In-vivo mapping of thalamic pathological mechanisms in pediatric patients with MS

Short title: Thalamic damage in pediatric multiple sclerosis

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Background. Both local inflammatory demyelination and changes secondary to axonal transection of fibers passing through focal white matter (WM) lesions can account for thalamic abnormalities in multiple sclerosis (MS) patients. Assessing location of microstructural abnormalities within the thalamus as a function of distance from cerebrospinal fluid (CSF) in pediatric-MS patients could help to individuate whether at beginning of disease, thalamic damage is due to CSF-mediated factors or thalamic neurodegeneration associated with macroscopic damage.

Objectives. The study goal is to investigate *in-vivo*, the pathological mechanisms underlying microstructural thalamic damage in pediatric-MS patients by applying quantitative-MRI techniques and to assess their contribution to clinical disability.

Methods. Seventy pediatric-MS patients and 26 age- and sex-matched healthy controls (HC) underwent 3T MRI and clinical evaluation. As quantitative-MRI metrics, we assessed diffusion tensor imaging measures - fractional anisotropy (FA) and mean diffusivity (MD)- and T1/T2-weighted ratio in whole thalamus and thalamic WM. We tested for: differences in thalamic volume and quantitative-MRI measures globally and within concentric bands originating from CSF/thalamus-interface; relation between thalamic, cortical, and WM metrics; and contribution of MRI metrics to clinical disability.

Results. Compared to HC, pediatric-MS patients had increased FA in whole thalamus, reduced FA with increased MD in thalamic WM but no atrophy. In pediatric-MS, significant abnormalities of FA were observed in bands nearest to CSF and in those nearest to WM, while significant abnormalities of MD and

T1/T2-weighted ratio were observed only in thalamic regions next to CSF. Significant correlations were found between the abnormalities detected at CSF/thalamus-interface and cortical thickness, while the alterations described at thalamus/WM-interface correlated with lesion volumes. No correlations were found between thalamic damage and clinical disability.

Conclusion. The abnormalities observed suggested that thalamic damage is determined by heterogeneous pathological processes according to the interface examined, confirming the thalamus as a critical barometer of neuronal pathology in MS.