Longitudinal fixel-based white matter damage predicts cognitive decline in multiple sclerosis

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Background

During the course of multiple sclerosis (MS), many patients experience cognitive deficits which are not easily related to lesion load or location. This discrepancy could be driven by an inability of current imaging methods to consider the full complexity of white matter (WM) structure both at a macro- and microstructural level.

Objective

To use a novel fixel-based approach to investigate specific patterns of WM degeneration, the evolution over time, the manifestation across different stages of the disease and their role in cognitive impairment.

Methods

Cognitive and 30-direction diffusion weighted MR data were included from 327 MS patients (mean age=48.34 years, 221 female) and 95 healthy controls (HCs; mean age=45.70 years, 55 female). Of those, 233 patients and 61 HCs had follow-up assessments five years after. Patients scoring 1.5SD or 2SD below HCs on at least 2 cognitive domains (BRB-N) were classified as mildly cognitively impaired (MCI) or cognitively impaired (CI), respectively, or otherwise cognitively preserved (CP). Fixel-based analysis of diffusion data was used to calculate fiber-specific measures (fiber density [FD], reflecting microstructural diffuse axonal damage; fiber cross-section [FC] reflecting macrostructural tract atrophy) within atlas-based WM tracts at each visit.

Results

At baseline, all fixel-based measures were significantly abnormal in MS compared to HCs ($p<0.05$). All measures showed a similar pattern, with SPMS patients having the most severe damage, followed by PPMS and RRMS. Similarly, damage was least severe in CP (n=177), more severe in MCI (n=63), and worst in CI (n=87; $p<0.05$). Microstructural damage was most pronounced in the cingulum, while macrostructural alterations were most pronounced in the corticospinal tract (CST), cingulum and superior longitudinal fasciculus (SLF). Over time, WM alterations worsened most severely in progressive MS ($p<0.05$), with WM atrophy progression mainly seen in the CST and microstructural axonal damage worsening in cingulum and SLF. Both cognitive decline and clinical disability at follow-up could best be predicted by baseline fixel-based measures (R^2 ranging from 0.36 to 0.45, $p<0.001$).

Conclusion

These results indicate that fixel-based approaches can have powerful predictive value in MS for both physical and cognitive disabilities. Longitudinal deterioration was worst in progressive MS, indicating that degeneration in WM remains important to study further in this phenotype.