STRUCTURAL CONNECTIVITY ABNORMALITIES UNDERLYING COGNITIVE IMPAIRMENT IN PEDIATRIC MULTIPLE SCLEROSIS

E. De Meo[1], M.A. Rocca[1,2], E. Pagani[1], L. Moiola[2], A. Ghezzi[3], P. Veggiotti[4], R. Capra[5], M.P. Amato[6], L. Vacchi[1], A. Fiorino[2], L. Pippolo[3], M.C. Pera[4], G. Comi[2], A. Falini[7], M. Filippi[1]

[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [2]Dept. of Neurology, and [7]Dept. of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; [3]MS Center, Ospedale di Gallarate, Gallarate, [4]Department of Child Neurology and Psychiatry, C. Mondino National Neurological Institute, Pavia, [5]MS Center, Spedali Civili of Brescia, Brescia, [6]Department of Neurology, University of Florence, Florence, Italy.

INTRODUCTION

A large proportion of pediatric patients with multiple sclerosis (MS) experiences cognitive deficits, with a prominent involvement of linguistic abilities in addition to memory, attention, and executive functions [1], but the factors associated with cognitive impairment remain largely unexplored.

Diffusion tensor (DT) magnetic resonance imaging (MRI) has proven to be a sensitive technique to detect normal appearing white matter (NAWM) damage, and a powerful tool to construct brain structural connectome.

Previous studies applied DT MRI to detect microstructural damage underlying cognitive impairment in pediatric MS patients, individuating in corpus callosum [2] and posterior brain regions [3] damage potential substrates of cognitive impairment.

In this study, we applied DT MRI to:

- **Describe brain structural network architecture in pediatric MS patients;**
- **Detect structural connectivity abnormalities underlying cognitive dysfunction across the different cognitive domains.**

METHODS

Subjects: 52 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 [4];
- 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.
- Pediatric patients with 3 or more test failed were considered cognitively impaired (CI).

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 filed-echo.

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	HCs	MS patients	*p* values	Pediatric CP MS patients	Pediatric CI MS patients	*p* values
Number of subjects	26	52	-	40	12	-
Female/male	13/13	18/34	0.22*	27/13	7/5	0.82*
Mean age (SD) [years]	15.2 (8.5-19.0)	15.3 (11.1-18.0)	0.72	15.2 (11.1-18.0)	16.1 (13.0-17.7)	0.83
Median disease duration (range) [years]	-	1.29 (0.1-8.1)	-	1.54 (0.1-6.8)	4.0 (0.8-8.1)	0.002
Median EDSS [range]	-	1.25 (0.0-4.0)	-	1.0 (0.0-4.0)	1.5 (1.0-4.0)	0.56
Mean T2 LV (SD) [ml]	-	6.6 (8.1)	-	4.3 (5.2)	12.5 (12.4)	0.08
Mean T1 LV (SD) [ml]	-	3.9 (5.1)	-	2.5 (3.1)	8.6 (9.3)	0.005
Mean NBV [ml] (SD)	1715 (90)	1657 (77)	0.01	1676 (68)	1587 (78)	0.004
Mean GMV [ml] (SD)	862 (72)	827 (54)	0.03	836 (56)	791 (40)	0.036
Mean WMV [ml] (SD)	853 (51)	829 (48)	0.85	840 (39)	796 (47)	0.006

* Chi square test.

Abbreviations: HCs=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=grey matter volume; WMV= white matter volume.

DW MRI Analysis (FSL software):

- Pre-processing: distortions and motion correction (topup tool), tensor estimation, non-linear registration into the MNI space (fnirt tool);
- Application of WM atlas to MS patients and HCs;
- Calculation of average fractional anisotropy (FA) of each connection;
- Derivation of 1 connectivity matrix per subject.

Network analysis:

- Small-worldness of structural brain networks tested against 100 matched random networks.
- *Global network analysis:*
  - Assessment of strength, assortativity, transitivity, global efficiency, average path length and local efficiency;
- *Local network analysis:*
  - Assessment of nodal strength (S) and betweeness centrality (B) [=fraction of all shortest paths in the network that pass through the given node];
  - Cortical hubs: regions with S or B at least 1.5 SD greater than the network average values.

Statistical analysis:

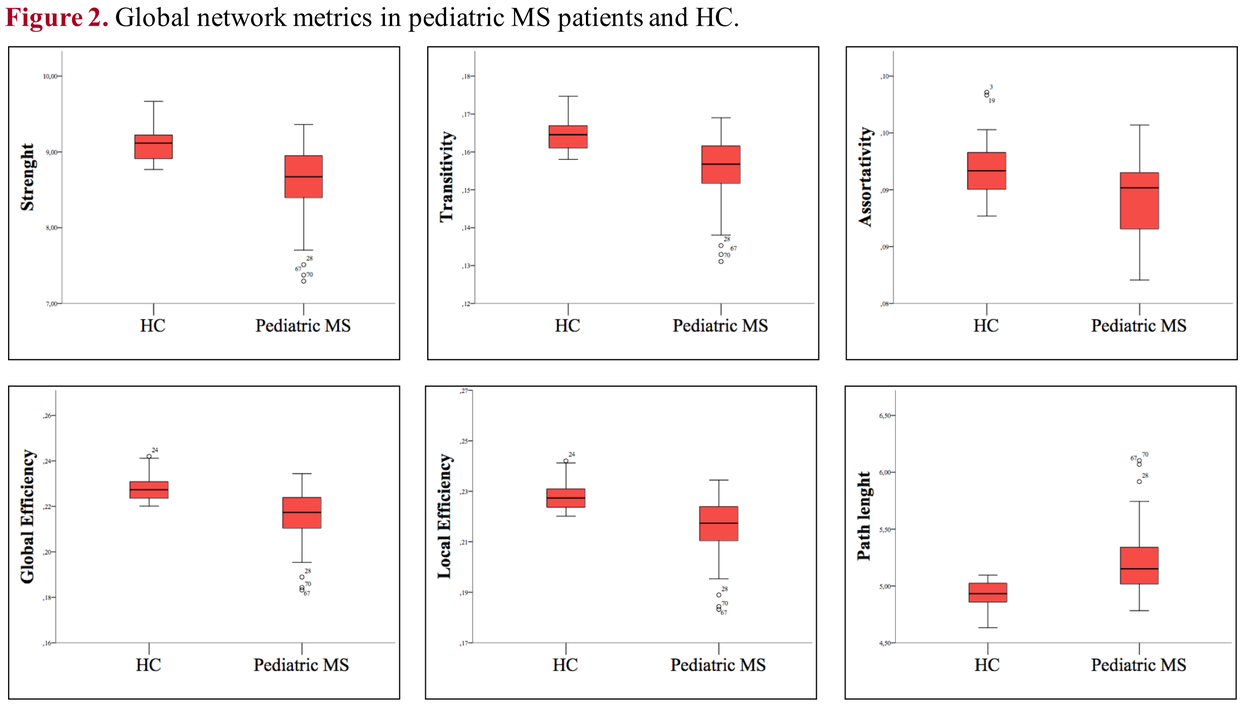
- *Between-groups comparisons*:
  - Global network parameters: two-sample t test.
  - Regional network parameters: Mann-Withney U test.
  - Comparisons between controls, CP and CI MS patients were performed using ANOVA models.

RESULTS

Global network analysis:

- Small-worldness was verified in HC and pediatric MS patients;
- Global network metrics were significantly different between pediatric MS patients and HCs (**Figure 1**).

Figure 2. Global network metrics in pediatric MS patients and HC.

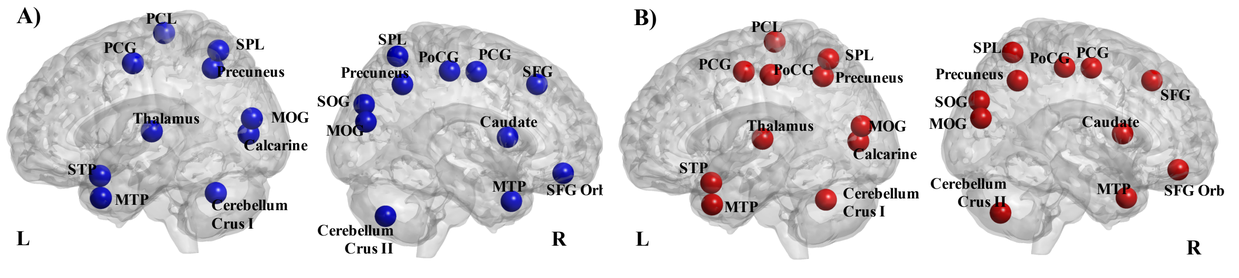


- No significant differences were found between CP and CI MS patients.

Local network analysis:

- Compared to HC, pediatric MS patients showed an additional hub in the left post-central gyrus (**Figure 2**);
- Compared to HC, pediatric MS patients had a significant reduction of the strenght in all the network nodes identified as hubs;
- No significant differences were found in hub distrubution between CP and CI MS patients.

Figure 2. Brain Hubs in HC (A) and pediatric MS patients (B).

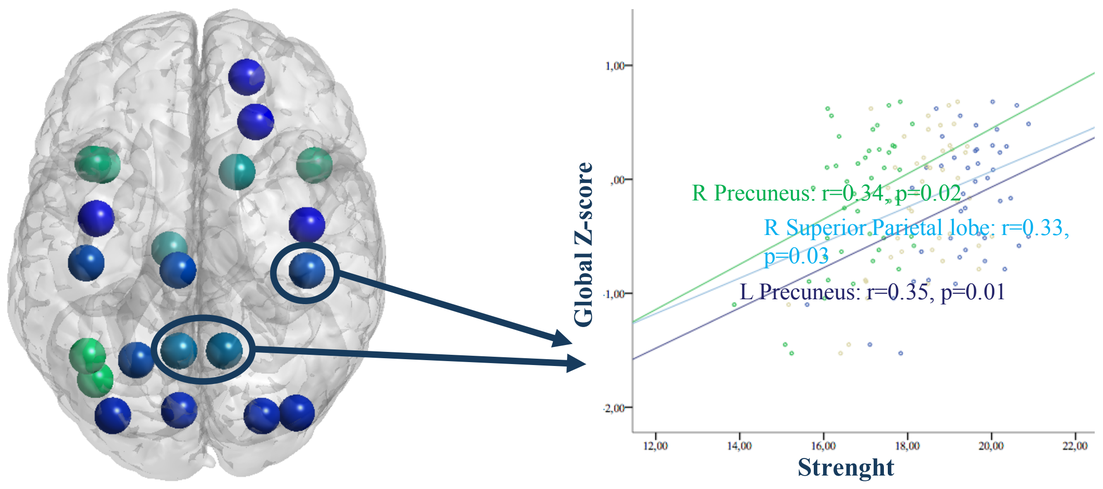


Abbreviations: STP= superior temporal pole; MTP= middle temporal Pole; PCG= pre-central gyrus; PCL= post-central lobule; MOG= middle occipital gyrus; SOG= superior occipital gyrus; SPL= superior parietal lobule; SFG= superior frontal gyrus, PoCG= post-central gyrus.

Correlation analysis:

- Significant correlations were found between nodal strenght and neuropsychological variables:
  - Global cognitive functioning showed significant positive correlation with the strength of connections of hubs located in the right superior parietal lobule and precuneus, bilaterally (**Figure 3**);
  - Impairment in language functions and verbal memory were significantly related to reduced strength of the hubs located in frontal and temporal lobes;
  - Visual-spatial memory, attention and information processing speed impairment were associated with a reduced strength of several hubs located in frontal, parietal and occipital lobes.

Figure 3. Correlations between Global Z score and nodal strenght.



CONCLUSIONS

- This study showed abnormalities in global network metrics in pediatric MS patients in comparison to matched HCs, with mild differences in hubs distribution suggesting a relative preservation of brain network structural architecture;
- A preserved brain architecture was also shown when comparing CI and CP MS patients;
- Our findings suggest that cognitive impairment in pediatric MS patients is likely to be mainly associated to a reduced strength of connections of structural hubs rather than local damage, resulting in alteration and loss of efficiency in information transmission

REFERENCES

1. Amato et al., Mult Scler 2016;
2. Till et al., Neuropsychol 2011;
3. Rocca MA et al., Neurology 2014;
4. Amato et al. Neurology, 2010;

DISCLOSURES

Ermelinda De Meo reporto no conflict of interests; 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., Elisabetta Pagani, Lucia Moiola, Pierangelo Veggiotti, Ruggero Capra, Laura Vacchi, Agnese Fiorino, Lorena Pippolo, Maria Carmela Pera and Andrea Falini report no conflict of interest. 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. 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. 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).

Acknowledgments

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).