DIFFERENTIAL CONTRIBUTION OF CEREBELLAR RESTING STATE FUNCTIONAL CONNECTIVITY ABNORMALITIES TO COGNITIVE IMPAIRMENT IN PEDIATRIC AND ADULT PATIENTS WITH MULTIPLE SCLEROSIS

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INTRODUCTION and PURPOSE

• Up to 10% of multiple sclerosis (MS) patients have their first attack during childhood [1].
• Cognitive impairment affects a large proportion of adult MS patients (depending on the population, tests and cut-off values applied) [2]. A large amount of pediatric MS patients also experience cognitive deficits, with a prominent involvement of linguistic abilities, memory, attention and executive functions [3].
• The cerebellum has a high intrinsic synaptic plasticity and is involved in many sensorimotor and cognitive tasks [4]. In healthy subjects, consistent functional connectivity (FC) between the cerebellum and temporal, parietal, and prefrontal regions has been demonstrated at rest and during the performance of cognitive tasks [5].
• The disruption of cerebellar resting state (RS) FC is likely to contribute to cognitive impairment in MS, with different mechanisms in adult and pediatric patients.

Aim of this study was to investigate whether RS FC abnormalities of different functional subregions of the cerebellum (right and left Crus I, Crus II and dentate nucleus) in pediatric and adult MS patients correlate to cognitive impairment.

METHODS

Subjects: 49 pediatric MS patients, 40 adult MS patients, 27 pediatric healthy controls (HC) and 40 adult HC were recruited.
Inclusion criteria: diagnosis of relapsing-remitting MS, right-handedness, relapse- and steroid-free for at least three months, no significant medical illnesses or substance abuse.

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

Table 1	Pediatric HC (N=27)	Pediatric MS patients (N=49)	p*	Adult HC (N=40)	Adult MS patients (N=40)	p*
Men/Women	12/15	18/31	0.5	17/23	17/23	0.9
Mean age (SD) [y]	15.3 (3.4)	15.0 (2.0)	0.4	35.9 (11.2)	36.2 (11.5)	0.9
Median EDSS [range]	-	1.0 (0.0-4.0)	-	-	1.5 (0.0-4.0)	-
Mean disease duration (SD) [y]	-	1.8 (2.0)	-	-	6.4 (4.4)	-

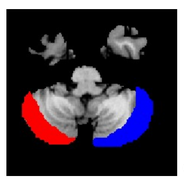
*Mann-Withney U test.

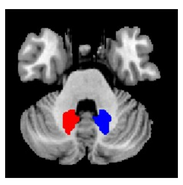
Study design:
• Neurologic examination: Expanded Disability Status Scale (EDSS) rating [6].
• Neuropsychological assessment:
- Pediatric patients: neuropsychological Battery for Children [7].
- Adult patients: brief Repeatable Battery of Neuropsychological Tests (BRB-N) [8].
• Cognitively impaired (CI) MS patients = abnormal performance in ≥3 tests.

MRI acquisition: 3.0 T Philips Intera scanner.
• *RS functional MRI*: T2*-weighted EPI scans (TR/TE=3000/35 ms, matrix=128x128, FOV=240x240 mm², 30 axial slices with thickness=4 mm; 200 sets of images acquired while subjects lied still in the scanner);
• *Structural MRI*: dual-echo (DE) turbo spin-echo (TSE) for the assessment of T2 lesion volume (LV).

RS fMRI analysis
• *Preprocessing (SPM8):* realignment, normalization, linear detrend, band-pass filter, removal of realignment parameters and of the average signal from white matter and ventricular CSF.
• *Seed-based RS FC:* masks of Crus I, Crus II and dentate nucleus extracted from AAL/WFU Pickatlas; correlation calculated between mean time series of the voxels within the seed and any other voxel of the brain [9].


Crus I


Crus II


Dentate nucleus

Statistical analysis:
• Between-group comparison of demographic, clinical and conventional MRI variables: Mann-Withney U tests and linear regression models to assess "age (pediatric/adult) *x* group (CP/CI)" interaction;
• Within-group RS FC: SPM8, one sample t tests ($p<0.05$, FWE corrected).
• Between-group comparison of RS FC: SPM8, full factorial models (sex- and age-adjusted, as appropriate, $p<0.001$), to assess the effect of group (HC/CP/CI), age (pediatric/adult), and "age *x* group" interaction.

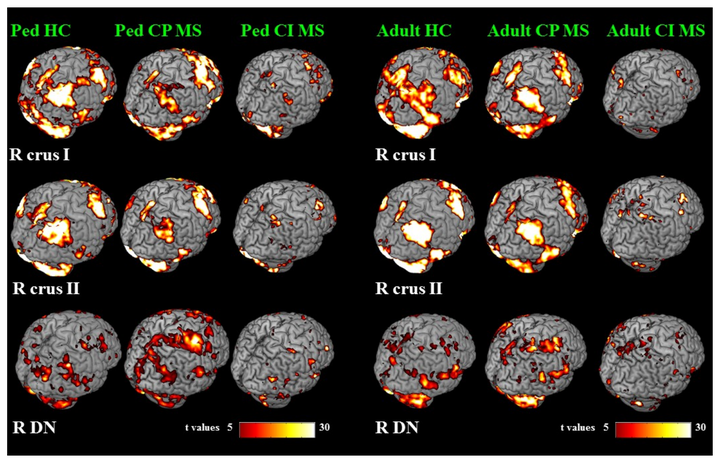
Table 2. Main demographic, clinical and conventional MRI characteristics of CP and CI MS patients.

Table 2	Pediatric CP MS (N=39)	Pediatric CI MS (N=10)	p*	Adult CP MS (N=31)	Adult CI MS (N=9)	p*	p**
M/F	14/25	4/6	0.8	17/14	0/9	0.01	0.02
Mean age (SD) [y]	14.7 (2.1)	15.8 (1.5)	0.1	31.8 (8.1)	41.3 (8.3)	<0.001	<0.001
Median EDSS [range]	1.0 (0.0-4.0)	1.5 (0.0-4.0)	0.3	1.5 (0.0-3.0)	2.0 (1.0-4.0)	0.07	0.5
Mean disease duration (SD) [y]	1.4 (1.5)	3.6 (2.7)	0.006	6.2 (3.9)	7.1 (6.1)	0.9	0.4
T2 LV (SD) [ml]	4.4 (4.5)	9.7 (12.6)	0.4	6.2 (6.0)	14.8 (16.2)	0.3	0.4

*Mann-Withney U test; **linear regression model, age x group interaction.

RESULTS

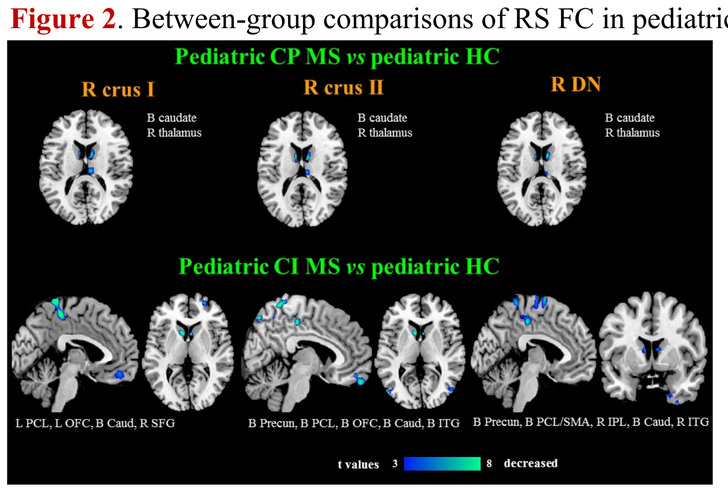
Figure 1. Spatial maps of RS FC with the selected seed regions (left=pediatric HC, pediatric CP and pediatric CI MS patients; right=adult HC, adult CP and adult CI MS patients, $p<0.05$, FWE corrected).



Abbreviations:
R=right; DN=dentate nucleus.

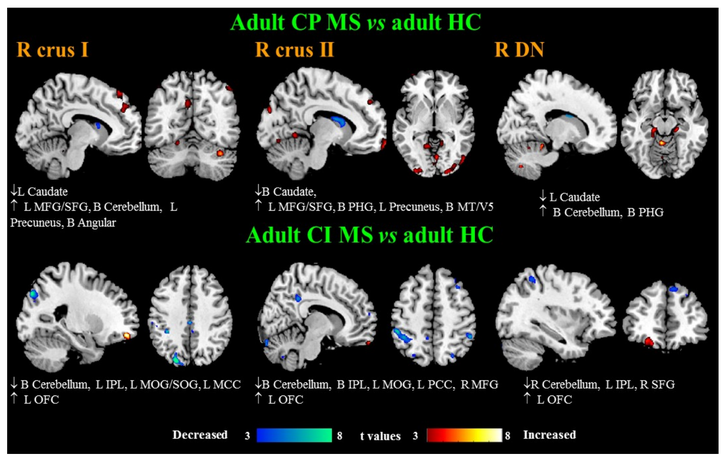
RS FC maps of the homologous regions of the left hemisphere were very similar to those obtained with seeds of the right hemisphere (data not shown).

Figure 2. Between-group comparisons of RS FC in pediatric subjects ($p<0.001$, uncorrected).



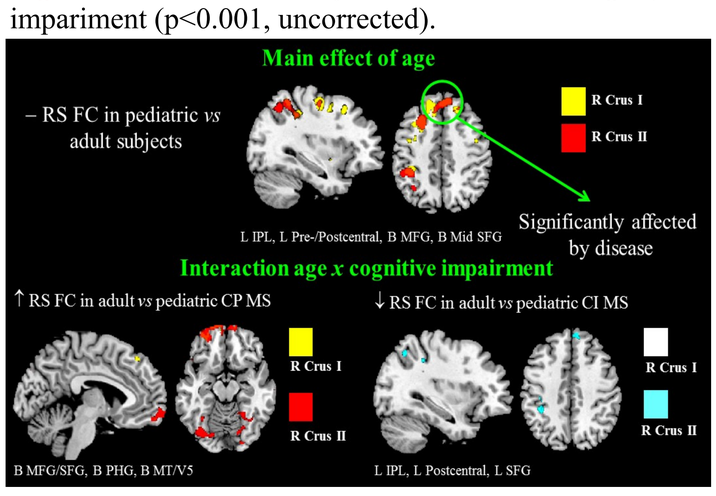
Pediatric MS: significantly reduced cerebellar RS FC.
- CP MS patients: decreased RS FC only in the basal ganglia;
- CI MS patients: widespread reduction of RS FC, especially in regions of the default mode network.

Figure 3. Between-group comparisons of RS FC in adult subjects ($p<0.001$, uncorrected).



Adult MS: complex pattern of RS FC abnormalities.
- CP MS patients: decreased RS FC in the basal ganglia and increased RS FC in several frontal, parietal and cerebellar regions;
- CI MS patients: widespread RS FC decrease in frontal, parietal and temporal regions, and focal RS FC increase in frontal regions.

Figure 4. Interaction analysis: main effect of age (adult *vs* pediatric), interaction age x cognitive impairment ($p<0.001$, uncorrected).



CONCLUSIONS

• Compared to HC, MS patients experience significant reduction of RS connectivity between the cerebellum and the basal ganglia, which is independent from age and does not contribute to cognitive performance.
• In pediatric MS patients, decreased RS FC between the cerebellum and fronto-parietal-temporal regions is related to the presence of cognitive deficits.
• In adult MS patients, a more complex pattern of RS FC abnormalities was detected, characterized by the concomitant presence of regions of increased and decreased connectivity, both contributing to cognitive decline.
• Abnormal maturation of frontal connections due to disease might influence a different functional reorganization in adult *vs* pediatric patients with MS.

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