# CORTICO-THALAMIC CONNECTIVITY ABNORMALITIES AS STRUCTURAL SUBSTRATE OF FATIGUE IN PEDIATRIC MULTIPLE SCLEROSIS

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## INTRODUCTION and PURPOSE

Fatigue is well characterized as a disabling symptom in adult multiple sclerosis (MS) patients, while there is limited available information in pediatric patients although it has been reported in a sizable proportion of children and adolescents with MS [1].

Previous studies [2] have suggested that behavioral problems could be related to fatigue, but the anatomical substrates of this symptom have not been investigated in pediatric patients with MS.

Recent studies conducted in adult MS patients have demonstrated that global measures of tissue loss are not strongly associated with fatigue in patients at the early stages of the disease.

Conversely, thalamic and cerebellar gray matter (GM) atrophy may have a role in explaining the presence of fatigue in these patients. Microstructural damage to the normal appearing white matter (NAWM), measured using diffusion tensor imaging (DTI), is another factor contributing to fatigue in MS patients [3].

**The objective of this study was to analyze the contribution of microstructural damage to the thalamus and cortico-thalamic connections to explain the presence of fatigue in pediatric patients with MS.**

## 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 were calculated.
- Pediatric patients with 3 or more test failed were considered cognitively impaired (CI).
- Fatigue assessment with Fatigue Severity Scale (FSS) [4].

**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=900s mm-2);
- Dual-echo TSE;
- 3D T1-weighted fast field-echo.

**Conventional MRI analysis:**
- Measurements of T2 hyperintense and T1 hypointense lesion volumes (LV);
- Quantification of normalized brain (NBV), WM (WMV) and GM (GMV) volumes (SIENAx).

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

| Table 1 | HC | MS patients | *p* values | Pediatric CP MS patients | Pediatric CI MS patients | *p* values |
|---|---|---|---|---|---|---|
| Number of subjects | 26 | 44 | - | 36 | 8 | - |
| Female/male | 13/13 | 15/29 | 0.19* | 12/24 | 3/5 | 0.82* |
| Mean age (SD) [years] | 15.2 (8.5-18.0) | 15.3 (11.1-18.0) | 0.83 | 15.2 (11.1-18.0) | 15.9 (13.0-17.7) | 0.27 |
| Median disease duration (range) [years] | - | 1.29 (0.1-8.1) | - | 1.54 (0.1-6.8) | 4.2 (0.8-8.1) | 0.01 |
| Median EDSS [range] | - | 1.0 (0.0-4.0) | - | 1.0 (0.0-4.0) | 1.5 (1.0-4.0) | 0.27 |
| 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 [ml] (SD) | 1715 (90) | 1651 (79) | <0.001 | 1663 (73) | 1592 (81) | 0.04 |
| Mean GMV [ml] (SD) | 862 (72) | 822 (58) | 0.01 | 827 (61) | 797 (39) | 0.24 |
| Mean WMV [ml] (SD) | 853 (51) | 829 (43) | 0.04 | 836 (39) | 795 (50) | 0.02 |

* Chi square test.

Abbreviations: HC=Healthy Controls; MS=Multiple Sclerosis; CP=cognitively preserved; CI=cognitively impaired; SD=standard deviation; EDSS=Expanded Disability Status Scale; LV=lesion volume; NBV=normalized brain volume; GMV=gray matter volume; WMV= white matter volume.

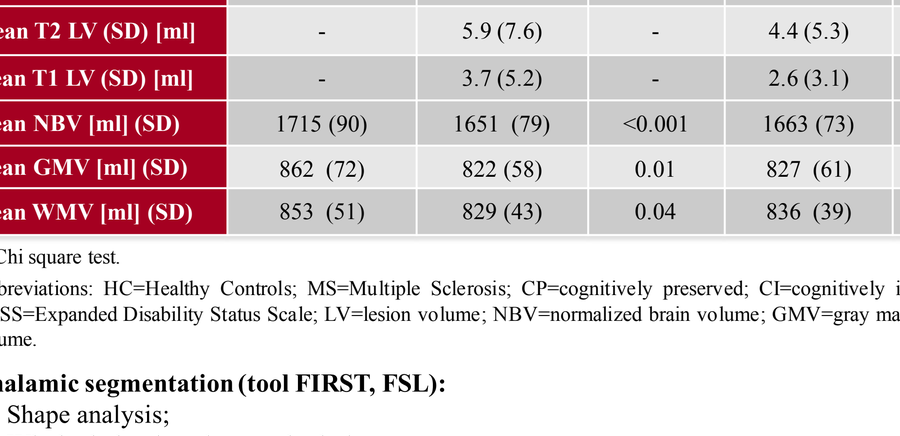
**Thalamic segmentation (tool FIRST, FSL):**
- Shape analysis;
- Whole thalamic volume calculation.

**Thalamic connectivity-based parcellation (tool FDT, FSL):**
- HCs only;
- Segmentation 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 FSS scores: Spearman's Rank correlation coefficient.

## RESULTS

**Regional microstructural thalamic analysis:**
- Pediatric MS patients compared to HC showed lower factional anisotropy (FA) and higher mean diffusivity (MD) in the temporal-CDR (T-CDR), bilaterally.

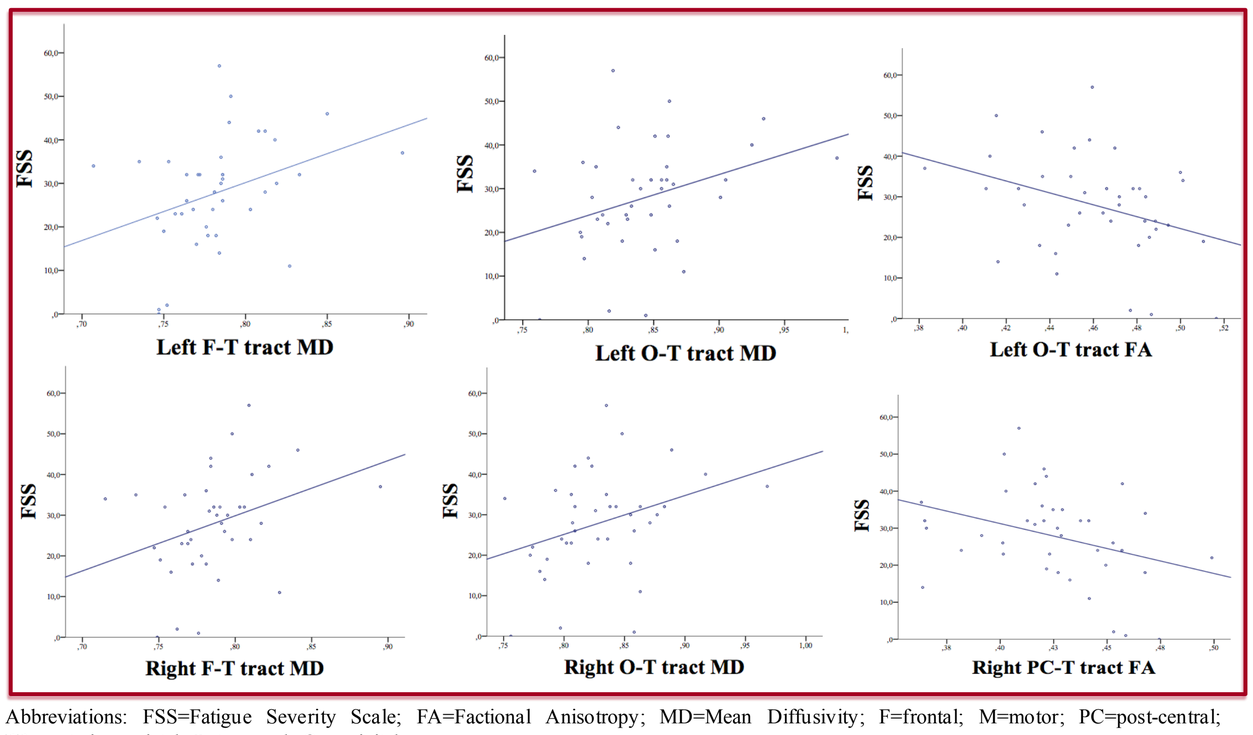
**Table 2.** DTI metrics of left and right thalamic cortico-thalamic tracts.

| 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; SD=standard deviation; F=frontal; M=motor; PC=post-central; PP=posterior parietal; T=temporal; O=occipital.

**Correlation analysis:**
- No significant correlations were found between FSS scores and DT MRI metrics in CDRs;
- FSS was significantly correlated with (Figure 2):
  - Increased MD in bilateral frontal cortico-thalamic tracts ($r$=0.43, $p$=0.005; $r$=0.39, $p$=0.001) and occipital (O-T) cortico-thalamic tracts (r=0.32, $p$=0.04; $r$=0.36, $p$=0.02);
  - Reduced FA in the right post-central thalamic tract ($r$=-0.38, $p$=0.01) and left O-T tract ($r$=-0.34, $p$=0.03).

**Figure 2.** Correlation analysis between FSS score and cortico-thalamic tract DT MRI metrics.




Abbreviations: FSS=Fatigue Severity Scale; FA=Factional Anisotropy; MD=Mean Diffusivity; F=frontal; M=motor; PC=post-central; PP=posterior parietal; T=temporal; O=occipital.

## CONCLUSIONS

- As demonstrated in adult MS patients, also in pediatric MS patients fatigue was associated with DT MRI abnormalities of the NAWM;
- In particular, this study confirmed the involvement of frontal lobes and specifically of their thalamic connections in determining fatigue.
- In contrast with previous findings in adult MS patients, FSS scores were not related with thalamic damage, suggesting that fatigue in the earliest phases of the disease is mainly due to NAWM pathology;
- In agreement with previous studies in adult MS patients, fatigue was related to local rather than global NAWM damage, as shown by the correlation between FSS scores and microstructural damage to specific WM tracts;
- This study supports the theory that also in pediatric patients with MS a fronto-subcortical WM disconnection might be the main structural substrate of fatigue.

## REFERENCES

1. Amato et al. Neurology, 2010;
2. Chrvet et al., J Child Neurology, 2016;
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## DISCLOSURES

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