IMPACT OF INTRA- AND JUXTA-CORTICAL PATHOLOGY ON COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS BY QUANTITATIVE T_2* MAPPING AT 7 T MRI

Céline Louapre[1], Sindhuja T Govindarajan[1], Costanza Giannì[1], Nancy Madigan[2], AS Nielsen[3], RP Kinkel[4], and Caterina Mainero[1]

[1]AA. Martinos Center for Biomedical Imaging, Charlestown, MA, United States, [2]Beth Israel Deaconess Medical Center, Boston, MA, United States, [3]Virginia Mason Medical Center, Seattle, WA, United States, [4]University of California San Diego, San Diego, CA, United States

Target audience: Neurologists, radiologists and neuroscientists interested in developing methods to better understand in vivo the impact of cortical pathology on cognitive impairment in multiple sclerosis

Purpose: Cortical pathology, including atrophy and cortical lesions, has been established to play a major role in cognitive impairment in multiple sclerosis (MS)[1]. However, the link between cognition and regional cortical degeneration, both across the whole cortical surface and across the cortical width, remains unclear. Previous data suggested that focal juxta- and leukocortical lesions better predict neuropsychological performance (NP) in MS than purely intracortical lesions[2], suggesting that the location of pathology within the cortical width might impact differently NP in MS. Additionally, the impact of diffuse subpial demyelination on cognitive performance is still unknown. In this study, we aim at determining the relation between NP and tissue damage at different depths through the cortical width up to the juxta-cortical white matter (WM), across the whole brain, using a quantitative, surface-based analysis of T_2* relaxation rates from ultra high resolution 7 Tesla MRI.

Methods: Thirty-one patients (5 early MS, 16 RRMS, 10 SPMS) underwent: 1) a modified version of the MACFIMS battery; 2) a 7T (Siemens) acquisition of multi-echo T_2* gradient echo sequences (0.33×0.33×1 mm^3) for T_2* maps; 3) a 3T MRI acquisition of T1-weighted images optimized for cortical surface reconstruction using FreeSurfer. T_2* maps were registered to cortical surfaces[3], and sampled along the cortex at 25%, 50%, and 75% depth from the pial surface, and at 0.5mm, 1mm, 1.5mm and 2mm below the cortex. The relation between T_2* at each depth, individual NP scores and a global cognitive index (CI), calculated from a principal component analysis on the whole battery, was tested by a General Linear Model (GLM) including age, gender, education and cortical thickness at each vertex as nuisance regressors ($p< 0.05$ corrected for multiple comparisons). In order to identify the contribution to cognitive impairment of cortical pathology independently from WM lesions, we also added WM lesion volume (WMLV) as covariate of no interest in the GLM involving intracortical T_2* surfaces.

Results: In MS patients, cortical T_2* increase (underlying decrease of myelin and iron content) correlated with global cognitive impairment as measured by CI, independently from WMLV **(Fig. 1)**. The clusters of correlation were located in cortical areas highly relevant for cognition belonging to the default-mode network. For each individual test, the regional association between cortical T_2* and cognitive impairment showed different patterns depending on cognitive domains tested. While processing speed impairment (SDMT, TMT) relied on widespread cortical degeneration, verbal memory impairment (CVLT) was associated mainly with precuneus, cingulate and parietal degeneration, visuo-spatial impairment (BVMT, JLOT) was associated with paracentral and superior frontal degeneration, and executive functioning (WCST) was associated with medial prefrontal and parietal degeneration.

From GLM analyses at each cortical and juxta-cortical depth, we calculated the total surface of clusters exhibiting either a positive or negative correlation (depending on the test) between T_2* and NP. Impairment of cognitive domains assessing cortical-subcortical functions was associated with pathology in deepest cortical layers, next to WM (75% depth from pial surface) **(Fig. 2)**. Reduced performance in executive functions (WCST), which mainly relies on cortical integrity, was better predicted by intracortical pathology closer to the pial surface (25% and 50% depth from pial surface).

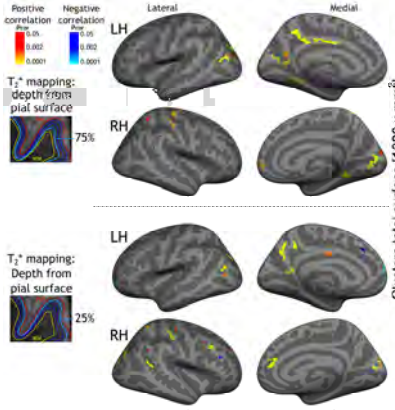

Figure 1. Overlay of the GLM significance map ($p<0.05$ corrected) showing clusters of correlation between T_2* at 75% and 25% depth from pial surface and global cognitive index (CI) in MS patients

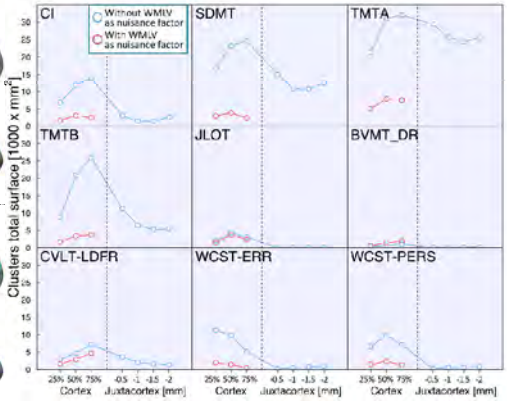

Figure 2. Total surface of clusters exhibiting a significant correlation ($p<0.05$ corrected) between T_2* at each depth and NP (for CI and each test individually).

Conclusion: Cognitive impairment in MS correlated with the degree of intracortical laminar quantitative T_2* changes (underlying demyelination and/or iron loss), independently from WM lesions and cortical atrophy, in areas highly critical for cognitive functioning. This association was larger in deepest cortical layers, next to WM for cognitive domains assessing cortical-subcortical functions, while reduced performance in executive functions, which mainly relies on cortical integrity, was better predicted by intracortical pathology closer to the pial surface.

Abbreviations: BVMT: Brief Verbal Memory Test; CI: cognitive index; CVLT: California Verbal Learning Test; GLM: general linear model; MACFIMS: Minimal assessment of cognitive function in multiple sclerosis; NP: neuropsychological performance; SDMT: Symbol digit modalities test; TMT: Trail making test; WCST: Wisconsin card sorting test; WM: white matter; WMLV: white matter lesion volume

References

[1] Calabrese M., et al *Arch Neurol*, 2009. [2] Nielsen AS. et al *Neurology*, 2013. [3] Cohen-Adad J. et al *Neuroimage*, 2011.

Funding: NMSS RG 4281-A-1; NIH RO1 R01NS078322-01A1; ARSEP; FISM