Functional brain states predict cognitive decline 5 years after a clinically isolated syndrome

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Short title: Dynamic functional connectivity in early MS

Background

Cognitive impairment in multiple sclerosis (MS) occurs in the earliest stages of the disease and is related to altered functional connectivity (FC). Recent findings indicated that FC fluctuates during a scan in specific reoccurring FC patterns called “states”.

Objective

This study aims to investigate the longitudinal evolution of dynamic FC states over 5 years following a clinically isolated syndrome (CIS) and their role in shaping cognitive impairment.

Methods

Thirty-two patients were enrolled after their first neurological episode suggestive of MS and followed after 1 and 5 years. Twenty-eight matched healthy controls were also included at baseline.

Cognitive scores and resting-state functional MRI were determined at each follow-up visit. Each fMRI dataset was divided into windows, and connectivity matrices were calculated for each window. States were determined using k-means algorithm and dynamic state parameters were determined.

Results

Cognitive performance was stable during the first year and declined after 5 years.

Five recurring FC states were identified. At baseline, number of transitions between states was lower in MS compared to controls ($p < 0.05$). Over time, the frequency of state 3 (high default-mode/limbic/sensorimotor connectivity) decreased in patients between year 1 and year 5, while frequency of state 4 (low FC in general) increased after 5 years ($p < 0.05$). FC of state 2 (high visual/frontoparietal/limbic connectivity) decreased over the first year, while FC of state 4 increased after 5 years ($p < 0.05$).

Cognitive performance at year 5 could best be predicted by the mean connectivity of state 2 at year 1.

Conclusion

Patients with CIS showed reduced functional network dynamics at baseline. Longitudinal changes showed longer time spent in a state of low FC, but less time spent and more connectivity disturbance in more integrative states. Disturbed FC within this more integrative state was especially predictive of future cognitive decline.

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