Multimodal imaging analysis in the assessment of gray and white matter damage in multiple sclerosis

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Target audience: This research is aimed at researchers and/or clinicians seeking to better understand the relationship between gray and white matter damage in the brain of multiple sclerosis patients.

Background/purpose: Advanced MRI techniques have increased the understanding of the gray matter's (GM) role in determining disability in multiple sclerosis (MS). However, there remain many unanswered questions, such as the exact relationship between GM and white matter (WM) damage. It has been hypothesized that independent processes affect both GM and WM in parallel while others have suggested that GM axonal loss is secondary to Wallerian and retrograde axonal degeneration occurring in the WM. The study of motor system components, including the corticospinal tract (CST) WM pathway and the corresponding cortical GM area, would have a significant clinical impact especially considering that disability in MS is mainly related to motor deficits. Diffusion tensor-based tractography allows for the identification of specific WM tracts of interest and measure their integrity with two principal parameters, mean diffusivity (MD) and fractional anisotropy (FA). The freely available FreeSurfer software package provides a useful set of tools for estimating cortical thickness and area measures from high resolution MRI data. We applied these two advanced techniques to the study of the CST and primary motor cortex in a group of patients affected by MS, with the aim to better understand the relationship between GM and WM damage in a clinically relevant system.

Methods: This was a cross-sectional study of 30 patients with established relapsing remitting (RR) MS and 25 age-matched healthy controls (HC) that were examined using 1.5T MRI. The MRI protocol included a 3D T1-weighted MP-RAGE with 1mm isotropic resolution, a dual-echo turbo spin echo, and a DTI acquisition (2 runs with 12 non-collinear diffusion gradients (b=900 s/mm^2) and 1 non-diffusion-weighted (b=0 s/mm^2). MS lesions were identified on proton density-weighted scans, using the corresponding T2-weighted images to increase confidence in lesion identification. We reconstructed the left and right CST of the 25 HC to generate a probabilistic atlas for obtaining probabilistic tractography data in the MS patients[1]. CST lesion load was calculated. FreeSurfer was used to obtain measures of cortical thickness and area from the MP-RAGE[2]. To test whether the anatomical relationship between a WM tract and the corresponding cortical area would be more significant than with a non-structurally connected cortical area, we included in our analysis the primary motor cortex (MC) and auditory cortex (AC), the former directly connected to the CST, the latter belonging to a separate neuronal pathway. A representative example of the intracranial section of the motor pathway is provided in figure 1. The cortical thickness and the surface area for the MC and AC were separately calculated for left and right hemispheres. To reduce the number of comparisons, the left and right measures were combined into a global value. Partial correlations, controlling for age, sex, and global cortical thickness, were used to explore the relationship between cortical thickness and area, CST lesion load, CST DTI indices, and disability as measured by EDSS. CST lesion loads were log-transformed due to positive skew. Due to the exploratory nature of the study, significance was set an alpha level of 0.05.

Results: Clinical and demographic features of patients are as follows: mean (SD) age: 39.5 years (10.3); median (range) EDSS: 3 (0-6.5); mean (SD) disease duration: 6.8 years (6.4); M/F 12/18. MC thickness correlated with CST MD ($r = -471$, $p = 0.013$), CST lesion volume ($r = -0.601$, $p = 0.001$), and EDSS ($r = -0.482$, $p = 0.011$). MC surface area correlated only with EDSS ($r = -.578$, $p=.002$). AC measures did not correlate with any CST measures (DTI indices nor lesion load.) FA did not correlate with any measures.

Discussion: Our study revealed a significant correlation between MC, but not AC, thickness and the integrity of the CST. This further confirms the hypothesis that the damage in specific GM areas is closely related to the anatomically and functionally corresponding WM tracts. Moreover, MC thickness and surface correlated with EDSS. There is increasing evidence supporting the role of GM atrophy in determining disability accrual[3]. Our findings, while confirming this notion, add relevant pieces of information, further characterizing the volume loss in terms of both cortical thinning and reduction of surface area. Lesions in the CST showed moderate correlations with the cortical thickness, supporting the link between GM pathology and WM damage. Furthermore, the relationship between altered CST integrity expressed by lesions and clinical disability confirms the role of focal damage in clinically eloquent areas. Longitudinal studies are warranted to better understand the temporal and possibly causal relationship between GM and WM damage in the brains of MS patients.

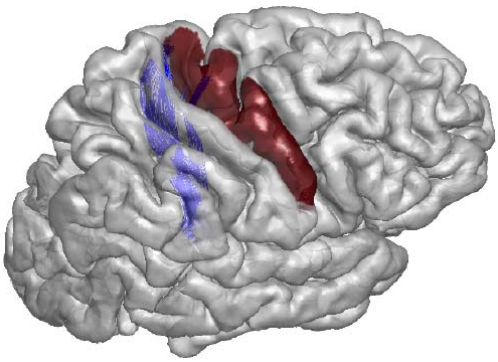

Figure 1: The CST of a representative subject, shown in blue, connecting to the primary motor cortex, in red.

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