ABNORMAL FUNCTIONAL CONNECTIVITY OF THALAMIC SUB-REGIONS CONTRIBUTES TO FATIGUE IN MS

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INTRODUCTION and PURPOSE

Fatigue is a subjective lack of physical and/or mental energy that interferes with daily-life activities [1]. By applying advanced MRI techniques, physical and cognitive fatigue in MS patients have been correlated to thalamic structural changes [2-4] and functional connectivity (FC) fMRI abnormalities [5-8]. Despite the relevance of the thalamus in MS, only limited data on whole and sub-regional thalamic FC [9-10] abnormalities are available.

The aim of this study was to investigate sub-regional thalamic resting state (RS) FC abnormalities in MS patients, and their correlation with the severity of cognitive, physical, and psychosocial domains of fatigue.

METHODS

MRI acquisition and analysis: Using a 3.0T scanner, axial DE TSE, sagittal 3D T_1-weighted FFE, pulsed-gradient SE EPI, and T_2*-weighted EPI sequences were acquired from **122 MS** patients and **94** sex and age-matched healthy controls (**HC**). Brain T_2-hyperintense and T_1-hypointense lesion volumes were measured (*Jim 6*). After T_1-hypointense lesion refilling, normalized brain, gray matter, WM, and thalamic volumes, were calculated (*FIRST*, *SIENAx*).

Neurological and neuropsychological evaluation: In MS patients, EDSS score [11], Rao's Brief Repeatable Battery of Neuropsychological Tests [12], Modified Fatigue Impact Scale (MFIS), and MFIS subscales [13] were assessed. Patients with MFIS scores >38 were classified as Fatigued (F). Cognitive impaired patients were excluded from the analysis.

Thalamic segmentation: The thalamus was segmented into frontal, motor, postcentral, occipital and temporal sub-regions, using the 3D T_1-weighted images (*FIRST* tool, *FMRIB*) [14], and performing a structural-parcellation derived from probabilistic tractography between thalamic voxels and five cortical regions (*Probtractx* tool, *FSL*) [15]. The obtained thalamic sub-regions were used to perform a seed-based RS fMRI analysis (*SPM12*).

Statistical analysis: Between-group comparisons of demographical, clinical and conventional MRI variables were performed (*SPSS*). Using *SPM12* and thalamic RS FC maps, the following analyses ($p<0.001$, uncorrected) were performed: a) average RS FC in HC, F-MS and non-fatigued (nF) MS patients; b) comparison of RS FC between HC, F-MS and nF-MS patients; and c) correlation of thalamic RS FC with MFIS scores.

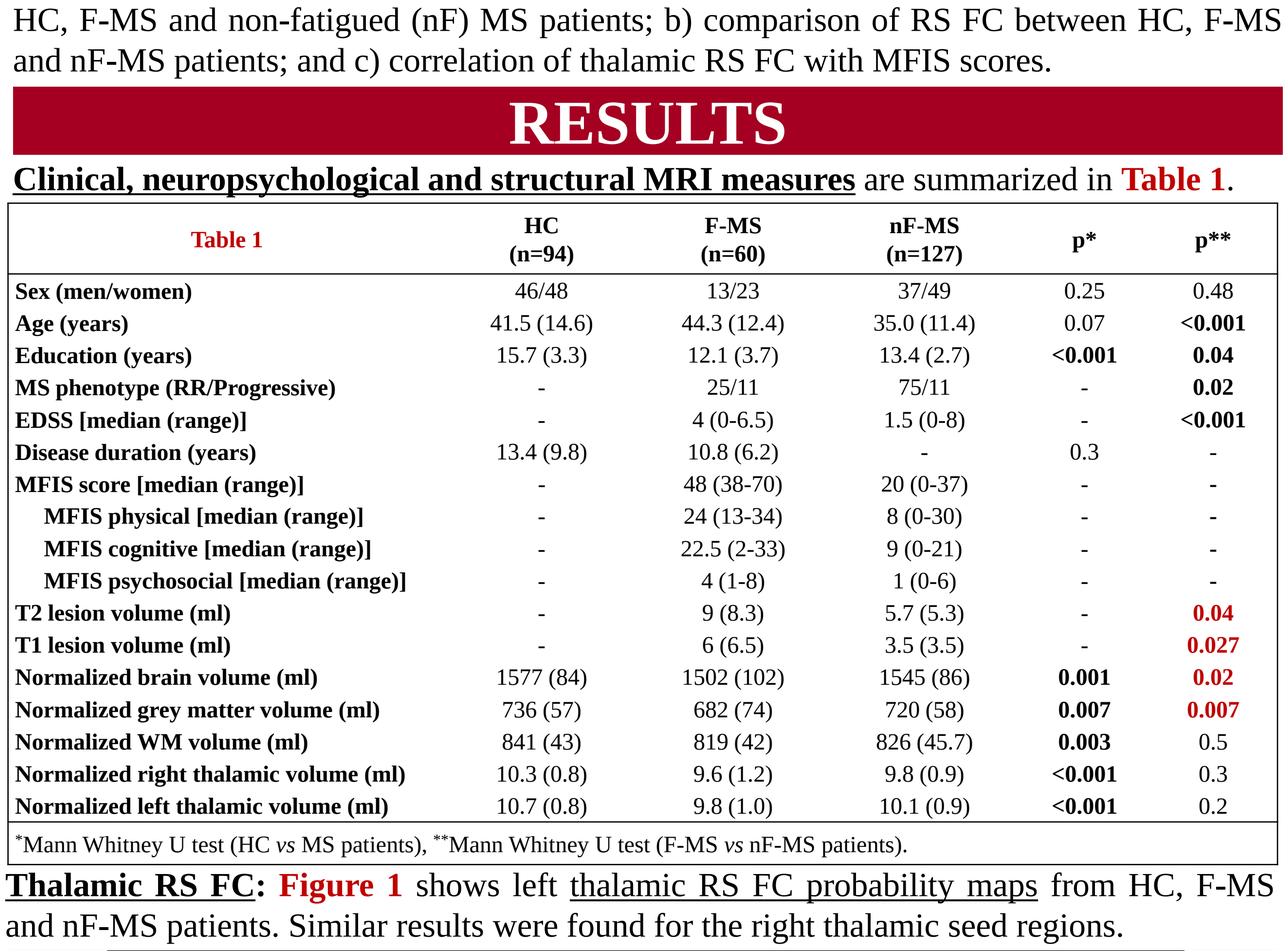
RESULTS

Clinical, neuropsychological and structural MRI measures are summarized in **Table 1**.

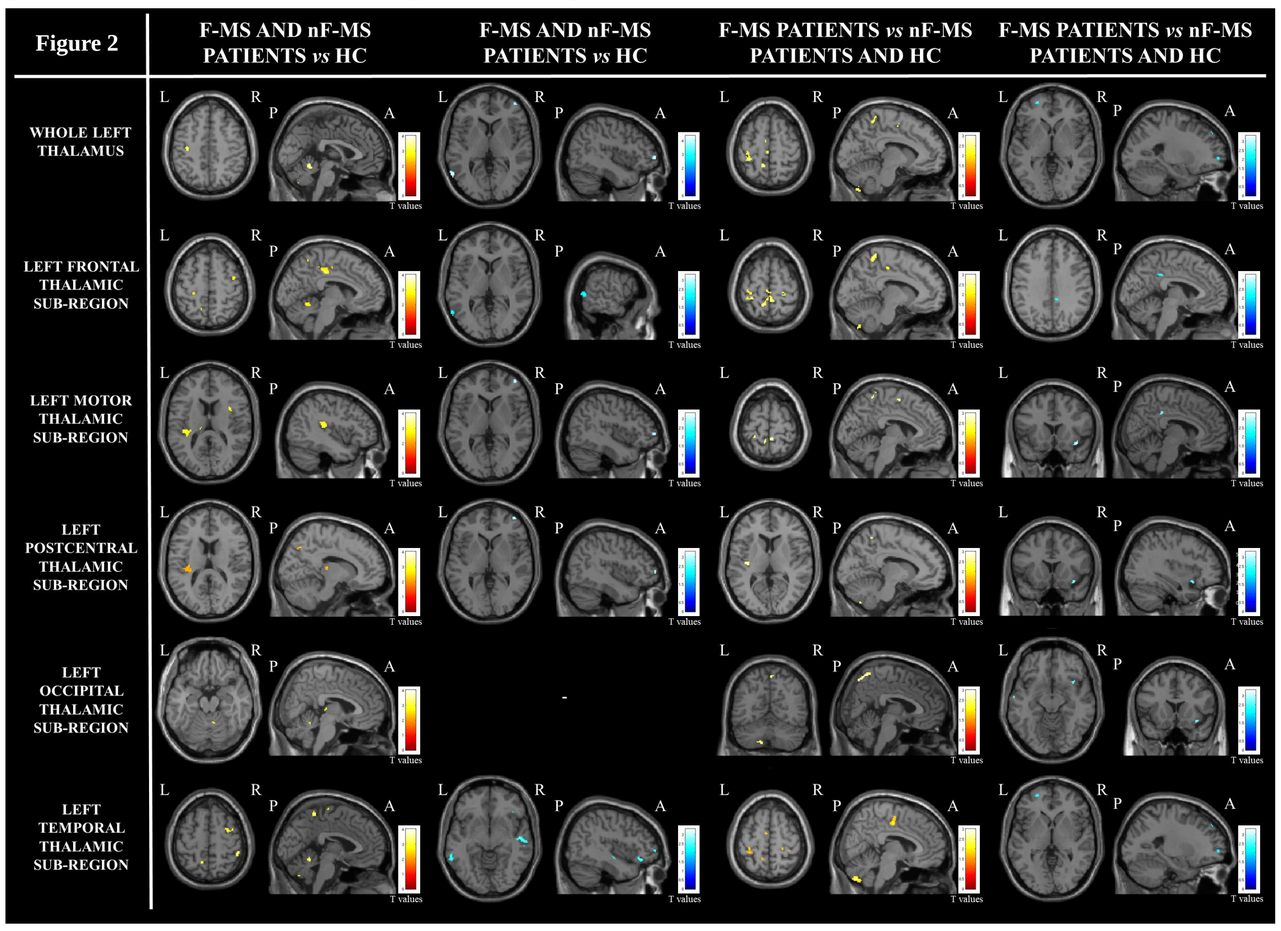
Table 1	HC (n=94)	F-MS (n=60)	nF-MS (n=127)	p*	p**
Sex (men/women)	46/48	13/23	37/49	0.25	0.48
Age (years)	41.5 (14.6)	44.3 (12.4)	35.0 (11.4)	0.07	**<0.001**
Education (years)	15.7 (3.3)	12.1 (3.7)	13.4 (2.7)	**<0.001**	**0.04**
MS phenotype (RR/Progressive)	-	25/11	75/11	-	**0.02**
EDSS [median (range)]	-	4 (0-6.5)	1.5 (0-8)	-	**<0.001**
Disease duration (years)	13.4 (9.8)	10.8 (6.2)	-	0.3	-
MFIS score [median (range)]	-	48 (38-70)	20 (0-37)	-	-
MFIS physical [median (range)]	-	24 (13-34)	8 (0-30)	-	-
MFIS cognitive [median (range)]	-	22.5 (2-33)	9 (0-21)	-	-
MFIS psychosocial [median (range)]	-	4 (1-8)	1 (0-6)	-	-
T2 lesion volume (ml)	-	9 (8.3)	5.7 (5.3)	-	**0.04**
T1 lesion volume (ml)	-	6 (6.5)	3.5 (3.5)	-	**0.027**
Normalized brain volume (ml)	1577 (84)	1502 (102)	1545 (86)	**0.001**	**0.02**
Normalized grey matter volume (ml)	736 (57)	682 (74)	720 (58)	**0.007**	**0.007**
Normalized WM volume (ml)	841 (43)	819 (42)	826 (45.7)	**0.003**	0.5
Normalized right thalamic volume (ml)	10.3 (0.8)	9.6 (1.2)	9.8 (0.9)	**<0.001**	0.3
Normalized left thalamic volume (ml)	10.7 (0.8)	9.8 (1.0)	10.1 (0.9)	**<0.001**	0.2

*Mann Whitney U test (HC *vs* MS patients), **Mann Whitney U test (F-MS *vs* nF-MS patients).

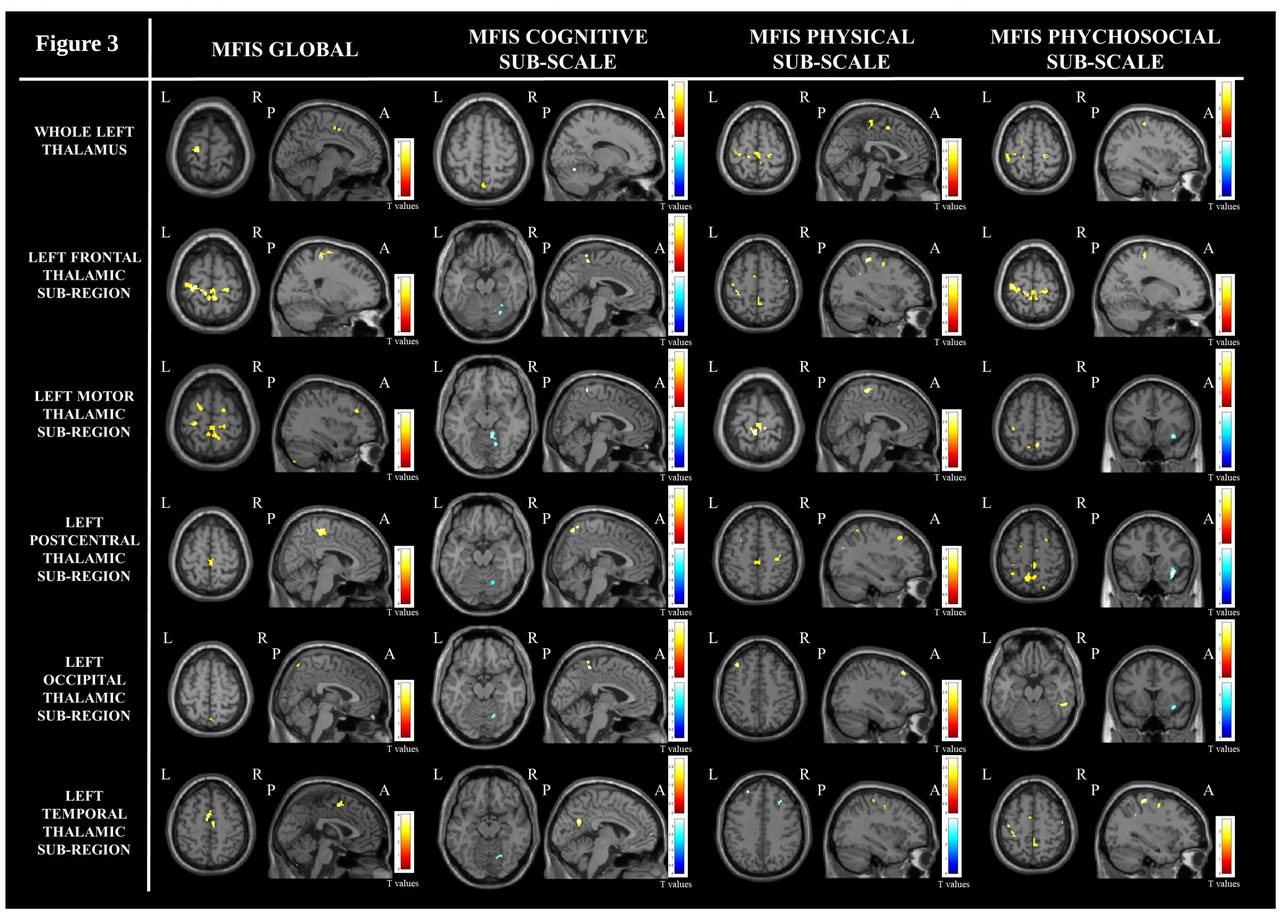
Thalamic RS FC: **Figure 1** shows left thalamic RS FC probability maps from HC, F-MS and nF-MS patients. Similar results were found for the right thalamic seed regions.



Brain regions with significant thalamic RS FC differences between HC, F-MS and nF-MS patients are summarized in **Figure 2** (red-yellow: increased RS FC, blue: decreased RS FC).



Correlations: No correlations were found between MFIS scores and structural MRI variables. Correlations between thalamic RS FC abnormalities and MFIS global, cognitive, physical and psychosocial scores in MS patients are summarized in **Figure 3.**



CONCLUSIONS

Selecting fatigued MS patients without cognitive impairment, this study provides novel insights into the pathophysiology of fatigue in MS. Specifically, we found that:

- Regional thalamic RS FC behaved differently between the main thalamic sub-regions.
- Regional thalamic RS FC abnormalities with the middle frontal gyrus, sensorimotor network, precuneus, insula and posterior lobes of the cerebellum, play an important role in differentiating F-MS patients from nF-MS patients and HC.
- Regional thalamic RS FC abnormalities may contribute to explain the different components of fatigue in these patients, with the involvement of the precuneus and posterior lobe of the cerebellum in the pathogenesis of cognitive fatigue, the participation of the sensorimotor network in the genesis of physical and psychosocial fatigue, and abnormalities of the anterior insula further contributing to explain psychosocial fatigue.

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DISCLOSURES

Dr. Hidalgo de la Cruz, Dr. D'Ambrosio, Dr. Valsasina, Dr. Pagani, Dr. Colombo, Dr. Rodegher and Dr. Falini have nothing to declare. **Dr. Rocca** received speakers honoraria from Biogen Idec, Novartis and ExecMED and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. **Prof. Comi** has received compensation for consulting services and/or speaking activities from Novartis, Teva Pharmaceutical Ind., Sanofi-Aventis Pharmaceuticals, Genzyme, Merck Serono, Biogen-Dompè, BayerShering, Actelion, Serono Symposia International Foundation, Almirall, Chugai and Receptos. **Prof. Filippi** serves on scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and GloriaGossweiler Foundation (Switzerland), and ARiSLA.

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