Early silent degeneration of the thalamocortical network in multiple sclerosis

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Background: Recent studies on patients with clinically isolated syndrome (CIS) and multiple sclerosis (MS) demonstrated thalamic atrophy. However, it remained unclear whether the volume loss was mainly a consequence of white matter (WM) degeneration or primarily caused by intrathalamic, WM-independent pathology.

Objectives: Here we addressed the following questions: i.) Can a “normal-appearing” thalamus already be atrophic in patients with CIS and early relapsing-remitting MS (RRMS) without extensive white matter lesion load (WMLL)? ii.) If so, is this early atrophy accompanied by “silent” (non-lesional) microstructural thalamic alterations?

Methods: 110 patients with RRMS, 12 with CIS, and 30 healthy controls were admitted to 3T magnetic resonance and diffusion tensor imaging (DTI). Fractional anisotropy (FA) was computed from DTI to assess thalamic and WM microstructure.

Results: The relative thalamic volume (RTV) and thalamic FA were significantly reduced in patients with CIS and RRMS relative to healthy controls. RTV and thalamic FA were also correlated. The age, gender, WMLL, thalamic FA, and gray matter volume corrected RTV was even in the absence of thalamic and extensive white matter lesions reduced. This was also found in patients with very short disease duration (≤ 24 months). A SPM voxel-based correlation analysis revealed that the RTV reduction had a significant effect on local WM FA - in areas next to the thalamus and basal ganglia. Interestingly, the FA-RTV correlation pattern was not congruent to the WM lesion probability map (Figure 1).
Figure 1 Combination of 1.) the MNI-152 T1-weighted image for spatial orientation, 2.) the significant voxels of the SPM8 correlation analysis with dependent variable FA and independent factor RTV (red), and 3.) the WM distribution in FLAIR images ("lesion probability map") (green). This comparison illustrates that the microstructural white matter damage (FA reduction) which is correlated with thalamic atrophy occurred mainly next to the thalamus and basal ganglia and showed nearly no overlap with the WM lesion distribution in FLAIR images.

**Conclusion:** Microstructural thalamic degeneration and atrophy can be present despite absence of thalamic or extensive WMLL. Early thalamic atrophy is mainly driven by silent microstructural thalamic alterations. Lesions do not disclose the early damage of thalamocortical circuits, which seems to be much more affected in CIS and RRMS than expected.