COGNITIVE RESERVE AND FUNCTIONAL CONNECTIVITY IN THE BRAIN AT REST IN RELAPSING REMITTING MUSLTIPLE SCLEROSIS

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Introduction The concept of "Cognitive Reserve" (CR) postulates the existence of functional brain mechanisms that are able to cope with cerebral damage (1). These mechanisms are believed to rely on pre-existing cognitive processes, or to enlist compensatory mechanisms. CR indicators include premorbid intelligence, formal education, lifetime experiences and current recreational activities. The CR is particularly evident in those clinical conditions which result in a progressive accumulation of cognitive disabilities (2). Cognitive functioning is frequently impaired in multiple sclerosis (MS) (3), but some patients are able to withstand considerable disease burden (e.g. white matter lesions, cerebral atrophy) without cognitive impairment. Previous studies (4) have focused on identifying potentially adaptive functional reorganization through recruitment of new brain regions that could limit expression of these deficits. Resting state Functional Magnetic Resonance Imaging (RS-fMRI) is traditionally used to investigate functional connectivity (FC), within different regions, across the brain at rest. Each RS network (RSN) reflects specific cognitive, motor or sensory processes. For instance, the default mode network (DMN) is involved in working memory, mind wondering or goal- directed behaviors, while the sensory-motor (SMN) or the visual networks are, respectively, involved in sensory-motor or visual functions. One hypothesis suggests that the neuronal mechanisms underpinning CR results on the ability of individuals with high CR to recruit alternative brain areas or networks to preserve specific functions in the presence of structural damage. Abnormal connectivity within specific RSNs can provide useful information on the patho-physiological events underlying several neurological disorders.

Purpose: Aim of this study was to investigate the association of FC, measured with RS-fMRI method, and levels of CR in a MS sample.

Methods: Twenty-eight patients with Relapsing-Remitting (RR)MS (M/F=8/20; mean age(SD)=36.0(8.8) years, EDSS(mdn)=2.0, range between 0-4), were recruited for this RS-fMRI study. All patients underwent an extensive neuropsychological examination to measure information processing speed, working memory and cognitive flexibility, praxis and visuo-spatial memory abilities. Further, arm and hand function, and ambulation ability were assessed through the Nine Hole Peg Test and the Timed 25-Foot Walk. Levels of CR were assessed by using a devoted questionnaire (1) assessing level and type of education, main occupation, cognitive-Leisure Activities, CLA), physical–LA (PLA), and social–LA, (SLA). The MRI acquisition protocol included conventional MRI acquisitions and 8 minutes of resting-state fMRI (gradient echo EPI, TE=30ms, TR=2.08). Functional data preprocessing was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm), after discarding the first 4 volumes. Images were realigned, corrected for slice-time, normalized into Montreal Neurological Institute (MNI) space, and smoothed with a 8mm^3 Gaussian kernel. Finally, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01-0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise. A model-free analysis was employed by using the independent component analysis (ICA) implemented in the GIFT package, in order to allow for a simultaneous separation into individual components. ICA was employed to identify, on a subject by subject basis, regions belonging to the identified RS networks and FC within the default-mode (DMN) and sensory-motor (SMN) networks was investigated (see Figure 1, for selected RSNs). Mean FC for each selected network was extracted, and correlations with neuropsychological scores and CR levels were performed.

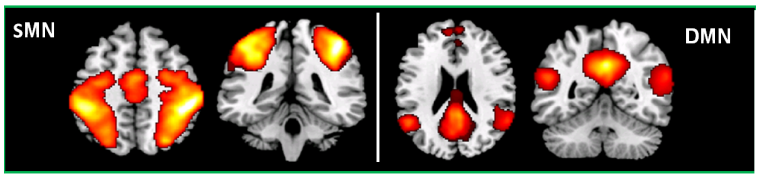

Figure 1. Selected Resting State-fMRI networks. The sensory-motor (SMN) and the default mode network (DMN) have been studied as these sub-serve sensory-motor and cognitive functions, that reflect peculiar clinical features in MS.

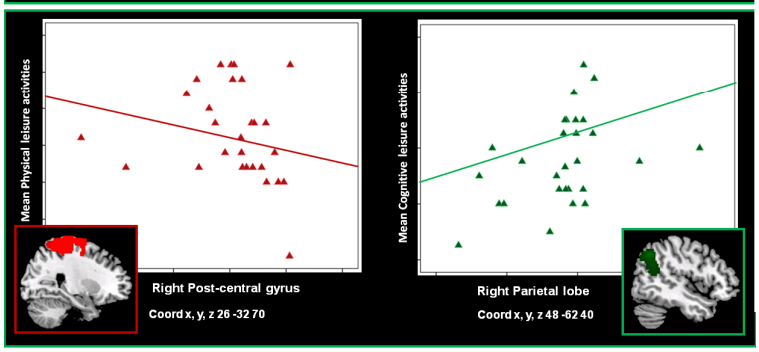

Figure 2. Plots showing significant correlation between SMN and DMN nodes and CR measures.
Left panel: Significant inverse association was found within the SMN between FC in the right post-central gyrus (MNI Coordinates x=26, y=-32, z=70) and the Mean Physical - Leisure Activities score.
Right panel: Significant positive correlation was found within the DMN between FC in the right parietal lobe (MNI Coordinates x=48, y=-62, z=40) and the Mean Cognitive – Leisure Activities score.

Results: Among the 20 components estimated by ICA, ten RSNs, already reported by others were identified (5). Correlation analyses have been performed with respect to the RSNs likely to be affected in MS, namely the SMN and the DMN (see Figure 1), and CR scores. Within the SMN, a significant inverse association was found between FC in the right post-central gyrus and mean Physical–LA ($r=-0.38$, $p>0.05$). Conversely, a positive association was found, within the DMN, between FC in the right parietal node and Cognitive-LA ($r=0.46$, $p>0.05$). No significant correlations were found between FC within the two selected networks and measures of cognitive functioning (see Figure 2).

Discussion: This study shows that FC within the DMN, traditionally involved in cognition, is positively related to Cognitive Leisure Activities , while FC in the SMN is inversely associated to Physical Leisure Activities, in MS. Motor disability is significantly relevant in RRMS, while these patients are relatively less impaired in their cognitive functioning. We thereby suggest that the inverse association between FC in the SMN and PLA, might rely on a neuronal compensatory mechanism of patients' motor impairment. While this mechanism does not involve cognitive functioning, which is traditionally not affected in RRMS (6).

Conclusion:This study suggests that investigating the association of CR and FC might represents an interesting tool to explain and maybe predict MS progression. Overall, these findings suggest the relevance of CR in modulating, not only cognition, but also the level of motor impairment in MS.

References:

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