Resting state fMRI helps to understand the pathophysiology of sensory-motor and cognitive disabilities in MS

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Introduction:

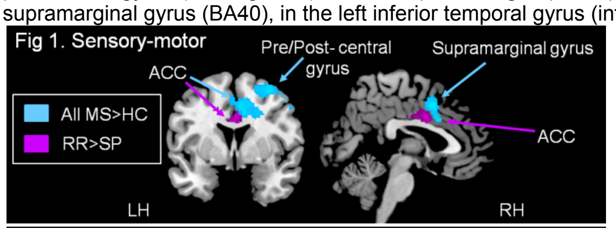
Multiple sclerosis (MS) has been traditionally associated to motor and sensory disabilities, although, more recently, an increasing attention has been dedicated to the occurrence of cognitive impairment. Functional Magnetic Resonance Imaging (fMRI) can be used *in vivo* to detect synchronous fluctuations in blood oxygenation level-dependent (BOLD) signal across the brain at rest. This technique, which is known as resting state (RS) fMRI, is traditionally used to investigate functional connectivity (FC) within well defined resting-state networks (RSNs), such as those related with sensory-motor, visual, auditory and cognitive functions. Abnormal connectivity within specific RSNs can provide useful information on the pathophysiological events underlying several neurological disorders (1). Reduced RS synchronization has been found in patients with depression (2), dementia (3), and, recently, in patients with MS and clinically isolated syndrome (4,5,6). The current study aimed at assessing whether there are specific patterns of functional brain disconnection for the two most frequent MS phenotypes, relapsing-remitting (RR) and secondary progressive (SP).

Subjects and Methods:

So far, we recruited 34 patients with RRMS [M/F ratio=8/26; mean (SD) age=35.70 (9.1) years] and 14 patients with SPMS [M/F ratio=6/8; mean (SD) age=44.6 (9.1) years], who underwent a clinical and neuropsychological examination, and MRI at 3T (Siemens Allegra system). Twenty-two healthy subjects were also recruited as controls [M/F ratio=8/14; mean (SD) age=35.8 (11.1) years]. 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. A second level analysis was performed on the resulting images using a full-factorial model in SPM5. Between-group differences were investigated for the sensory-motor networks and the default mode network (DMN). Differences were considered as significant at p values voxel level uncorrected < 0.05.

Results:

Among the 20 components estimated by ICA, 10 RSNs, already reported by others (7), were identified (i.e., DMN, parietal, medial frontal cortex, primary visual, temporal, auditory, sensory-motor and both left and right hemisphere networks). So far, the second level analysis has been performed on the sensory-motor network and the DMN, the latter widely considered as associated to global cognition. When investigating the sensory-motor network, significant increases of FC were observed in both groups of MS patients, compared against healthy controls (HC), in the pre/post-central gyrus (somatosensory areas), the supramarginal gyrus (BA40), and the anterior cingulate cortex (ACC). Additionally, increased FC was found in the ACC of RR- as compared to SPMS patients (see Figure 1). Within the DMN, increased FC was observed in both RR and SPMS patients, compared against HC, in the parietal operculum, extending to the post-central gyrus (see Figure 2). Between patients' group comparison revealed that SPMS patients have stronger FC than RR, in the supramarginal gyrus (BA40), in the left inferior temporal gyrus (infTG), and in the posterior cingulate cortex (PCC) and precuneus.



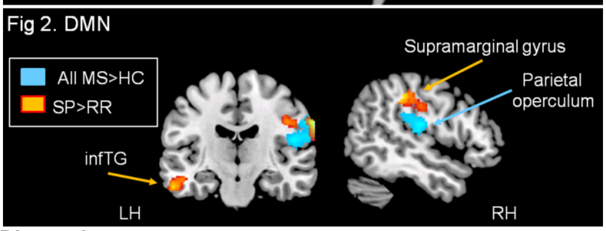


Figure 1. Within the sensory-motor network, all MS patients, compared against healthy controls (HC), showed increased functional brain connectivity (regions in blue) within the pre- and post-central gyrus (somatosensory areas; Talairach coordinates: x, y, z = 40, -8, 52 Z=3.52), the supramarginal gyrus (BA40; x, y, z = 68, -36, 34 Z=3.38), and the anterior cingulate cortex (ACC; x, y, z = 8, 10, 42 Z=3.64). Also, increased FC was observed in the ACC (x y, z = 8, 10, 42 Z=3.64) when contrasting RR- against SPMS patients (regions in violet). The opposite contrast did not reveal any significant difference.

Figure 2. When considering the DMN, again all patients showed an increase in FC in the parietal operculum (x, y, z = 52, -18, 18 Z=3.28), extending to the post-central gyrus (x, y, z = 32, -14, 22 Z=3.19), compared to HC (regions in blue). Between MS groups comparison revealed increased FC in SPMS patients (regions in orange) in the supramarginal gyrus (BA40; x, y, z = 68, -16, 32 Z=3.58), in the left inferior temporal gyrus (infTG; x, y, z = -58, -18, -24 Z=2.97) and (not shown in the figure) in the posterior cingulate cortex /precuneus.

Discussion:

Our study provides evidence for an abnormal increase of patients' FC in the sensory-motor component and in the DMN, which represent two critical networks for the understanding of MS disabilities. Overall, in both networks, the increase of patients' FC might reflect the recruitment of additional brain areas, to compensate for the accumulation of structural brain damage (functional reorganization hypothesis). In the RRMS patients, who are on average less cognitively impaired than SPMS patients, we found a predominant increase of FC within the sensory-motor network. This might represent a compensation mechanism for motor disabilities that, in most cases, precede the occurrence of cognitive decline. Conversely, SPMS patients showed a less remarkable increase in sensory-motor FC than RRMS. This might represent a reduced capability of these patients in brain reorganization, which might account for their more severe motor disability. Similarly, the DMN revealed a more remarkable (compensatory) pattern of FC in SPMS patients. This might represent a contrast mechanism against cognitive decline, which is more frequently observed in progressive MS.

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