Structural constraints of functional connectivity drive cognitive impairment in the early stages of multiple sclerosis

I.Koubiyr^{1,2}, M. Deloire³, B. Brochet^{1,2,3}, P. Besson^{4,5}, J. Charre-Morin³, A. Saubusse³, T. Tourdias^{1,2,3}, A. Ruet^{1,2,3}

¹Univ. Bordeaux, F-33000 Bordeaux, France, ²Inserm U1215 - Neurocentre Magendie, F-33000 Bordeaux, France, ³CHU de Bordeaux, F-33000 Bordeaux, France ⁴Department of Radiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, ⁵Department of Neurological Surgery, Neurological Surgery,

Background

Multiple sclerosis (MS) is associated with brain dysconnectivity that leads to changes in network organisation. However, given the inconsistent results obtained by studies of structural and functional connectivity, the relationship between the structural and functional deficits in MS is unclear.

Objectives

This longitudinal prospective study explored structurefunction relationships during the early stages of MS and their role in cognitive performance.

- Methods
- 32 patients recruited less than 6 months after a CIS with at least two asymptomatic cerebral lesions on FLAIR and 10 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.
- Graph theoretical analysis was used to investigate 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.
- Linear mixed effects (LME) models were used to investigate the association between network parameters and clinical outcomes.

Results

Patients mean (SD) age was 37.7 (10.4) 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, and a global cognitive decline after 5 years. Median EDSS score significantly decreased between 1 year and 5 years (1 [0-3] vs 1.75 [0-4]; p < 0.05).

- Structural network (Figure 1)
- After 5 years, the extent of the structural alterations was significantly greater compared to that at the 1-year visit, as was the clustering coefficient indicating **strengthened short-distance connections**. This was also indicated by the significant decrease in characteristic path length compared to both the 1-year and baseline visits suggesting a **loss of long range connections** as well.
- Functional network (Figure 2)
- The degree was significantly lower after 5 years than at the 1-year visit, while the characteristic path length was significantly shorter than at baseline; this suggested **functional recruitment of closer brain regions**.

Figure 1. Structural connectivity alterations

Structural-functional coupling (Figure 3)

- Structural-functional coupling changed significantly over time, with a significant increase seen at the 5-year follow-up visit compared to the 1-year visit due to greater constraint of functional connectivity by direct anatomical connections.
- Only structural-functional coupling explained the change in global cognitive score (estimate = -2.79, P < 0.05, BIC = 175.93)
- Clinical disability, as denoted by the EDSS score, was also associated only with structural-functional coupling (estimate = 6.29, P < 0.05, BIC = 251.93)





Conclusions

- Cognitive (information processing speed, episodic memory, executive functions) decline and disability (EDSS) progression were depicted 5 years after a CIS.
- Structural connectivity results indicated strengthened short-distance connections and loss of long-range connections.
- Functional connectivity results suggested stronger local short-distance connections.
- > After 5 years of evolution, increased SC-FC coupling indicated greater constraint of functional connectivity by direct anatomical connections.
- After a compensation period, increased coupling seems to lead to a network collapse, in turn resulting in cognitive decline and clinical disability.

Reference:

Koubiyr I, Deloire M, Brochet B, Besson P, Charré-Morin J, Saubusse A, Tourdias T and Ruet A (In Press) Structural constraints of functional connectivity drive cognitive impairment in the early stages of multiple sclerosis. **MSJ**.



Disclosure: This study was supported by TEVA, Labex Translational Research And Advanced Imaging Laboratory (TRAIL). It also received support from the ARSEP Foundation and the EDMUS Foundation. Authors thank the Observatoire Français de la Sclérose en plaques (OFSEP).

Koubiyr I : Personal grant from TRAIL; Besson P : Nothing to disclose; Deloire M : Nothing to disclose; CharreMorin J : Nothing to disclose; Saubusse A : Nothing to disclose; Tourdias T : Nothing to disclose; Brochet B : Pr Brochet has received consultancy fees, speaker fees, research grants (nonpersonal), or honoraria from Novartis, BiogenIdec, Merck, Bayer Schering, Roche, Medday, Bayer, Actelion, Teva and Genzyme Sanofi outside the submitted study; Ruet A : has received consultancy fees, speaker fees, research grants (nonpersonal), or honoraria from Novartis, BiogenIdec, Roche, Teva and Merck outside the submitted study.