THALAMIC FUNCTIONAL CONNECTIVITY IN MULTIPLE SCLEROSIS: THE ROLE OF TEMPORAL THALAMIC SUB-REGION IN MALADAPTATION

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INTRODUCTION and PURPOSE

In spite of the well-known importance of the thalamus in MS, only limited data on whole and sub-regional thalamic functional connectivity (FC) are available.

Aim of this study was to investigate sub-regional thalamic resting state (RS) FC in MS patients and to correlate RS FC abnormalities with clinical/cognitive measures.

METHODS

Diffusion tensor (DT), 3D-T1 weighted and RS functional MRI data were acquired from 200 right-handed MS patients and 100 age- and sex-matched healthy controls (HC) **(Table1)**.

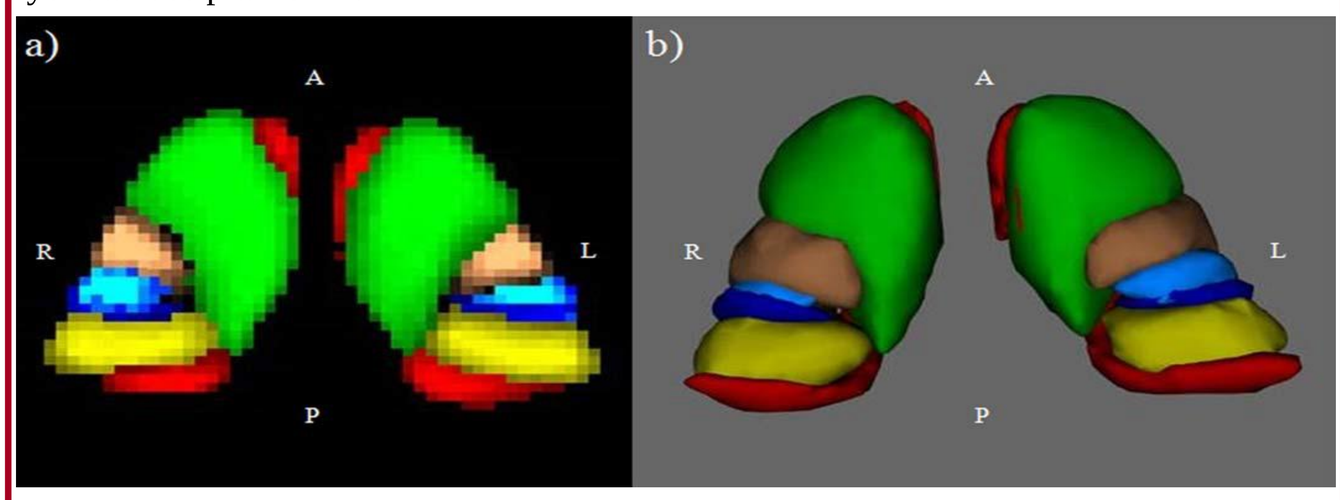
Table 1. Main demographic and clinical measures from all subjects.

Variable	HC	MS	RRMS	SPMS	PPMS	p value[a]
n	100	200	145	46	9	-
Mean age (SD), years	41.3 (14.5)	40.7 (12.6)	37.2 (11.6)	49.2 (9.7)	53.7 (12.2)	0.8
Females / Males	51/49	107/93	76/69	25/21	6/3	0.6
Median disease duration, years (range)	-	12 (0-44)	10.1 (0-36)	17.5 (3-44)	12.2 (7-27)	-
Median EDSS (range)	-	2.0 (0-8.0)	1.5 (0-6.0)	6.0 (3.5-8.0)	6.5 (3.5-7.5)	-

Abbreviations: RR=Relapsing-Remitting; SP=Secondary Progressive; PP= Primary Progressive; SD=Standard Deviation; EDSS= Expanded Disability Stasus Scale.
p-value[a] = Mann-Whitney test for the comparison between HC *vs* MS patients (as a whole).

In MS patients, a clinical and cognitive assessment was performed. DTI data were used to parcellate the thalamus into five sub-regions, according to their structural connectivity profile (frontal, motor, post-central, occipital and temporal regions) (**Figure 1**).

Figure1. Thalamic connectivity defined regions (CDRs) probability maps from HCs, thresholded at 33%, in Montreal Neurological Institute space:
(a) axial 2D view; (b) ventral 3D view.
Green=frontal CDR, copper=motor CDR, blue=postcentral CDR, red=temporal CDR, yellow=occipital CDR.



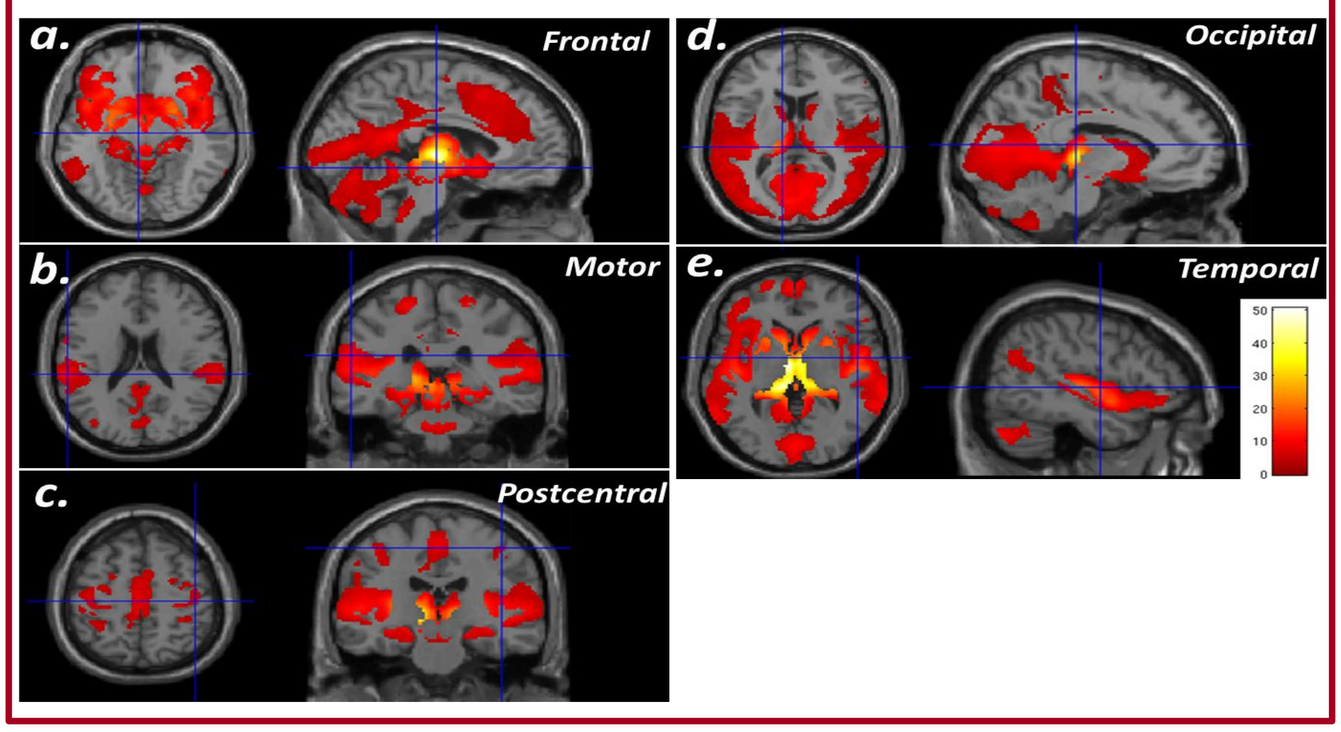
Abbreviations: L=left; R=right; A=anterior; P=posterior (adapted from Bisecco et al. 2015).

For each sub-region, a seed based RS FC analysis was performed. Multiple regression models were run to assess correlations between thalamic RS FC and clinical/cognitive variables.

RESULTS

Both in MS patients and HC, each thalamic sub-region RS FC map resembled structural connections with cortical areas **(Figure 2)**.

Figure 2. RS FC maps of seed based analysis in HC from: (a) frontal, (b) motor, (c) postcentral, (d) occipital and (e) temporal thalamic sub-regions.



Compared to HC, MS patients had an higher intra- and inter-thalamic RS FC in almost all thalamic sub-regions (**Figure 3a**).

The temporal thalamic sub-region showed reduced intra- and inter-thalamic RS FC and higher RS FC with frontal and hippocampal areas (**Figure 3b**).

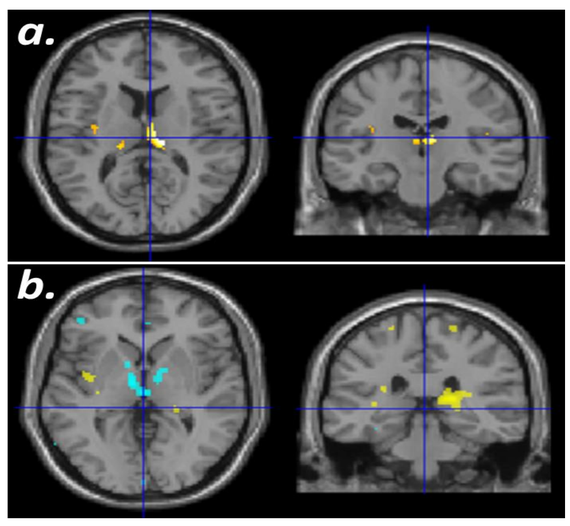
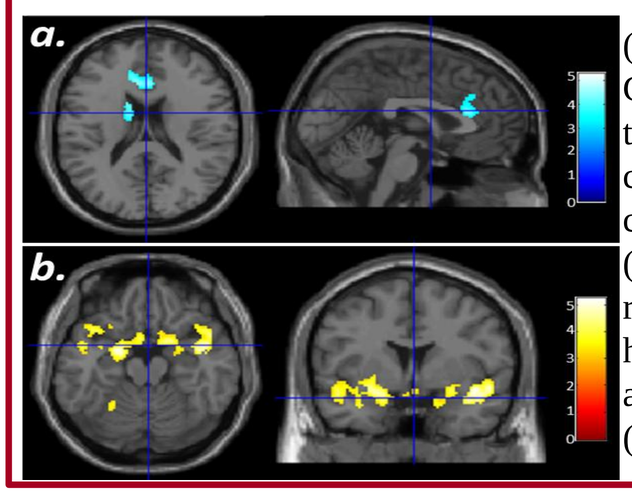


Figure 3. Sub-regional thalamic RS FC in MS patients compared to HC.
(a) The frontal-thalamic sub-region of MS patients showed, as the majority of thalamic sub-regions, higher intra and inter thalamic RS FC (yellow).
(b) The temporal-thalamic sub-region of MS patients showed lower intra-thalamic RS FC (cyan) and higher RS FC with frontal and hippocampal areas (yellow).

Compared to cognitively preserved (CP), cognitively impaired (CI) MS patients had lower RS FC between thalamic sub-regions and the caudate nucleus, anterior cingulate cortex and supplementary motor area, as well as higher RS FC between the thalamic temporal sub-region *vs* inferior frontal areas and the para-hippocampal gyrus (**Figure 4**).

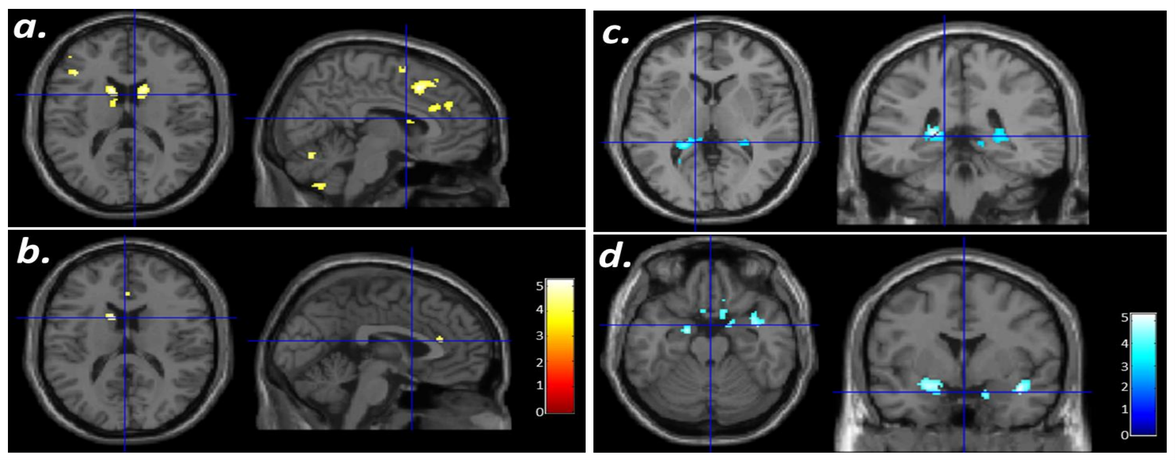
Figure 4. Sub-regional thalamic RS FC in CI compared to CP MS patients.



(a) The frontal-thalamic sub-region of CI MS patients showed, as almost all thalamic sub-regions, lower FC with caudate nucleus and anterior cingulate cortex (cyan).
(b.) The temporal-thalamic sub-region of CI MS patients showed higher FC with inferior frontal areas and para-hippocampal gyrus (yellow).

Higher RS FC of thalamic temporal sub-region was correlated with poor motor and cognitive performance, whereas higher RS FC between thalamic sub-regions and caudate and cingulate cortex correlated with better motor and cognitive performance (**Figure 5**).

Figure 5. Correlation analysis between thalamic sub-regional RS FC and clinical/cognitive variables.
(a) Higher RS FC between frontal thalamic sub-region and caudate nuclei, anterior cingulate cortex (yellow) is related to better performance at 9-HPT and (b) global cognitive score. (c) Higher RS FC between temporal thalamic sub-region and para-hippocampal gyrus, inferior frontal areas (cyan) is related with worse performance at 9-HPT and (d) global cognitive score.



CONCLUSIONS

In MS patients, the different behaviour of temporal thalamic sub-region, compared to other thalamic sub-regions, could contribute to explain the high variability of thalamic RS FC findings in previous studies.

The increased RS FC between temporal thalamic sub-region and temporal/frontal regions seen in MS patients compared to HC, as well as in cognitively impaired compared to preserved MS patients is likely to be a maladaptive mechanism, associated with more severe clinical/cognitive impairment.

DISCLOSURES

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