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

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Background

Cognitive impairment in multiple sclerosis (MS) can occur in the earliest stages of the disease and is related to altered functional connectivity (FC). While the majority of studies investigated FC under the assumption that patterns are stable, recent findings indicated that FC fluctuates during a scan in specific reoccurring FC patterns called "states".

Objectives

To investigate the longitudinal evolution of dynamic FC states over 5 years following a clinically isolated syndrome and their role in shaping cognitive impairment.

Methods

- 32 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.
- 3T brain MRI scan included 3D T1 weighted images, FLAIR and resting-state fMRI (rs-fMRI).
- All participants were also evaluated using a comprehensive neuropsychological battery.
- Cognitive scores and resting-state functional MRI were determined at each follow-up visit.
- Each fMRI dataset was analysed using a sliding window approach, and connectivity matrices were calculated for each window. Five states were determined using a k-means algorithm and dynamic state parameters were determined.
- We finally characterized different aspects of these states using: (i) the frequency as the number of occurrences of each state, (ii) the mean dwell time as the average consecutive time points spent in each state, (iii) the number of transitions between states, and (iv) the mean connectivity within each state.
- Multiple linear regression investigated the predictive power of functional brain states for cognitive decline.

Results

Figure 1. Recurring brain states represented for patients at each visit
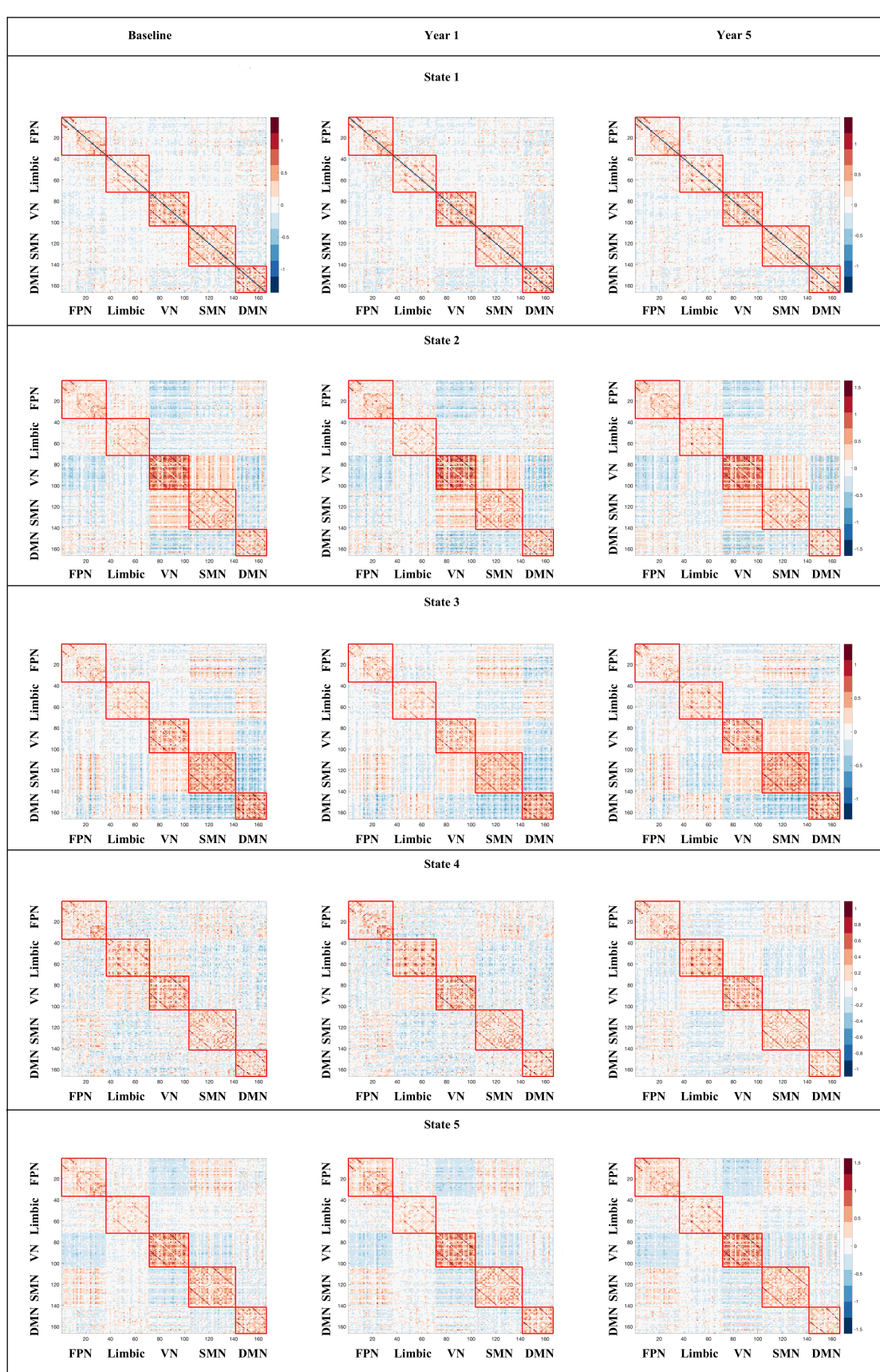
FPN: frontoparietal network; VN: visual network; SMN: sensorimotor network; DMN: default mode network.

Patients mean (SD) age was 38.3 (7.9) years with 78% females. 63% of patients had a high level of education. MS patients showed preserved cognitive performances after 1-year, while their scores declined after 5 years of disease evolution.

➢ **Functional connectivity states**
- Five recurring FC states were identified (**Fig 1**).
- At baseline, number of **transitions** between states was lower in MS compared to controls ($p < 0.05$; **Fig 2A**).
- 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 ($p < 0.05$; **Fig 2B**). **FC** of **state 2** (high visual/frontoparietal/limbic connectivity) decreased over the first year, while **FC** of **state 4** increased after 5 years ($p < 0.05$; **Fig 2D**).

➢ **Altered network states and cognitive performance**
- Cognitive performance at year 5 could best be predicted by the **mean connectivity of state 2** at year 1 (average performance, episodic memory and processing speed).

Figure 3. Comparisons of brain states parameters between patients and healthy controls
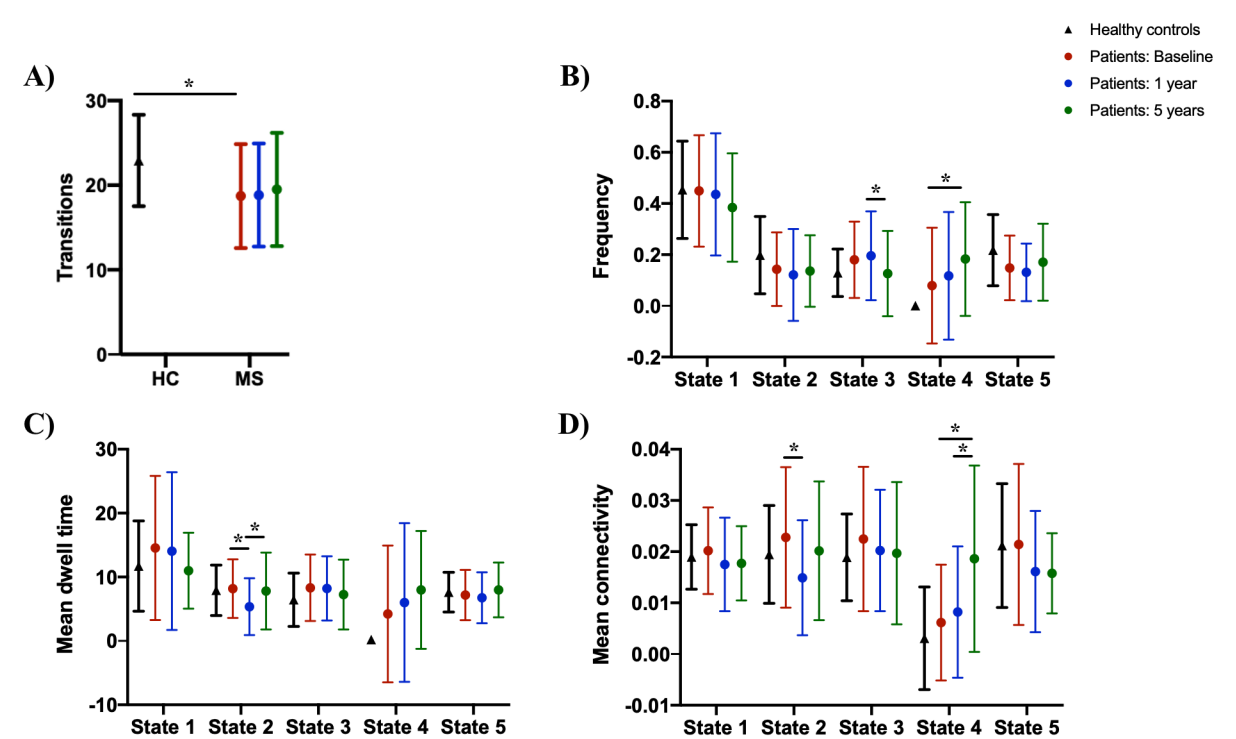
Comparisons of brain states parameters between patients and healthy controls. A) number of transitions, B) frequency, C) mean dwell time and D) mean connectivity.
* $p < 0.05$.

Conclusions

➢ Patients with a clinically isolated syndrome 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 with high within and between network FC.
➢ Disturbed FC within this more integrative state was especially predictive of future cognitive decline.