REGIONAL GREY MATTER ATROPHY IN PEDIATRIC PATIENTS WITH MULTIPLE SCLEROSIS: A LONGITUDINAL MRI STUDY

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Introduction and purpose

Multiple sclerosis (MS) has long been considered an inflammatory disease, however today there is a growing evidence that it is also characterized by a neurodegenerative component.
In adult MS patients, grey matter (GM) damage has been demonstrated from the earliest clinical stages of the disease. Previous cross-sectional MRI studies have shown that also pediatric MS patients have reduced thalamic [**1**] and brain [**2**] volumes compared to age- and sex-matched healthy controls (HC). To date only one longitudinal study has been conducted in this cohort of patients concluding that onset of MS during childhood limits age-expected primary brain growth and leads to subsequent brain atrophy [**3**]. Advanced MRI techniques of analysis, such as Voxel-Based Morphometry (VBM) and Tensor-Based Morphometry (TBM), represent a powerful instrument to assess GM damage in vivo and track its longitudinal changes.

Against this background, we applied VBM and TBM:

- **To assess the regional patterns of GM damage in pediatric MS patients;**
- **To define the regional patterns of GM atrophy progression in pediatric MS patients;**
- **To explore the correlations between GM atrophy and clinical and conventional MRI measures.**

Methods

Subjects: 31 right-handed pediatric MS patients and 26 age- and sex-matched HCs from San Raffaele Hospital were enrolled. In addition, data of 119 pediatric HC from NIH-funded MRI Study of Normal Brain Development were used as normal growth reference (NIH HC). Longitudinal scans at a mean follow-up of 3.2 years were available from pediatric MS patients and NIH HC. Pediatric MS patients underwent a neurological evaluation at baseline and at follow-up.

Neurological examination:

- Clinical evaluation;
- EDSS score rating.

MRI Acquisition (3.0 T scanner) of pediatric MS patients and HC from San Raffaele Hospital (HSR HC):

- Dual-echo TSE;
- 3D T1-weighted fast field-echo scan.

MRI Acquisition (1.5 T scanner) of pediatric NIH HC:

- Dual-echo TSE;
- 3D T1-weighted fast field-echo scan.

Conventional MRI analysis:

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

Table 1 shows the main demographic and clinical characteristics of the enrolled study subjects at baseline and follow-up.

Table 1	Baseline				Follow-up		
	HSR HC	NIH HC	Pediatric MS patients	*p* values	NIH HC	Pediatric MS patients	*p* values
Number of subjects	26	119	31	-	119	31	-
Female/male	13/13	64/55	19/12	0.45*	64/55	19/12	0.82*
Mean age (SD) [years]	15.2 (8.5-18.0)	14.9 (12.0-18.0)	15.5 (12.5-18.0)	0.72	19.0 (14.0-22.4)	18.0 (13.9-24.0)	0.83
Median disease duration (range) [years]	-		1.29 (0.1-8.1)	-		5.38 (1.35-12.9)	-
Median EDSS [range]	-		1.0 (0.0-3.5)	-	-	1.0 (0.0-3.5)	-
Mean T2 LV (SD) [ml]	-		4.9 (6.5)	-	-	6.5 (4.0)	-
Mean T1 LV (SD) [ml]	-		2.7 (3.5)	-	-	4.1 (5.5)	-

* Chi square test.

Abbreviations: HC=Healthy Controls; MS=Multiple Sclerosis; SD=standard deviation; EDSS=Expanded Disability Status Scale; LV=lesion volume.

MRI analysis (SPM12 software):

- ***VBM (regional GM differences at baseline)*:**
  - Segmentation into GM, WM and CSF;
  - GM and WM segmented images of all subjects were used to produce GM and WM templates and to drive the deformation to the templates;
  - Affine registration between the customized GM template and the SPM GM template in the Montreal Neurological Institute (MNI) space.
- ***TBM (regional pattern of GM atrophy progression)*:**
  - Pairwise longitudinal registration to align the first and second scan of each subject;
  - Volume change quantification;
  - Production from the GM and WM segmented images of GM and WM templates;
  - Normalization to MNI space.

Statistical analysis:

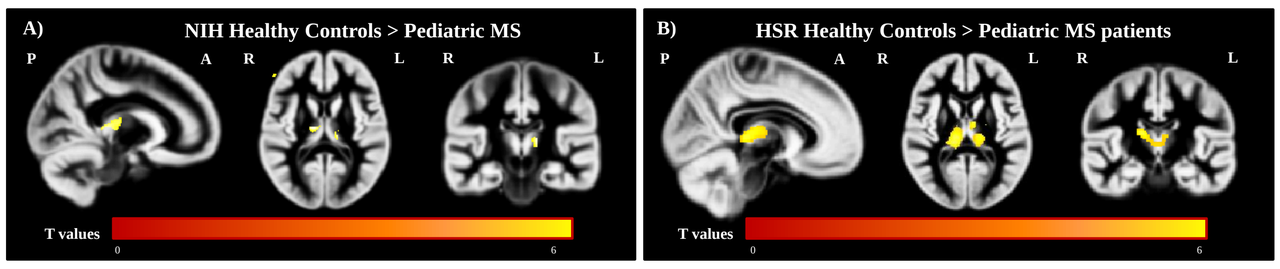
- Full factorial model: GM differences at baseline (HSR HC *vs* NIH HC; MS *vs* NIH HC; MS *vs* HSR HC);
- One sample t test: longitudinal GM changes within group (NIH HC and MS);
- Analysis of covariance (ANCOVA): longitudinal GM volume changes between-groups;
- Multiple regression model: correlations between GM volume changes and clinical and conventional MRI variables.

Results

Regional GM differences at baseline:

- No significant differences were found when comparing HC to NIH HC.
- Compared to NIH HC and HSR HC, MS patients showed reduced thalamic volume, bilaterally.

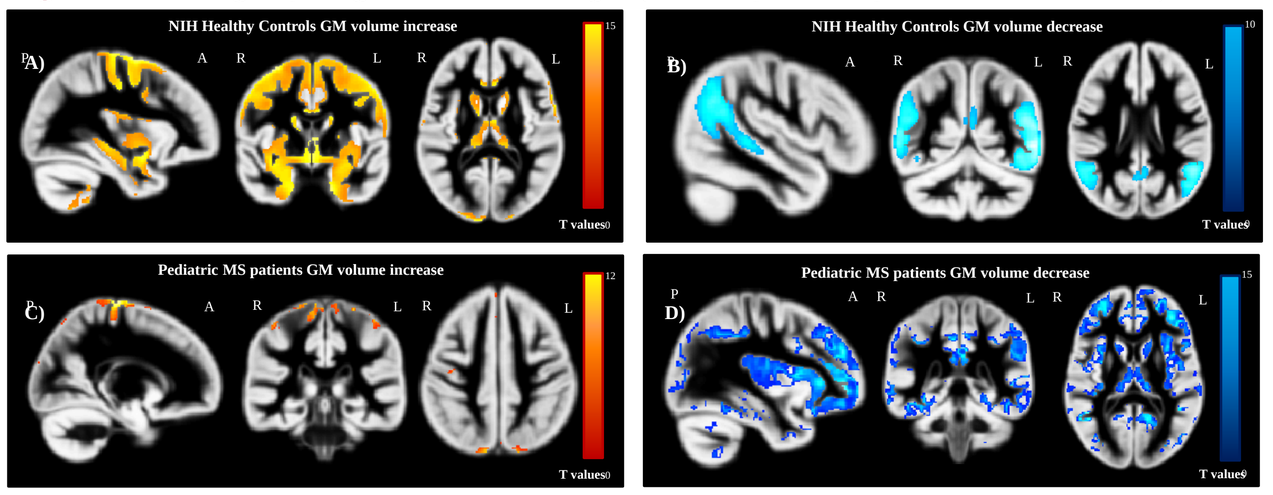
Figure 1. Comparison between pediatric MS patients *vs* NIH HC (A) and pediatric MS patients *vs* HSR HC (B) (two-sample t test, p<0.05 FWE corrected).



Longitudinal GM changes:

- Pediatric NIH HC (**Figure 2**):
  - Regions of increased GM volume: basal ganglia, thalamus, frontal lobes, MTG, inferior temporal gyrus (ITG) and cerebellum (A);
  - Regions of decreased GM volume: posterior part of superior temporal gyrus (STG) and MTG, angular gyrus, fusiform gyrus and precuneus (B);
- Pediatric MS patients (**Figure 2**):
  - Regions of increased GM volume: precentral gyrus (PCG), PoCG, lingual gyrus (C);
  - Regions of decreased GM volume: thalamus, middle frontal gyrus, ITG, temporal pole, lingual and fusiform gyri, middle occipital gyrus (D).

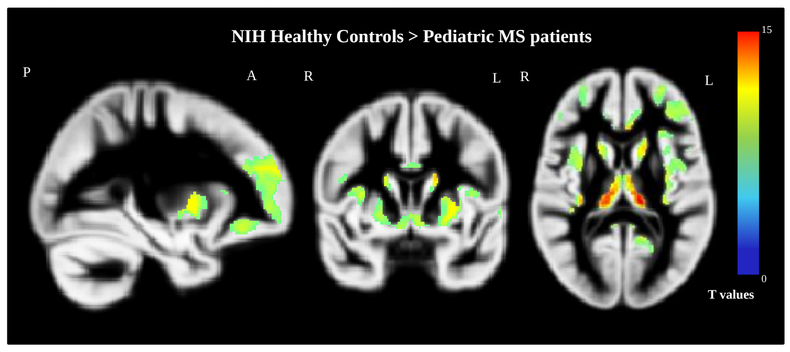
Figure 2. Within-group longitudinal GM changes (one-sample t test, p<0.05 FWE corrected).



Between-group comparisons (Figure 3):

- Compared to NIH HC, MS patients showed GM atrophy in bilateral thalamus, hippocampus, MTG, inferior frontal gyrus (IFG), left insula, fusiform and lingual gyri and right calcarine cortex.

Figure 3. Between-group comparisons (ANCOVA, p<0.05 FWE corrected).



Correlation analysis:

- No correlations were found between GM atrophy development and disease duration or age at onset, as well as between GM atrophy and EDSS scores as assessed at baseline, at FU and its changes over time.
- Significant correlations were found between GM atrophy in bilateral thalamus, hippocampus and right IFG and T2 LV and T1 LV, both baseline and at FU (*r* ranging from 0.59 to 0.75, *p*<0.001).

Conclusions

- By comparing pediatric MS patients to normally developing children, this study gave us the opportunity to describe the effect of the disease on the developing brain;
- The GM pattern of atrophy found allowed us to suppose that MS is likely to be responsible of a failure of age-expected GM trajectories of development in pediatric patients;
- Significant atrophy and continuous progression of atrophy were found at the level of the thalamus, suggesting that the reduced volume of this structure might result from both a failure of age-expected brain growth as well as a subsequent and progressive reduction in established brain volume, as a consequence of WM lesion formation;
- Our findings confirm that neurodegeneration represent an early aspect of MS pathology, only partially related to inflammation, rather than a late effect of chronic disease, emphasizing the importance of implementing neuroprotective strategies in order to prevent the accrual of disability starting form the earliest phases of disease.

References

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Disclosures

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