Microstructural white matter correlates of motor fatigue in multiple sclerosis - a diffusion weighted imaging study

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Methods

Fifty mildly disabled relapsing-remitting MS patients were recruited from the Danish MS Centre along with 25 age- and gender-matched healthy controls (HC). Fatigue was evaluated with Fatigue Scale for Motor and Cognitive Functions (FSMC). Additionally, all subjects underwent a standard MS test battery and magnetic resonance imaging (MRI) including conventional structural MRI to assess lesion load and diffusion weighted imaging (DWI) to assess microstructural WM changes:

- Fractional anisotropy (FA) was used to assess the WM integrity. FA measures the degree of diffusion directonality, and is influenced by, e.g., axonal myelination, diameter and organization.

- Anatomical connectivity mapping (ACM) was used to assess the disruption of neural fibers connecting specific brain areas. ACM reflects the connectedness of each WM voxel to the entire brain (3).

- Using FSL’s Randomise, we assessed voxelwise group differences in FA and ACM between MS and HC. In addition, we assessed the correlation between voxelwise FA and ACM values and FSMC scores in the MS group.

- We hypothesized that MS patients with fatigue will have disease-related microstructural alterations in central motor fiber bundles including the corticospinal tracts and the superior longitudinal fasciculus.

Results

The MS group had a mean EDSS score of 2.3 (range: 0-3.5) and mean disease duration of 6 years (range: 0-28). The FSMC total, motor and cognitive mean scores were 60 (range: 20-92), 29 (range: 10-45) and 31 (range: 10-48). Relative to HC, MS patients showed reduced FA and ACM values in the body of corpus callosum (CC) (p < 0.01 and p < 0.01 respectively, family-wise error corrected at the cluster level) (Figure 1). In addition, reduced FA values were found in the right and left ATR and in forceps major. Region of interest (ROI) analyses of the superior longitudinal fascicules (SLF) and corticospinal tracts (CST) revealed a cluster with significant negative correlation between the FSMC cognitive scores and ACM in the right SLF (p = 0.02). (MNI coordinates: 32, -16, 36). However, no statistically significant correlations were found for the FSMC motor scores. Further, in agreement with the vast majority of the existing literature, we did not find any association between global lesion load and fatigue at a macrostructural level.

Reduced FA and ACM values in corpus callosum in MS patients

Discussion

In this study, we investigated the microstructural correlates of fatigue in a cohort of patients with relapsing-remitting MS. The origin of fatigue is highly debated and there are several plausible players as the disease causes diverse immunological, structural and functional pathological changes in the brain. We observed that patients, compared to HC, exhibited reduced FA in a cluster in the corpus callosum (CC) covering the interhemispheric motor fibres (4). This suggests that individuals with MS have a changed WM integrity in the commissural motor fibres connecting the primary motor cortices, which could explain some of the motor disability seen in MS. Moreover, patients showed reduced connectedness in the anterior body of CC. In addition, we found a cluster in the right SLF, where the ACM values correlated negatively with the subjective fatigue scores, suggesting that the microstructural WM alterations could be critical for the development of MS-related fatigue.

Conclusion

The microstructure of CC, including the transcallosal motor fibres, was significantly altered in the MS group relative to HC. This suggest that patients MS have altered interhemispheric connectivity and local WM integrity in the commissural fibres. Our preliminary results concerning fatigue and microstructural alterations need further validation.

References