



Patterns of regional changes in thalamic shape and volume are related to performance in specific cognitive domains in MS

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Disclosures

- Rocco Capuano, Renato Docimo, Alessandro d'Ambrosio, Mario Cirillo, Giuseppina Caiazzo, Francesca Trojsi, Antonio Russo have no disclosures.
- Alvino Biseco has received speakers honoraria and/or compensation for consulting service from Biogen, Merck and Genzyme.
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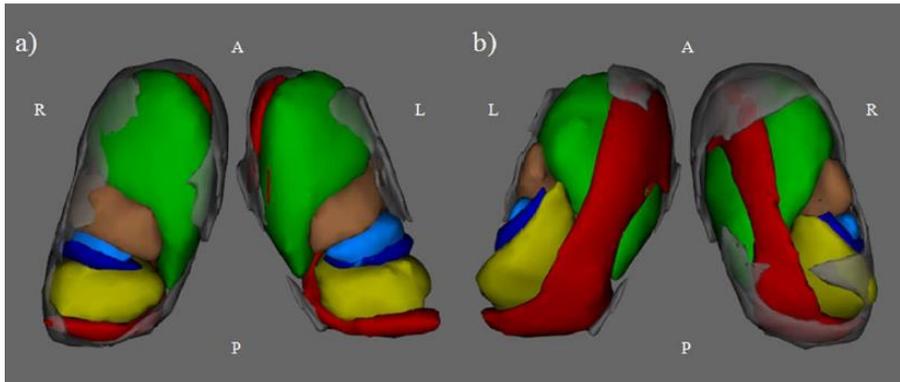
Background(I)

- Cognitive impairment (CI) is a common and disabling symptom in multiple sclerosis (MS) (Langdon DW et al. 2011; Chiaravalloti ND et al. 2008)
- Several MRI studies have shown that thalamus, among other gray matter (GM) structures, is one of the most relevant for cognitive performance in MS (Batista S et al. 2012; Benedict RH et al. 2006; Bisecco A et al. 2018)

Background(II)

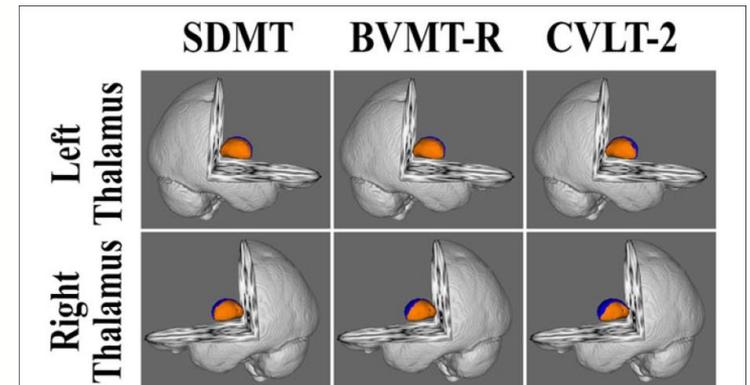
- A relationship between CI and more pronounced focal atrophy of the anterior thalamic regions has been previously described

CI vs CP MS patients



Biseco A et al. 2015

Correlations



Bergsland N et al. 2016

Objectives

To assess the relationship between thalamic regional volumes/shape and performance in global and all specific cognitive functions most involved in MS

Methods

Subjects

118 RRMS patients

41/77 men/women
mean age= 36.7 years

52 HC

19/33 men/women;
mean age= 37.3 years

Clinical Evaluation

- Expanded Disability Status Scale (**EDSS**)
- Italian version of the Rao's Brief Repeatable Battery (**BRB**) + Stroop Test (**ST**)
- **Z-scores** of cognitive function were calculated for Attention/information processing speed (A-PS); Verbal memory; Visual memory; Verbal fluency; Executive function; Global function

Methods

MRI protocol



3T MRI protocol including structural **DP/T2**, **3D-T1** sequences (on GE scanner)

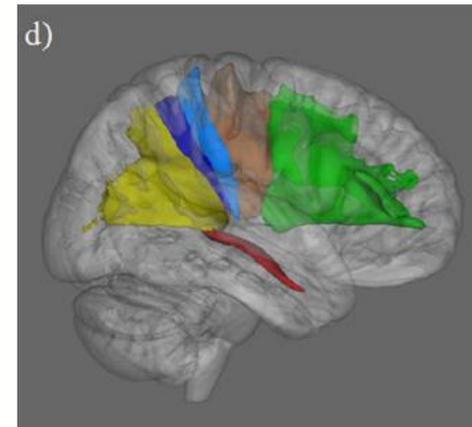
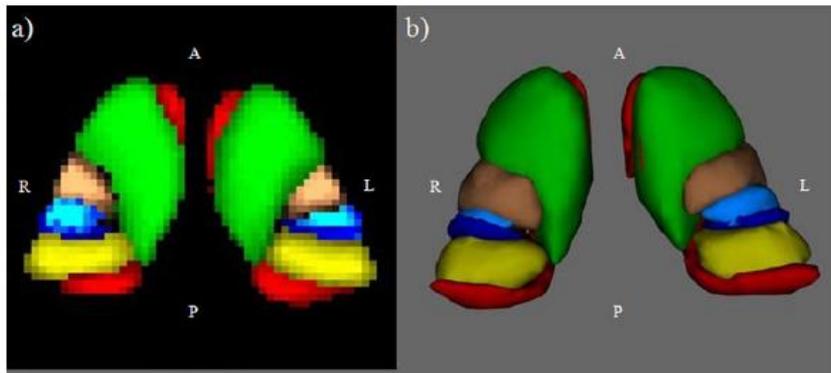
MRI analysis

- Measurements of T2 hyperintense lesion volume (**T2 LV**) → **MIPAV software** (Medical Image Processing, Analysis and Visualization; version 4.2.2; <http://mipav.cit.nih.gov>).
- Quantification of normalized brain (**NBV**), WM (**NWMV**), GM (**NGMV**, **NPGMV**) volumes → **SIENAx**, after lesion refilling of T1 hypointense lesions (Smith et al. 2002; Battaglini M et al. 2012).
- Thalamic segmentation → **FIRST tool from the FMRIB Software Library** (Patenaude B et al. 2011).
- To assess group differences (HC vs MS) of thalamic shape/volume and correlation with cognitive variables (in MS group) → **Vertex analysis** (Patenaude B et al. 2011).

Methods

MRI analysys

Thalamic subregions showing significant changes at the Vertex analysis were labeled using a previously derived **connectivity-defined atlas** that includes probability maps of thalamic parcellation in frontal, motor, postcentral, posterior parietal, occipital, and temporal connectivity defined regions (Bisecco A et al. 2015)



Methods

Statistical analysis

SPSS Statistics version 2.0

- Demographic, clinical, neuropsychological and MRI conventional measures: **t-test, Mann-Whitney test and chi-square test**, as appropriate
- Correlations between global/specific cognitive functions and demographic, clinical and conventional MRI variables were assessed using the **Spearman Rank Correlation Coefficient**
- All the analysis were adjusted for age and gender
- A $p < 0.05$ was considered statistically significant, after correction for multiple comparison (**Bonferroni**)

Results

Main demographic, clinical and conventional MRI characteristics of RRMS and HC

	HC (52)	MS patients (118)	p
Disease duration [m] – mean, median (SD; range)	-	116.4, 85.5 (105.8; 3/528)	-
Education [y] – mean, median (SD; range)	13.56, 13.00 (3.45; 5/18)	12.9, 13.00 (3.6; 5-26)	n.s.*
EDSS – median (range)	-	2.4, 2 (1.47; 0/6)	-
Attention/Executive functions [z-score] – mean, median (SD; range)	-0.37, 0.001 (0.86; -2/1)	-1.05, -1 (1.00; -4/1)	0.001*
Global memory [z-score] – mean, median (SD; range)	-0.35, 0.001 (0.623; -2/1)	-0.81, -1 (0.73; -2/1)	0.001*
Verbal memory [z-score] – mean, median (SD; range)	-0.04, 0.001 (0.77; -2/2)	-0.63, -1 (0.96; -3/1)	0.001*
Visual memory [z-score] – mean, median (SD; range)	-0.1, 0.001 (0.78; -1/1)	-0.42, 0.001 (0.96; -3/1)	n.s.*
Verbal fluency [z-score] – mean, median (SD; range)	-0.79, -1 (0.83; -2/1)	-1.25, -1 (0.89; -3/1)	0.03*
Global cognitive [z-score] – mean, median (SD; range)	-0.35, 0.001 (0.623; 0.001)	-0.81, -1 (0.73; -2/1)	0.002*
T2 LV – mean (SD)	-	8.2 (9.6)	-
NBV – mean (SD)	1529.2 (83.7)	1471.4 (88.8)	0.001+
NGMV – mean (SD)	840.3 (610.2)	808.7 (651)	0.04+
NWMV – mean (SD)	689 (41.3)	660.9 (380.2)	0.001+
NPGMV – mean (SD)	643.9 (48.9)	620.4 (48.4)	n.s.
Thalamus – mean (SD)	11 (1.2)	10.2 (1.1)	0.001+
Right thalamus – mean (SD)	10.8 (1.2)	10.1 (1.1)	0.001+
Left thalamus – mean (SD)	11.1 (1.2)	10.3 (1.1)	0.001+

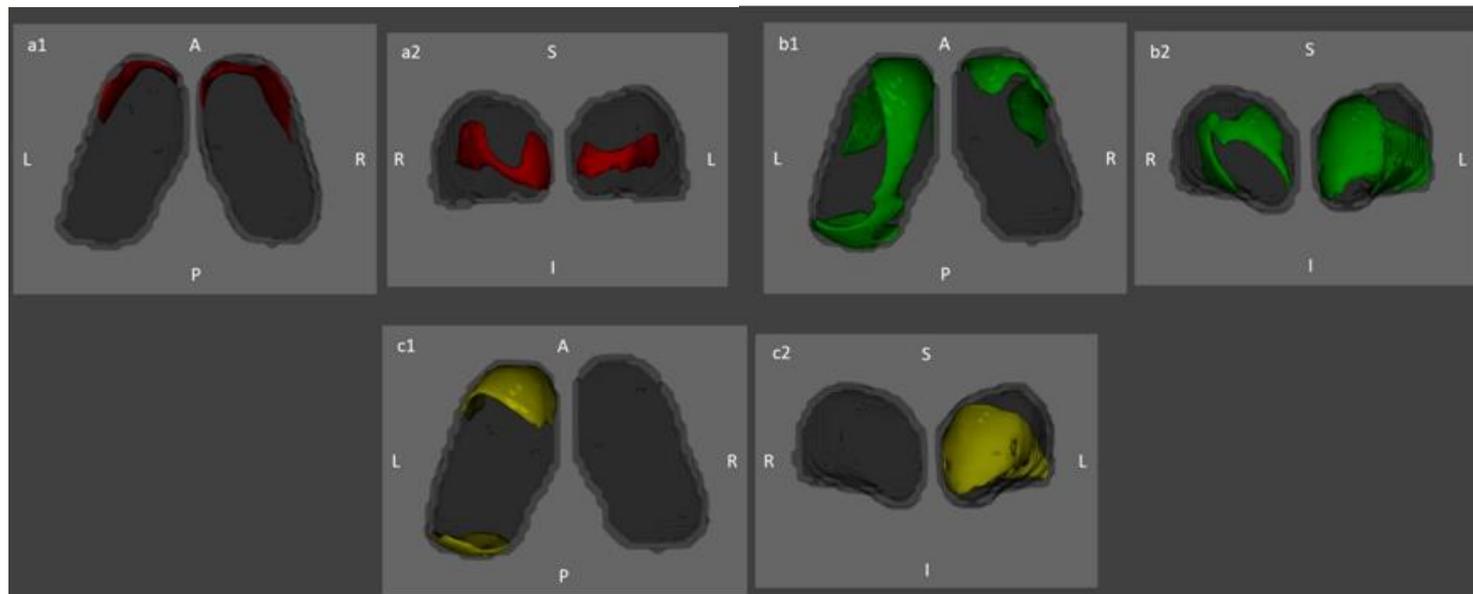
Results

Vertex Analysis

Comparison between HC and MS: MS patients showed a significant atrophy ($p < 0.01$) in all thalamic subregions, bilaterally.

Correlation between regional thalamic volume/shape and:

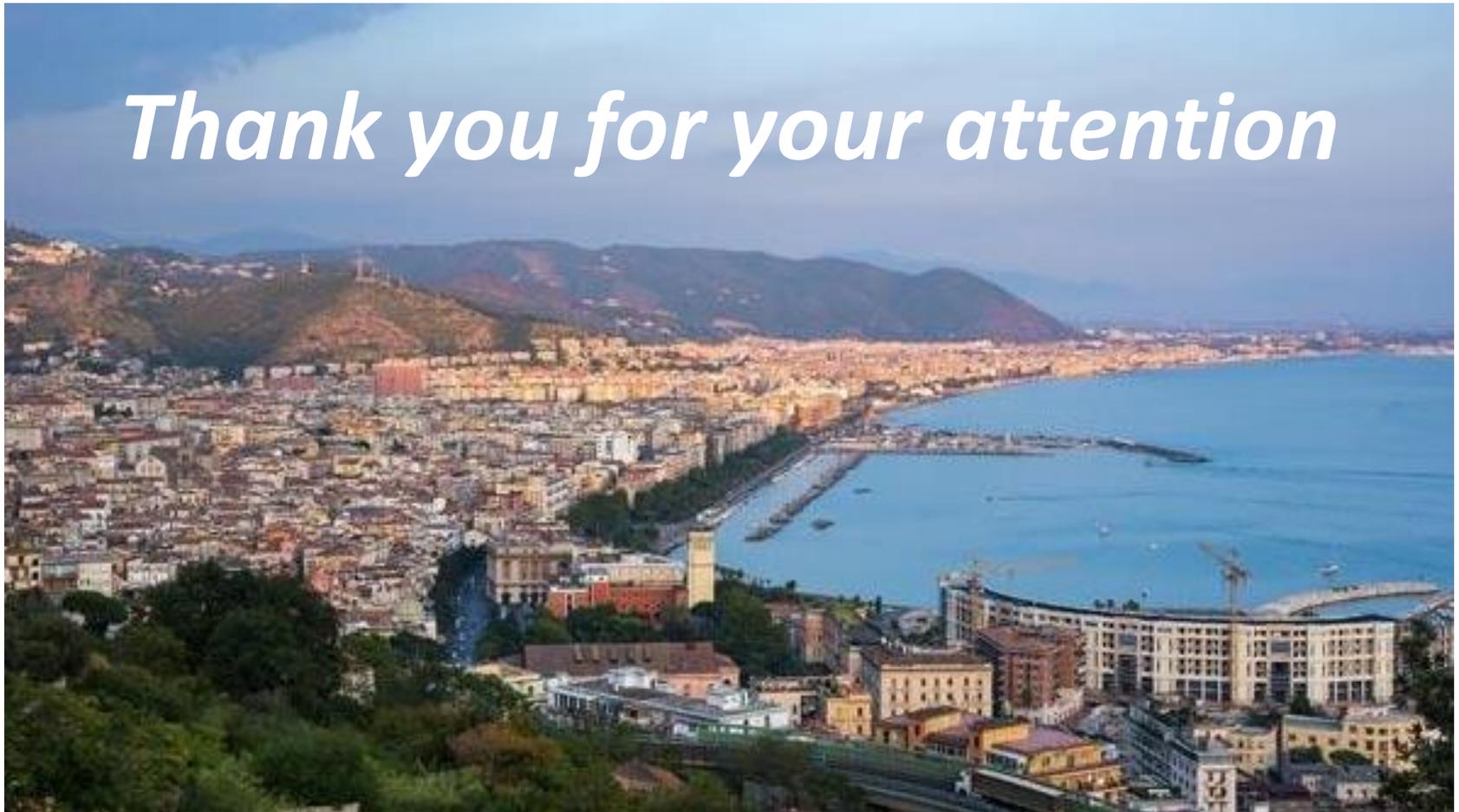
- A-PS \rightarrow atrophy of bilateral frontal-connected and right (R) motor-connected thalamic subregions ($p < 0.01$)
- Verbal fluency \rightarrow atrophy of the left (L) whole thalamus and R frontal/temporal-connected thalamic subregions ($p = 0.05$)
- Executive functions \rightarrow atrophy of all thalamus subregions, bilaterally ($p < 0.01$), (not shown)
- Global cognitive function \rightarrow atrophy of L frontal/temporal-connected subregions ($p < 0.01$)



Conclusion

- The results obtained in this study further confirm the relationship between cognitive impairment and global and regional thalamic atrophy in MS
- Atrophy of thalamic subregions is related to decline in specific cognitive functions in MS
- A-PS and verbal fluency dysfunctions in MS are most related to atrophy in specific thalamic subregions
- Executive dysfunction in MS is subtended by diffuse damage of the thalamus
- Global cognitive status is related mostly to left thalamic atrophy, localized in particular in frontal- and temporal-connected subregions

Thank you for your attention



Results

- **Correlations between global/specific cognitive performance and demographic, clinical and conventional MRI variables**
- A-PS: age ($r = -0,404$; $p = 0,002$), EDSS ($r = -0,390$; $p = 0,002$), T2 LL ($r = -0,317$; $p = 0,002$); thalamic volume ($r = 0,342$; $p = 0,002$), right thalamic volume ($r = 0,329$; $p = 0,002$), left thalamic volume ($r = 0,346$; $p = 0,002$), NGMW ($r = 0,374$, $p = 0,002$), NWMV($r = 0,29$; $p = 0,02$), NBV($r = 0,403$; $p = 0,002$), NPGMV ($r = 0,372$; $p = 0,002$)
- Verbal Memory: age ($r = -0,336$; $p = 0,002$)
- Visual Memory: age ($r = -0,326$; $p = 0,002$), EDSS ($r = -0,41$; $p = 0,002$), T2 LL ($r = -0,353$; $p = 0,002$); thalamic volume ($r = 0,312$; $p = 0,02$), right thalamic volume ($r = 0,308$; $p = 0,02$), left thalamic volume ($r = 0,301$; $p = 0,02$), NWMV($r = 0,28$; $p = 0,04$), NBV($r = 0,325$; $p = 0,002$), NPGMV ($r = 0,278$; $p = 0,04$)
- Verbal Fluency: education ($r = 0,321$; $p = 0,002$)
- Executive function: age ($r = -0,376$; $p = 0,002$), disease duration ($r = -0,311$, $p = 0,02$) EDSS ($r = -0,297$; $p = 0,02$), T2 LL ($r = -0,376$; $p = 0,002$); education ($r = 0,342$; $p = 0,002$), thalamic volume ($r = 0,337$; $p = 0,002$), right thalamic volume ($r = 0,316$; $p = 0,002$), left thalamic volume ($r = 0,348$; $p = 0,002$), NGMW ($r = 0,301$, $p = 0,02$), NBV($r = 0,315$; $p = 0,02$), NPGMV ($r = 0,333$; $p = 0,002$)
- Global cognitive function: age ($r = -0,378$; $p = 0,002$), EDSS ($r = -0,440$; $p = 0,002$), T2 LL ($r = -0,378$; $p = 0,002$); thalamic volumes ($r = 0,356$; $p = 0,002$), right thalamic volume ($r = 0,365$; $p = 0,002$), left thalamic volume ($r = 0,344$; $p = 0,002$), NGMW ($r = 0,366$, $p = 0,002$), NWMV($r = 0,416$; $p = 0,002$), NBV ($r = 0,455$; $p = 0,002$), NPGMV ($r = 0,360$; $p = 0,002$)