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

- 41 patients recruited less than 6 months after a CIS with at least two asymptomatic cerebral lesions on FLAIR and 19 healthy controls (HC) matched for age, sex and educational level.
- 3T brain MRI scan included 3D T1 weighted images, FLAIR, diffusion tensor imaging (DTI) and resting-state fMRI (rs-fMRI).
- All participants were also evaluated using a comprehensive neuropsychological battery.
- After filling lesions, FreeSurfer v5.3 was used to define a custom-made atlas including 83 gray matter regions per hemisphere.
- Structural and functional connectomes were constructed for each subject.
- Five modules were extracted using the Louvain algorithm: the frontoparietal network (FPN), the salience network (SN), the default mode network (DMN), the visual network (VN), and the somatomotor network (SMN).
- Graph theoretical analysis was used to investigate whole-brain level and modular level networks properties.
- Structural-functional coupling was defined as the correlation coefficient between strengths of the structural and functional networks. For each participant, this correlation was constrained by edges of **non-zero** structural connectivity.

Results

Patients mean (SD) age was 38.3 (11.2) years with 78% females. 63% of patients had a high level of education. CIS patients showed preserved cognitive performances after 1-year of disease evolution.

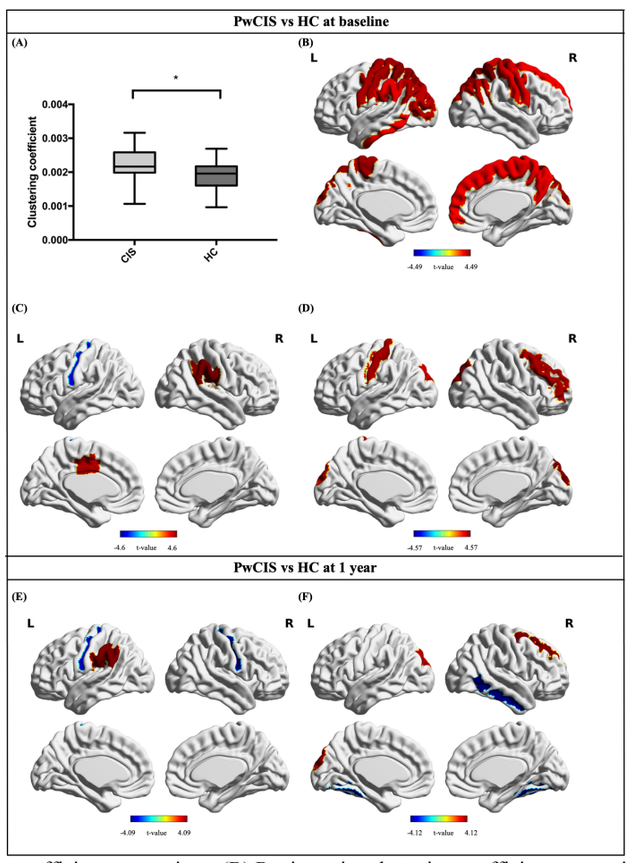
➢ **Structural network**

- At baseline, the clustering coefficient was significantly increased in patients compared to HC (**Fig 1 A,B**). At the modular level, alterations were also noticed in both the participation coefficient and the within-module degree z-score (**Fig 1 C,D**).
- At Year 1, there was no difference between patients with CIS and HC in the overall network metrics. However, at the modular level, alterations were still present (**Fig 1 E,F**).

➢ **Functional network**

- At baseline, no differences were noted in the overall network metrics between CIS patients and HC nor in the modular level metrics (**Fig 2 A,B**).
- After 1 year, betweenness centrality was significantly increased in patients compared to controls. Additionally, modular-level alterations were also present at this stage of the disease (**Fig 2 C,D**).

Figure 1. Structural connectivity alterations

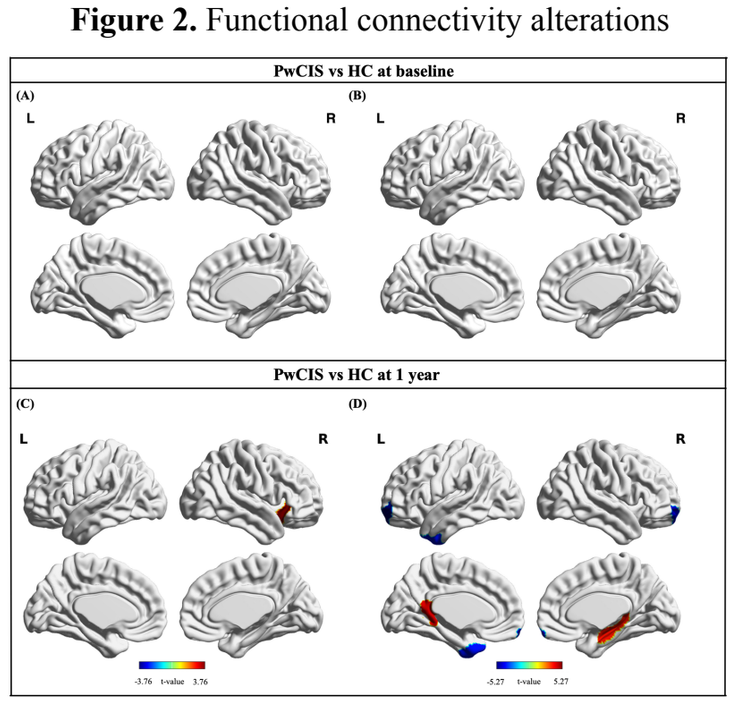


(A) Overall clustering coefficient comparison, (B) Region-wise clustering coefficient comparison, (C) PC comparison between PwCIS and HC, (D) WD comparison between PwCIS and HC, (E) PC comparison between PwCIS and HC, and (F) WD comparison between PwCIS and HC. Boxes show median and interquartile range and whiskers show minimum and maximum values.
PC, participation coefficient; WD, within-degree module z-score; PwCIS, patients with CIS; HC, healthy controls

➢ **Structural-functional coupling**

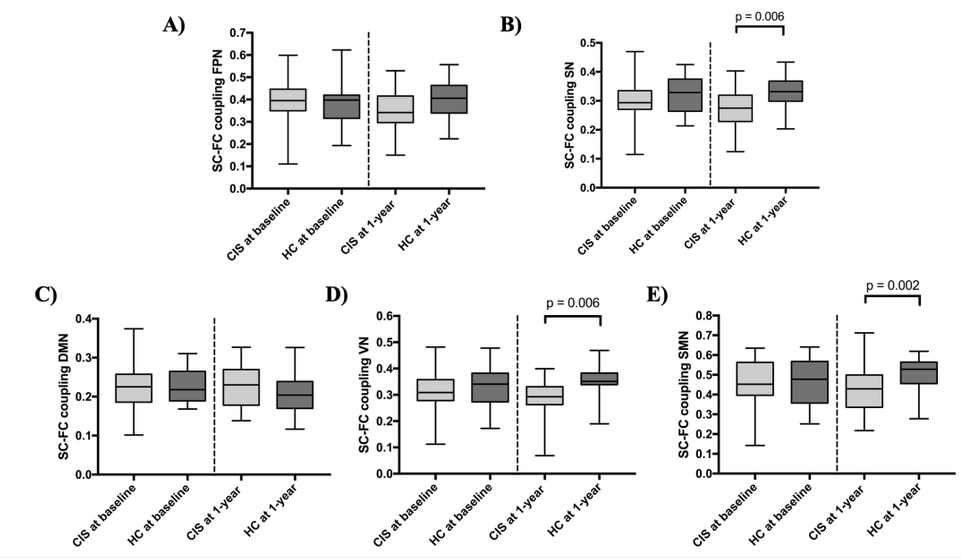
- At baseline, structural-functional coupling was preserved in patients compared to healthy control subjects at both the whole-brain and the modular levels (**Fig 3**).
- After 1 year of evolution, whole-brain coupling was still preserved; however, structural-functional decoupling was observed in three networks (SN, VN and SMN) (**Fig 3**).

Figure 2. Functional connectivity alterations



(A) PC comparison between PwCIS and HC at baseline, (B) WD comparison between PwCIS and HC at baseline, (C) PC comparison between PwCIS and HC, and (D) WD comparison between PwCIS and HC.
PC, participation coefficient; WD, within-degree module z-score; PwCIS, patients with CIS; HC, healthy controls

Figure 3. Structural–functional (SC-FC) coupling at the network level at baseline and 1-year



Conclusions

- These results depict structural damage preceding functional reorganization at a global and modular level during the first year following CIS.
- Normal cognitive performances suggest a compensatory mechanism at this stage of the disease.
- Structural–functional decoupling observed for the first time in MS suggests that functional reorganization occurs along indirect anatomical pathways.

Reference:
Koubiyr I, Besson P, Deloire M, Charré-Morin J, Saubusse A, Tourdias T, Brochet B and Ruet A (2019) *Dynamic modular-level alterations of structural-functional coupling in clinically isolated syndrome*. **Brain**.

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