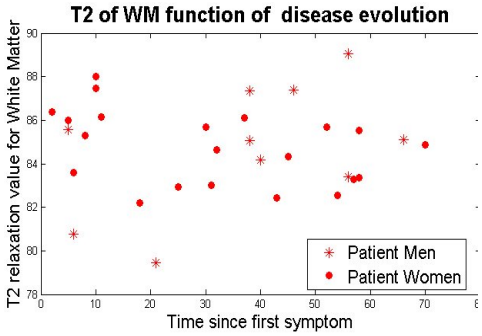

Figure2 *. T2 relaxation time as function of disease duration from the first symptoms*

T2 (ms)	GM	WM	Thalamus	Caudate	Putamen	Pallidum	Cerebellum GM	Cerebellum WM
Controls (n=18)	102.66 ± 3.51	**83.13 ± 2.11**	92.64 ± 6.45	102.62 ±14.96	74.55 ± 2.77	78.82 ± 3.40	100.85 ± 3.55	87.22 ± 2.11
Patients (n=31)	103.83 ± 3.52	**84.74 ± 2.13**	96.80 ± 8.40	98.10 ± 9.44	74.76 ± 2.53	81.03 ± 5.78	103.17 ± 3.65	88.56 ± 2.48
p-value	*0.347*	*0.031*	*0.139*	*0.547*	*0.851*	*0.441*	*0.067*	*0.086*

Table 1. T2 relaxation time of cortical and subcortical regions for controls and patients with associated p-values

References: 1. Compston et al., 2008 2. Calabrese et al., 2010; 3. Lucchinetti et al., 2000; 4. Stumpf et al., 2011; 5 Neema et al., 2009 6. Klein et al, 2010; 7 Roche et al., 2011