BEYOND FOCAL CORTICAL LESIONS IN MULTIPLE SCLEROSIS: AN *IN VIVO* QUANTITATIVE AND SPATIAL IMAGING STUDY AT 7 T

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Target audience: Neurologists, radiologists and neuroscientists interested in developing methods to better understand in vivo the link between focal cortical lesions and diffuse cortical pathology in multiple sclerosis

Purpose: Cortical demyelinating lesions (CL) are thought to represent a major hallmark of physical and cognitive deterioration in multiple sclerosis (MS). Diffuse areas of subpial demyelination that extend beyond focal cortical lesions (CL) have been also observed mainly in neuropathological studies of MS, being consistently associated with progressive disease. Ultra high field MRI using T_2* gradient echo imaging has shown improved detection of focal MS cortical lesions [1-4] but in vivo quantification of subpial demyelination remains challenging. Moreover histopathological-MR correlation at 7 Tesla (T) highlighted that focal CL visible on MR scans may not account for the full spectrum of MS cortical pathology [2, 4]. Thus, the contribution of focal CL on the overall cortical T_2* changes, and across disease stages is unclear. Here, we investigated 7 T T_2* relaxation rates in the cortex of subjects with relapsing-remitting (RR) and secondary-progressive (SP) MS to determine: 1) quantitative T_2* changes in and beyond visible focal CL, 2) the spatial distribution of focal MS CL across the cortex, 3) the impact of focal CL on the surrounding peri-lesional cortex.

Methods: Twenty-nine MS patients (18 RRMS and 11 SPMS, mean age= 44.1 years) showing at least 2 cortical lesions, and 17 age-matched controls underwent 7 T (Siemens) acquisition of 1) multi-echo T_2*-gradient-echo sequences (0.33×0.33×1 mm^3) for T_2* cortical decay (ms) maps reconstruction; 2) single echo T_2*-gradient-echo sequence (0.33×0.33×1 mm^3) for segmentation of cortical lesions, and 3 T acquisition of 3) a 3D MEMPR T1-weighted scan (0.9mm isotropic) for cortical surface reconstruction using FreeSurfer., We segmented intracortical lesions (ICL) and leukocortical lesions (LCL, extending through the grey matter/white matter surface without reaching the pial surface) using Slicer 4.0.3. The spatial distribution of ICL and LCL on cortical surface was assessed by building a lesion probability map after projection of the lesions on each subject's cortical surface and normalization on FreeSurfer fsaverage surface template. ICL, LCL masks and T_2* maps were registered to the 3 T T1 scan using boundary based registration [5]. Mean T_2* in each lesion mask was compared with normal appearing cortical grey matter (NACGM) T_2* in each patient's group (by paired t-test), and with cortical grey matter T_2* in controls (by linear regression using age as nuisance factor). Finally, using a region-growing algorithm, we computed T_2* as a function of distance from ICL in each patient. T_2* change surrounding ICL was modelled as an exponential decay and compared across patient's groups.

Results: 1) Quantitative T_2* in CL and NACGM

In all MS, median ICL count was 9 (range: 0-55) and median LCL count was 6 (range: 0-137). ICL and LCL count and volume were significantly higher ($p<0.05$) in SPMS compared to RRMS.

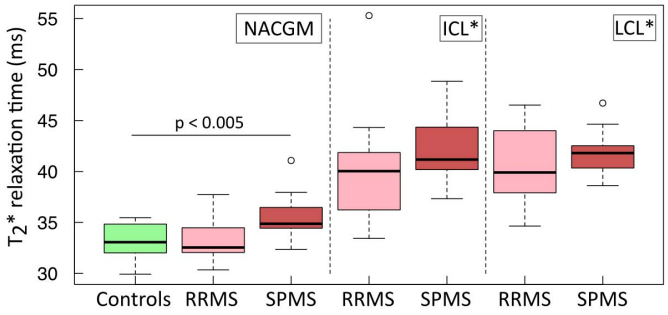

Figure 1. Mean T2* in cortical tissue compartments across subgroups

In both RRMS and SPMS, ICL and LCL had longer T_2* than controls (*$p<10^{-5}$) cortical T_2*, and also relative to NACGM T_2* (*$p<10^{-6}$). NACGM T_2* (ms) was significantly longer in SPMS patients relative to NACGM in RRMS and to cortex in controls.

Conclusion: MS focal CL exhibit longer T_2* than healthy cortex, consistent with myelin and iron loss. Quantitative T_2* changes extend beyond visible CL in SPMS. Cortical lesions, however, have the same impact on surrounding cortex across disease stages. Therefore, T_2* changes in SPMS NACGM may not depend only on MRI visible CL but be the expression of a diffuse pathological process, as suggested by post mortem studies. Quantitative T_2* mapping at 7T shows improved sensitivity to focal and diffuse aspects of cortical pathology in MS.

References: [1] Mainero C., et al *Neurology*, 2009. [2] Pitt D. et al *Arch Neurol,* 2010. [3] Cohen-Adad J et al. *Neuroimage*, 2011. [4] Yao, B et al. *PlosOne*, 2014. [5]. Greve D. et al *Neuroimage,* 2009.

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2) Spatial distribution of focal cortical lesions

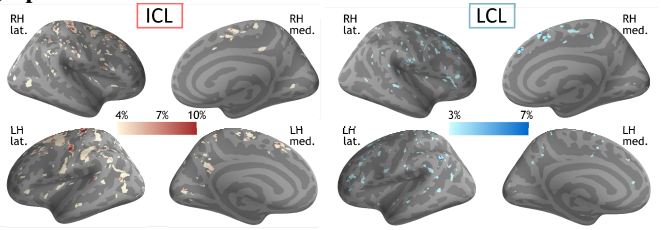

Figure 2. Lesion probability map of cortical lesions in all MS patients

Highest distribution of ICL was in superior, middle frontal areas and central sulcus, followed by parietal and temporal cortex. LCL distribution was widespread across the cortex.

3) Impact of ICL T_2* increase on perilesional cortex

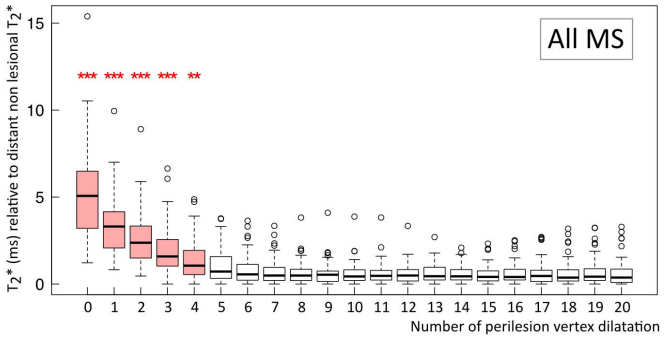

Figure 3. T_2* decrease in cortical tissue surrounding ICL in all MS patients, as a function of distance from the lesions. *** $p < 10^{-6}$ ** $p < 10^{-3}$

We observed an exponential T_2* decrease in the perilesional cortical tissue, which remained significantly higher than distant NACGM T_2* up to 4 vertex dilations around ICL (~ 4mm). The exponential fit parameters of perilesional cortical T_2* decrease were not different across the MS subgroups.