CHARACTERIZING FUNCTIONAL AND STRUCTURAL IMAGING FEATURES OF COGNITIVE PHENOTYPES IN MULTIPLE SCLEROSIS

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INTRODUCTION AND AIMS

Cognitive impairment (CI) affects 40 to 70% of multiple sclerosis (MS) patients and is a significant contributor to socioeconomic burden and reduced quality of life [1]. CI can be seen even in early MS cases and is more severe in progressive than relapsing forms [2]. Functional reorganization and brain plasticity play an important role in preserving cognition in MS, especially in the earlier phases [3]. Till recently, patient were merely divided into cognitively impaired or preserved, resulting in heterogenous patient groups for assessment. Recently, a data-driven classification into distinct cognitive phenotypes was proposed [4]. To date, a comprehensive characterization of structural and functional MRI features of cognitive phenotypes was never performed.

Purpose

This study aims at identifying distinct cognitive phenotypes in a large cohort of MS patients and characterize their clinical, structural MRI and resting state (RS) functional connectivity (FC) features.

METHODS

Subjects. Three hundred and ninety (390) right-handed MS patients and 168 age-and sex-matched healthy controls (HC).

Neurological evaluation. Disease duration, Expanded Disability Status Scale (EDSS) and clinical phenotypes: relapsing-remitting (RR) or progressive [secondary (SP), primary (PP)].

Neuropsychological evaluation. Rao Brief Repeatable Battery of Neuropsychological tests (BRB-N; score below 1.5 SD on at least two tests assessing a minimum of two different cognitive domains were classified as cognitively impaired); Modified Fatigue Impact Scale (MFIS; score ≥ 37 indicating fatigue) and Montgomery-Åsberg Depression Scale (MADRS; score ≥ 9 defined the presence of depressive symptoms).

Brain MRI acquisition (two 3.0 T scanners).

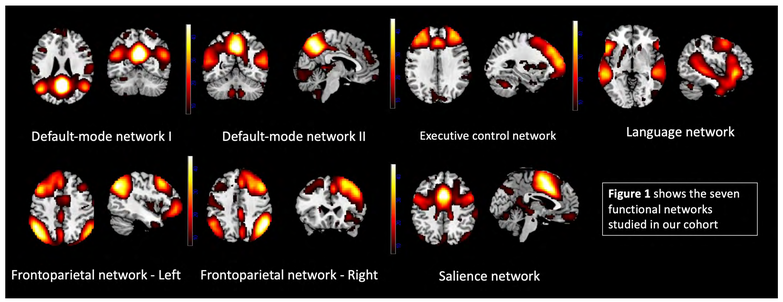
- Dual-echo (DE) turbo spin echo sequence [Scanner I] or fluid-attenuated inversion recovery (FLAIR) [Scanner II]: quantification of T2 hyperintense white matter (WM) lesions.
- Sagittal 3D T1-weighted sequence: quantification of normalized brain, gray matter (GM), WM, and subcortical (including thalamic, hippocampal and other deep GM) volumes on lesion-filled images *[FSL SIENAx, FSL-FIRST]*.
- T2*-weighted echo planar imaging (EPI) sequence for RS functional MRI (fMRI).

fMRI processing. The CONN toolbox was utilized to process RS fMRI data.

Independent Compenent Analysis (ICA). RS FC was assessed using ICA and the GIFT software. We identified 7 cognitive functional networks: two default-mode networks (DMN I and DMN II), one executive control (ECN), one fronto-parietal (FP) network lateralized to the left hemisphere and one lateralized to the right hemisphere, one language network and one salience network (**Figure 1**). Identified networks were ComBat-harmonized across scanners and an average Z-score of RS FC for each network was calculated.

Statistical analysis. Latent Profile Analysis (LPA) performed on cognitive Z-scores identified MS cognitive phenotypes [4]. The demographic and clinical differences between cognitive phenotypes were compared by one-way ANOVA, Kruskal-Wallis test, $\chi 2$-test or Fisher's exact test. Linear regression modelling compared structural MRI and RS FC Z-scores among cognitive phenotypes.

RESULTS



❖116 MS patients (29.7 %) were classified as cognitively impaired with attention/information processing speed being the most frequently affected domain (38.9 %).

❖LPA identified four cognitive phenotypes: ***preserved cognition*** (PC) (n=67 [18.2%]), ***mild single domain-verbal fluency*** (MSD-VF) (n=37 [10.0%]), ***mild single domain-attention*** (MSD-A) (n=197 [53.4%]), and ***severe-multidomain*** (SMD) (n=68 [18.4%]).

Table 1 summarizes the main demographic and clinical characteristics of cognitive phenotypes

Characteristics	PC	MSD - VF	MSD - A	SMD	P value*	Significant post-hoc differences#
Age (y), mean (SD)	41.2 (9.7)	38.9 (10.3)	44.4 (11.7)	46.3 (11.8)	0.003	d, e
Gender, n (%) : Female	45 (67.2)	21 (56.8)	116 (58.9)	37 (54.4)	0.475	-
Male	22 (32.8)	16 (43.2)	81 (41.1)	31 (45.6)		
Education (y), median (IQR)	13.0 (13.0; 17.0)	13.0 (13.0; 16.0)	13.0 (10.0; 17.0)	13.0 (10.3; 13.0)	0.009	c
Disease duration (y), median (IQR)	9.2 (2.4; 16.2)	5.9 (1.7; 17.9)	13.0 (3.8; 20.3)	16.4 (6.9; 22.3)	0.002	c, e
Disease course, n (%)						
- RRMS	57 (85.1)	32 (86.5)	129 (65.5)	29 (42.6)	<0.001	c, e
- SPMS	6 (9.0)	4 (10.8)	51 (25.9)	24 (35.3)		
- PPMS	4 (6.0)	1 (2.7)	17 (8.6)	15 (22.1)		
EDSS score, median (IQR)	1.5 (1.0; 3.0)	1.5 (1.0; 3.3)	2.0 (1.5; 4.8)	5.0 (2.5; 6.0)	<0.001	b, c, e, f
MFIS score, median (IQR)	21.0 (10.0; 35.0)	26.0 (10.0; 36.0)	32.0 (20.0; 46.0)	32.0 (20.3; 46.8)	0.001	b, c
MADRS score, median (IQR)	5.0 (1.3; 10.8)	7.0 (3.3; 10.8)	8.0 (4.0; 13.0)	10.0 (5.0; 15.5)	0.011	c

*Significant at p<0.05 (ANOVA, Kruskal Wallis test, Chi square test or Fisher's exact test, where applicable)
#Letters indicate significant post-hoc differences ($p < .05$; corrected for multiple comparisons by Bonferroni method) as follows: *a* = between PC and MSD-VF; *b* = between PC and MSD-A; *c* = between PC and SMD; *d* = between MSD-VF and MSD-A; *e* = between MSD-VF and SMD; *f* = between MSD-A and SMD.

❖ SMD had longer disease duration than PC **(p=0.01)** and MSD-VF patients **(p=0.006)**; they also presented more severe clinical disability compared to all other phenotypes and most (57.4%) had progressive MS.

❖ Patients with PC (*vs* HC) had lower volumes of subcortical structures. Compared to PC patients, SMD showed decreased cortical and subcortical volumes **(p<0.001 for all).**

❖ **PC patients had similar RS FC to HC, while MSD-VF patients presented with increased RS FC of the ECN (p=0.03) and language (p=0.02) network compared to SMD patients.** MSD-A patients tended to have higher language network RS FC compared to SMD (p=0.09). **Finally, SMD patients had significantly decreased DMN II RS FC compared to all remaining phenotypes (p=0.01 to 0.04) (Figure 2).**

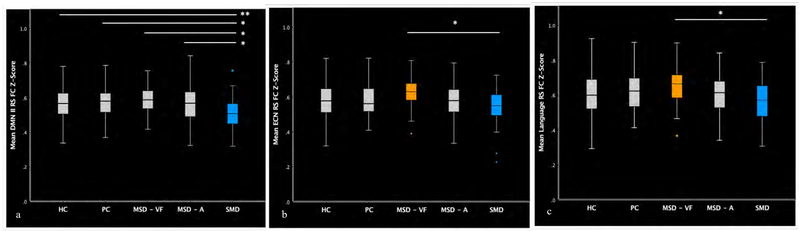


Figure 2: Significant RS FC changes among cognitive phenotypes within the [a] DMN II,; [b] ECN; and [c] Language network [* Significance at p < 0.05; ** Significant at p < 0.01]

❖ We observed a significant quadratic trend for **DMN II (p=0.005), ECN (p=0.005), and language (p<0.001)** networks with RS FC increasing from HC to PC to MSD–VF groups, thereafter, decreasing in MSD–A group to finally reach their lowest values in the SMD phenotype.

CONCLUSIONS

❖ LPA was able to classify MS patients into meaningful cognitive phenotypes going beyond a basic dichotomous classification, thus helping to strategize targeted interventions in a more accurate way.

❖ While PC patients exhibited normal RS FC, SMD patients presented widespread structural abnormalities and widespread DMN RS FC decrease.

❖ Patients with milder impairment tended to have increased RS FC in networks subserving the involved domains, possibly suggesting compensatory phenomena.

❖ Overall, we observed functional changes that likely represent a continuum from compensation in milder stages of MS to a complete breakdown in severe phases of the disease.

❖ As patients in the earlier stages of the disease manage to compensate for some of the cognitive deficits, enhancing brain plasticity may be a potential target of future therapy.

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Cognition refers to one's ability to process and retain information, ability to multitask, problem solving, memory and learning, and linguistic abilities, among others. Cognitive impairment is common in people with multiple sclerosis (40-70%). Functional magnetic resonance imaging (fMRI) is an imaging modality that measures brain connectivity by detecting changes in cerebral oxygenation. We used fMRI to characterize brain network connectivity at rest in patients with different cognitive profiles. This will help to select people with MS who are likely to benefit from early cognitive rehabilitative strategies.

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