MICROSTRUCTURAL THALAMIC AND CORTICO-THALAMIC CORRELATES OF COGNITIVE IMPAIRMENT IN PEDIATRIC MULTIPLE SCLEROSIS

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INTRODUCTION and PURPOSE

- The thalamus is a critical node in networks supporting cognitive functions, including memory and executive functions as well as attention and information processing speed [1].
- Thalamic involvement in MS has been reported by both pathologic and imaging studies.
- A few MRI studies have shown thalamic atrophy in pediatric patients with MS.
- The thalamus is an extremely complex structure, organized in nuclear groups with specific functions and connections with cortical and subcortical areas.
- The study of the whole thalamus could be inadequate to explain deficits of specific cognitive functions.
- Integration of DT tractography with high-resolution T1 structural anatomical imaging has allowed a connectivity-based parcellation of the thalamic subregions and tracing their connections with the cortex.

Objectives:

- **To apply connectivity-based segmentation to define the distribution of regional thalamic damage (microstructural DT MRI abnormalities and atrophy) in pediatric MS patients;**
- **To assess the role of abnormalities of thalamic connectivity defined regions (CDR) and their cortical connections for cognitive impairment in pediatric MS patients.**

METHODS

Subjects: 44 right-handed pediatric MS patients and 26 age- and sex-matched healthy controls (HCs) were enrolled.

Neurological examination:

- Clinical evaluation;
- EDSS score rating.

Neuropsychological assessment:

- Extended Neuropsychological Battery for Children, standardized and validated for Italian pediatric MS [2].
- Z-scores for each of cognitive domain (attention, verbal memory, spatial memory and verbal fluency) and a global Z-score of cognitive function (obtained by averaging Z-scores of all tests) were calculated.

MRI Acquisition (3 T scanner):

- Pulsed-gradient SE EPI with SENSE (acceleration factor=2) and diffusion gradients applied in 35 non-collinear directions. Two optimised b factors were used for acquiring diffusion weighted images (b=0 and b=900 s mm-2);
- Dual-echo TSE;
- 3D T1-weighted fast filed-echo scan.

Conventional MRI analysis:

- Measurements of T2 hyperintense and T1 hypointense lesion volumes (LV);
- Quantification of normalized brain (NBV), white matter (WMV) and gray matter (GMV) volumes (SIENAx).

Table 1 shows the main demographic and clinical characteristics of the enrolled study subjects.

Table 1	Pediatric HCs	Pediatric MS patients	p* value	Pediatric CP MS patients	Pediatric CI MS patients	p value
Boys/girls	13/13	15/29	0.19*	12/24	3/5	0.82*
Mean age (range) [years]	15.2 (8.5-19.0)	15.3 (11.1-18.0)	0.83	15.2 (11.1-18.0)	15.9 (13.0-17.7)	0.27
Median EDSS (range)	-	1.25 (0.0-4.0)	-	1.0 (0.0-4.0)	1.5 (1.0-4.0)	0.27
Mean disease duration (range) [years]	-	1.29 (0.1-8.1)	-	1.54 (0.1-6.8)	4.2 (0.8-8.1)	0.01
Mean T2 LV (SD) [ml]	-	5.9 (7.6)	-	4.4 (5.3)	12.5 (12.4)	0.03
Mean T1 LV (SD) [ml]	-	3.7 (5.2)	-	2.6 (3.1)	8.6 (9.3)	0.03
Mean NBV (SD) [ml]	1715 (90)	1651 (79)	<0.001	1663 (73)	1592 (81)	0.04
Mean GMV (SD) [ml]	862 (72)	822 (58)	0.01	827 (61)	797 (39)	0.24
Mean WMV (SD) [ml]	853 (51)	829 (43)	0.04	836 (39)	795 (50)	0.02

* Chi square test

Thalamic segmentation (tool FIRST, FSL):

- Shape analysis,
- Whole thalamic volume.

Thalamic connectivity-based parcellation (tool FDT, FSL):

- HCs only,
- Segmentation Definition of six cortical target (CT) regions: Frontal, Motor, Post-Central, Posterior-Parietal, Temporal, Occipital (based on Harvard-Oxford Atlas),
- Tractography (seeds: thalamus; targets: 6 cortical targets),
- Output: six Connectivity-Defined Regions (CDRs).

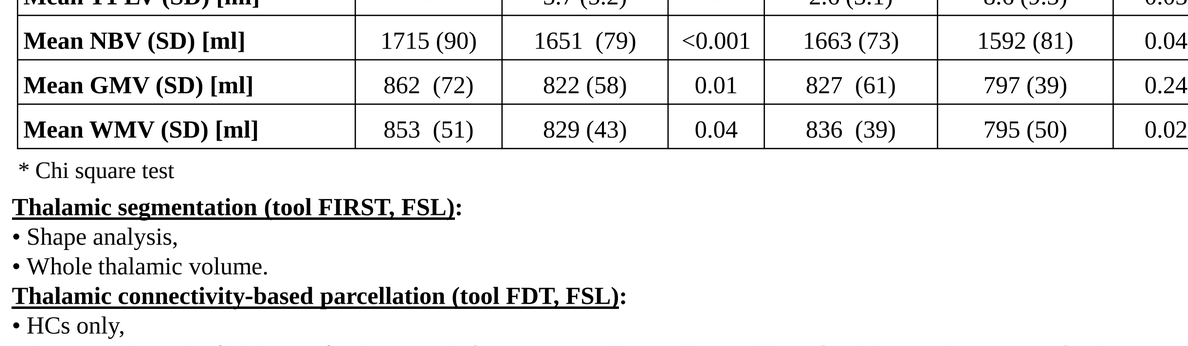
Other measures:

- WM tracts connecting thalamic CDRs with the cortex (CDR>CTx),
- CTs volumes.

Probability maps:

- Generation of thalamic CDRs (Figure 1A) and cortico-thalamic tract (Figure 1B) probability maps → creation of binary masks, thresholded at 33%;
- Application of masks to all subjects to estimate average values of DTI indexes and T2/T1 LV within cortico-thalamic tracts and thalamic CDRs.

Figure 1. CDR and cortico-thalamic tract probability maps.



Statistical analysis:

- Between-group comparisons: Mann-Whitney test, t test for non paired data and Chi-square test, as appropriate.
- Relationships between DT MRI parameters and neuropsychological and conventional MRI variables: Spearman's Rank correlation coefficient.
- Random forest analysis (RF): to identify the best predictor, among all MRI explored variables, of global cognitive impairment as well as of impairment at specific cognitive domains.

RESULTS

Table 2. DTI metrics of left and right thalamic CDRs.

Table 2		Left thalamus			Right thalamus		
		HCs	**Pediatric MS patients**	***p* values**	**HCs**	**Pediatric MS patients**	***p* values**
nVol [ml] (SD)		6.78 (1.39)	6.57 (0.94)	0.38	6.80 (1.47)	6.53 (0.85)	0.25
Whole (SD)	FA	0.29 (0.02)	0.29 (0.01)	0.98	0.30 (0.02)	0.30 (0.02)	0.95
	MD	0.77 (0.02)	0.77 (0.02)	0.27	0.76 (0.02)	0.77 (0.02)	0.51
F-CDR (SD)	FA	0.28 (0.01)	0.28 (0.02)	0.88	0.29 (0.02)	0.29 (0.02)	0.58
	MD	0.76 (0.02)	0.77 (0.02)	0.07	0.77 (0.02)	0.78 (0.03)	0.14
M-CDR (SD)	FA	0.30 (0.03)	0.31 (0.06)	0.70	0.32 (0.03)	0.32 (0.04)	0.57
	MD	0.72 (0.03)	0.72 (0.02)	0.59	0.72 (0.02)	0.72 (0.02)	0.77
PC-CDR (SD)	FA	0.31 (0.04)	0.33 (0.05)	0.47	0.32 (0.04)	0.34 (0.04)	0.36
	MD	0.73 (0.03)	0.72 (0.02)	0.94	0.74 (0.02)	0.73 (0.03)	0.82
T-CDR (SD)	FA	0.28 (0.02)	0.26 (0.03)	0.01	0.28 (0.03)	0.26 (0.03)	0.02
	MD	0.92 (0.06)	1.06 (0.14)	<0.0001	0.92 (0.08)	1.01 (0.16)	<0.0001
O-CDR (SD)	FA	0.27 (0.02)	0.28 (0.02)	0.20	0.27 (0.03)	0.28 (0.03)	0.05
	MD	0.76 (0.03)	0.77 (0.04)	0.07	0.75 (0.03)	0.76 (0.04)	0.12

Table 3. DTI metrics of left and right thalamic cortico-thalamic tracts.

Table 3		Left thalamus			Right thalamus		
		HCs	**Pediatric MS patients**	***p* values**	**HCs**	**Pediatric MS patients**	***p* values**
F-T tract (SD)	FA	0.44 (0.02)	0.43 (0.02)	0.03	0.43 (0.02)	0.43 (0.02)	0.12
	MD	0.77 (0.02)	0.78 (0.03)	0.01	0.77 (0.02)	0.79 (0.03)	0.01
M-T tract (SD)	FA	0.46 (0.03)	0.46 (0.03)	1.00	0.46 (0.02)	0.46 (0.03)	0.99
	MD	0.72 (0.04)	0.73 (0.04)	0.12	0.73 (0.03)	0.74 (0.03)	0.03
PC-T tract (SD)	FA	0.43 (0.03)	0.41 (0.03)	0.16	0.44 (0.03)	0.43 (0.03)	0.13
	MD	0.73 (0.04)	0.75 (0.04)	0.16	0.73 (0.03)	0.75 (0.04)	0.02
PP-T tract (SD)	FA	0.39 (0.06)	0.38 (0.05)	0.27	0.42 (0.03)	0.41 (0.04)	0.20
	MD	0.76 (0.04)	0.79 (0.05)	0.01	0.76 (0.04)	0.78 (0.04)	0.01
T-T tract (SD)	FA	0.37 (0.03)	0.34 (0.03)	<0.0001	0.36 (0.03)	0.33 (0.04)	<0.0001
	MD	0.99 (0.06)	1.07 (0.08)	<0.0001	0.98 (0.06)	1.06 (0.07)	<0.0001
O-T tract (SD)	FA	0.49 (0.02)	0.46 (0.03)	<0.0001	0.49 (0.03)	0.46 (0.03)	0.01
	MD	0.80 (0.03)	0.84 (0.05)	<0.0001	0.79 (0.03)	0.83 (0.04)	<0.0001

Abbreviations: MS=multiple sclerosis; CDR=Connectivity Derived Region; FA= Factional Anisotropy; MD= Mean Diffusivity.

Correlation analysis:

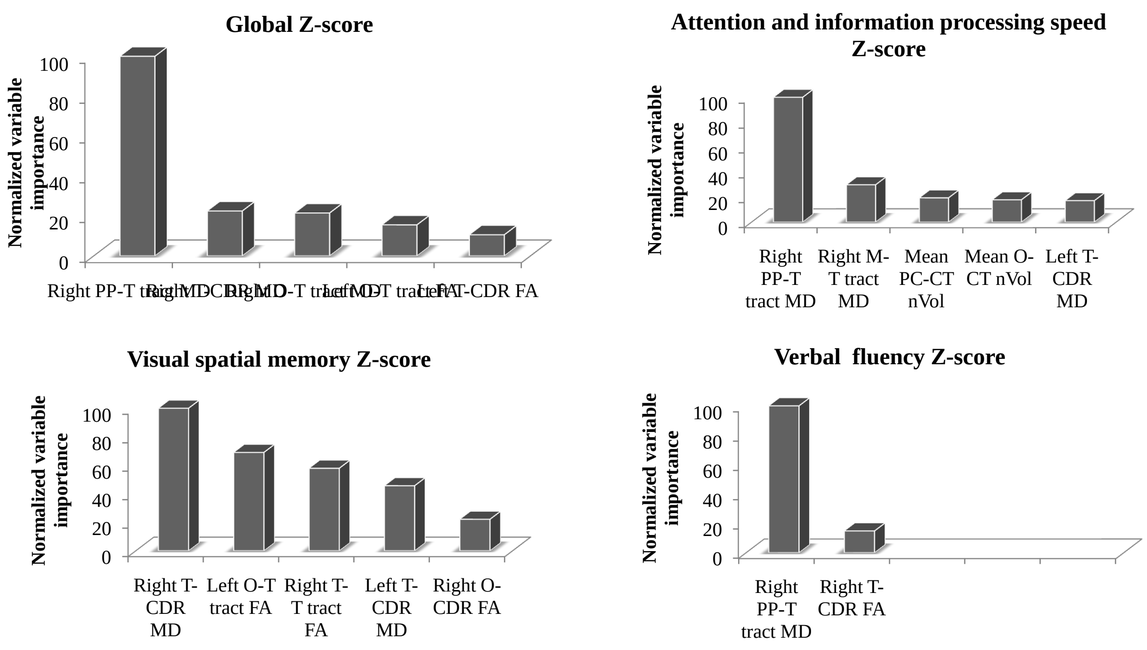
FA values in bilateral T-CDR:

- Positive correlation with FA in the corresponding cortico-thalamic tract (*p* ranging from 0.004 to <0.001, r=0.4-0.6);
- Positive correlation with NBV and GMV (*p* ranging from 0.02 to <0.0001, *r*=0.4-0.6);
- FA values in the left T-CDR were also related to T1 LV (*p*=0.04, *r*=-0.3).

MD values in bilateral T-CDR:

- Negative correlation with NBV and GMV (*p* ranging from 0.02 to <0.0001, *r*=-0.6);
- Positive correlation with T2 LV and T1 LV while (*p* ranging from 0.04 to <0.0001, *r*=0.6);
- Positive correlation with MD values, T2 LV and T1 LV in the corresponding cortico-thalamic tract (*p* <0.0001, *r*=0.7).

Figure 2. Results of random forest analysis performed to identify the best predictor of cogntive performance.



CONCLUSIONS

- Similarly to what has been described in adults, both regions of increased and decreased thalamic FA were detected in pediatric MS patients, which might reflect a complex interplay between GM (increased FA) and WM (decreased FA) damage at the level of this structure.
- Damage to specific thalamo-cortical connections in addition to regional thalamic damage explained patients' global cognitive profile as well as impairment at specific cognitive tests, suggesting that cognitive impairment in pediatric MS is likely due to a cortico-subcortical disconnection.

REFERENCES

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DISCLOSURES

Maria A. Rocca received speakers honoraria from Biogen Idec, NOVARTIS, Genzyme and Excemed and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. Ermelinda De Meo, Pierangelo Veggiotti, Lucia Moiola, Ruggero Capra, Andrea Falini, Agnese Fiorino, Lorena Pippolo and Maria Carmela Pera report no conflict of interest. Maria Pia Amato received personal compensation from Merck Serono, Biogen, Bayer Schering, Genzyme, Teva and Novartis for serving on scientific advisory board and for speaking, received financial support for research activites from Merck Serono, Biogen Idec, Bayer Schering, Genzyme, Novartis, Genzyme and Teva. Angelo Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Merck Serono, Biogen Idec, Bayer Schering Pharma, and Novartis, Serono Symposia International; served as a consultant for Novartis; and receives research support from Sanofi-Aventis, Biogen Idec, and Merck Serono. Giancarlo Comi has received personal compensation for activities with Teva Neuroscience, Merck Serono, Bayer-Schering, Novartis, Sanofi-Aventis Pharmaceuticals, and Biogen Idec as a consultant, speaker, or scientific advisory board member. Massimo Filippi serves on scientific advisory boards 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 Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Partially supported by a grant from Italian Ministry of Health (GR-2009-1529671) and Fondazione Italiana Sclerosi Multipla (FISM2011/R/19 & FISM 2012/R/8).