

FUNCTIONAL CORRELATES OF IMPAIRED WORKING MEMORY IN MS PATIENTS: A MULTICENTRE STUDY

Paola Valsasina¹, Maria A. Rocca¹, Alvino Biscecco¹, Khaled Abdel-Aziz², Frederik Barkhof³, Christian Enzinger⁴, Franz Fazekas⁵, Antonio Gallo⁶, Hanneke Hulst³, Xavier Montalban⁷, Nils Muhlert², Gianna C Riccitelli¹, Alex Rovira⁸, Gioacchino Tedeschi⁶, Giancarlo Comi⁹, and Massimo Filippi¹

¹Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, MI, Italy, ²Dept. Brain Repair and Rehabilitation, Institute of Neurology, UCL, London, GB, United Kingdom, ³Department of Radiology, Free University Medical Centre, Amsterdam, NL, Netherlands, ⁴Division of Neuroradiology, Medical University of Graz, Graz, AT, Austria, ⁵Department of Neurology, Medical University of Graz, Graz, AT, Austria, ⁶Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Naples, NA, Italy, ⁷Department of Neurology-Neuroimmunology, Vall d'Hebron University Hospital, Barcelona, CT, Spain, ⁸Department of Radiology, Vall d'Hebron University Hospital, Barcelona, CT, Spain, ⁹Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, MI, Italy

Target Audience. Neurologists and Neuroradiologists.

Purpose. In this multicentre study, we assessed the fMRI correlates of frontal lobe dysfunction in multiple sclerosis (MS) patients with and without cognitive impairment to prove the validity of this technique for treatment monitoring in the context of clinical trials.

Methods. This study was conducted at six European sites using 3.0 Tesla scanners. fMRI scans during a N-back task were acquired from 42 right-handed relapsing remitting (RR) MS patients and 52 sex-matched right-handed healthy controls (HC). MS patients underwent the Rao battery and the Wisconsin Card Sorting test. Patients with at least two abnormal tests were considered as cognitively impaired (CI).¹ fMRI data were analysed modelling regions showing a load-dependent activation/deactivation with increasing task difficulty. fMRI activity was compared between HC and all MS, as well as between HC, cognitively preserved (CP) and CI patients. Correlations of fMRI activity with clinical, neuropsychological and conventional MRI variables were also assessed.

Results. Twenty-two MS patients were cognitively preserved (CP) and 20 (47%) were CI. Task-related activations/deactivations were found in similar regions for HC and MS (Figure 1). Compared to HC, MS showed a reduction of fMRI activity with increasing task difficulty in the bilateral parietal, left inferior frontal and left middle frontal regions. While CP showed fMRI patterns similar to those detected in HC, CI patients had a distributed reduced fMRI activity (in bilateral parietal and frontal regions, and in the bilateral insula) and fMRI deactivations (in the bilateral precuneus, posterior cingulate cortex and parahippocampal gyrus) compared to HC and CP patients (Figure 2). A failure of activation of frontal regions was correlated with a longer disease duration, higher T2/T1-lesion volumes, lower Z-score of global cognitive, attention-executive and visual functions.

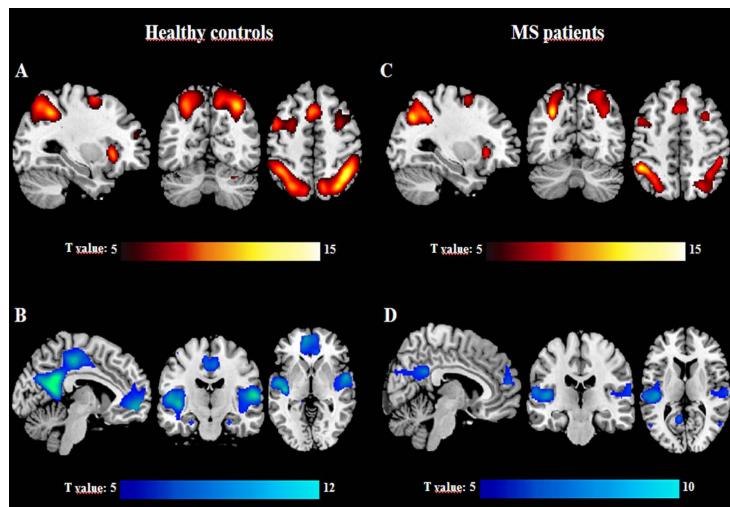


Figure 1. Brain regions linearly increasing (or decreasing) fMRI activity with increasing n-back task difficulty in HC (left) and MS patients (right) (one-sample t tests, $p<0.05$ family-wise error corrected for multiple comparisons). (A, C) “load” activation; (B, D) “load” deactivation.

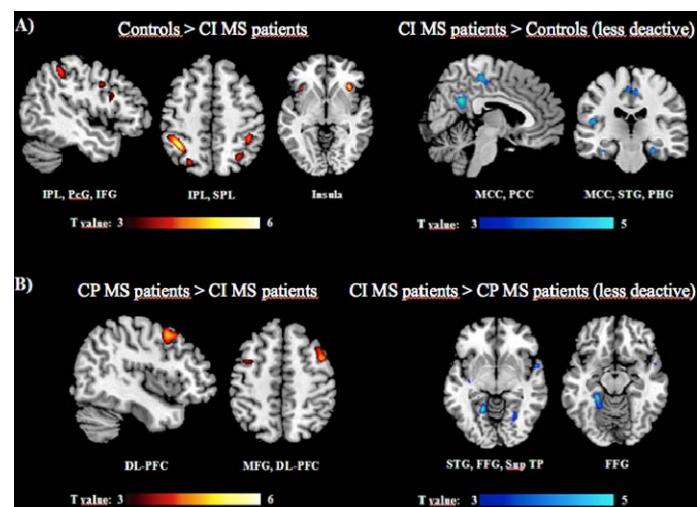


Figure 2. Brain regions with significantly different fMRI activations/deactivations with increasing n-back task difficulty in CI MS patients vs the other study groups. A) CI MS patients vs HC; B) CI vs CP MS patients.

Discussion and Conclusion. This multi-centre study, conducted on a homogenous MRI and cognitive dataset, shows that integrity of frontal lobe activity is associated with a better cognitive profile in MS patients and contributes to validate the use of fMRI in treatment trials.

References.

1. Boring JB, Lazeron RH, Reuling IE et al. The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. *Mult Scler* 2001;7(4):263-267.