Dynamic modular-level alterations of structural–functional coupling in clinically isolated syndrome

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Background: Structural and functional connectivity abnormalities have been previously reported in multiple sclerosis (MS). However, little is known about how each modality evolution relates to the other. Recent studies in other neurological disorders have suggested that structural–functional coupling may be more sensitive in detecting brain alterations than any single modality.
Objectives: This study aimed to investigate the longitudinal evolution of structural– functional coupling, both at the global and modular levels, in the first year following a clinically isolated syndrome (CIS). We hypothesized that during the course of MS, patients exhibit a decoupling between functional and structural connectivity due to the disruptive nature of the disease.
Methods: Forty-one consecutive patients with CIS were prospectively enrolled in this study, along with 19 age-, sex- and educational level-matched healthy controls. These participants were followed for one year and underwent resting-state functional magnetic resonance imaging and diffusion tensor imaging at each time-point, along with an extensive neuropsychological assessment.
Results: Graph theory analysis revealed structural reorganization at baseline that appeared as an increase in the clustering coefficient in patients compared to controls ($P < 0.05$), as well as modular-specific alterations. After one year of follow-up, both structural and functional reorganization was depicted with abnormal modular-specific connectivity and an increase of the functional betweenness centrality in patients compared to controls ($P < 0.01$). More importantly, structural–functional decoupling was observed in the salience, visual, and somatomotor networks. These alterations were present along with preserved cognitive performance at this stage.
Conclusion: These results depict structural damage preceding functional reorganization at a global and modular level during the first year following CIS along with normal cognitive performance, suggesting a compensatory mechanism at this stage of the disease. Principally, structural–functional decoupling observed for the first time in MS suggests that functional reorganization occurs along indirect anatomical pathways.