SUPERFICIAL WHITE MATTER AND CORTICAL GRAY MATTER ABNORMALITIES IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS AND ASSOCIATION WITH COGNITIVE PERFORMANCE

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INTRODUCTION and PURPOSE

Superficial white matter (SWM) is a thin layer of white matter located beneath the cerebral cortex, composed primarily of cortico-cortical U-fibers that connect adjacent gyri. During development, SWM undergoes increased myelination, which is reflected by higher fractional anisotropy (FA) values [1]. In children and adolescents, age-related increases in FA within SWM are correlated with cortical thinning, a phenomenon potentially associated with selective synaptic pruning [2]. SWM plays a critical role in cortical information processing and integration [3] and is particularly vulnerable to multiple sclerosis (MS) pathology [4].

The aims of this study were: (1) to investigate the impact of pediatric-onset MS (POMS) on maturational changes in SWM FA, cortical thickness, and cortical volume; and (2) to assess the associations between impaired maturation of SWM, cortical thickness, and cortical volume, and clinical and cognitive outcomes in these patients.

METHODS

Subjects. A total of 105 patients with POMS, defined as disease onset before the age of 18, underwent clinical, cognitive, and MRI evaluations at San Raffaele Hospital in Milan, Italy. Two groups of healthy controls (HCs) were also included: (1) 34 age- and sex-matched HCs recruited at San Raffaele Hospital; and (2) 174 healthy children, adolescents, and young adults from the NIH-funded MRI Study of Normal Brain Development [5].

Clinical assessment. All POMS patients underwent clinical examination, including Expanded Disability Status Scale (EDSS) to assess global disability [6].

Cognitive assessment. In all study participants verbal memory was assessed using the Selective Reminding Test; information processing speed with the Digit Symbol Coding test; visuospatial abilities with the Block Design test; verbal reasoning and concept formation with the Similarities test; and word knowledge and concept formation with the Vocabulary test. All test scores were adjusted according to age-appropriate normative data [7,8,9,10].

MRI acquisition. Subjects enrolled at San Raffaele Hospital underwent 3.0 T MRI using two 3.0 Tesla scanners (Achieva and Ingenia; Philips Medical Systems). HCs from the NIH-funded MRI Study of Normal Brain Development were scanned at 1.5 T across five centers [5].

Conventional MRI analysis. Included T2-lesion volume assessment, and normalized brain volume quantification using the SIENAx software [11].

Cortical thickness and volume analysis. WM and GM surfaces were reconstructed from T1 weighted images using the FreeSurfer software, and cortical thickness and cortical volume were estimated. Regional values were averaged by lobe using the Desikan–Killiany atlas [12].

SWM analysis. The diffusion tensor was estimated in each voxel, and FA maps were derived using FMRIB's Diffusion Toolbox [13]. After registration to T1 weighted images, SWM FA was sampled at 3 mm depth beneath the WM surface and averaged per lobe using the Desikan–Killiany atlas [12].

Statistical analysis. Cortical thickness, volume, and SWM FA were normalized to age-, sex-, and site-adjusted reference values from HCs to compute z-scores. One-sample t-tests assessed deviations in POMS patients. Linear models examined associations with lesion volume and brain volume. Correlation analysis tested relationships with disease duration, EDSS, and cognition.

RESULTS

Table 1 shows the main demographic, clinical and MRI characteristics of study participants.

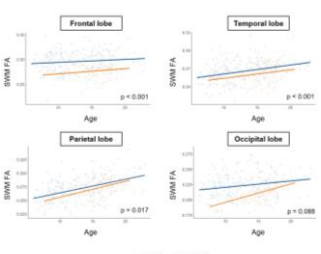
	POMS patients	SRH HC	NIH HC	p
Number	105	34	174	
Females, No (%)	71 (68)	17 (50)	89 (51)	0.10[a]
Age, median (IQR), y	15.6 (14.2 to 17.0)	15.3 (12.3 to 18.1)	11.7 (9.4 to 15.4)	0.82[a]
Disease duration, median (IQR), y	1.0 (0.4 to 2.2)	-	-	-
EDSS, median (IQR)	1.0 (1.0 to 1.5)	-	-	-
Subjects scanned with: Achieva Scanner/ Ingenia Scanner, No (%)	72 (69) / 33 (31)	22 (65) / 12 (35)	-	0.83[a]
T2 lesion volume, mean (SD), mL	5.4 (7.3)	0.0 (0.0)	-	**< 0.001[a]**
Normalized brain volume, mean (SD), mL	1654 (66)	1690 (69)	-	**< 0.001[a]**

Comparisons were performed using the Chi-squared test (sex), Mann-Whitney U test (age), and scanner-adjusted linear models (T2 LV transformed on a logarithmic scale and normalized brain volume).
Letters indicate significant differences as follows: [a]POMS patients vs SRH HCs.
Abbreviations: IQR=interquartile range; NIH HC=healthy controls from the NIH-funded MRI Study of Normal Brain Development; SD=standard deviation; SRH HC= healthy controls from San Raffaele Hospital.

Cortical thickness and volume. POMS patients exhibited decreased cortical thickness and cortical volume in all cortical lobes ($p \leq 0.002$).

SWM in POMS. As shown in **Figure 1**, reduced SWM FA values were detected in the frontal, temporal and parietal lobe in POMS patients.

Figure 1. Scatterplots with linear trend of FA of the SWM in POMS and HCs. POMS patients exhibited lower SWM FA than HCs in the frontal, temporal and parietal lobe. P values of the one-sample t-test on age-, sex- and scanner-adjusted SWM FA z-scores are reported.



Associations between cortical measures and SWM. z-SWM FA correlated with z-cortical thickness across lobes in both HCs (**Table 2**) and POMS (**Table 3**). z-SWM FA correlated with z-cortical volume in HCs (temporal, parietal, occipital lobes; **Table 2**), but in POMS only in the occipital lobe (**Table 3**).

Associations between brain volume, T2 lesion volume and SWM. In HCs, no significant associations with normalized brain volume were found (**Table 2**). In POMS, normalized brain volume was positively associated with frontal and parietal cortical thickness. Moreover, higher T2 lesion volume was associated with lower parietal cortical volume, lower SWM FA in temporal, parietal, and occipital lobes (**Table 3**).

Table 2. Correlations between FA of the SWM and cortical thickness and volume in HCs.

	z-SWM FA			
	Frontal	**Temporal**	**Parietal**	**Occipital**
NBV	NS	NS	NS	NS
z-cortical thickness				
Frontal	r=0.25, p<0.001	NS	r=0.23, p<0.001	r=0.15, p=0.031
Temporal	NS	r=0.17, p=0.016	r=0.15, p=0.032	NS
Parietal	r=0.26, p<0.001	r=0.24, p<0.001	r=0.38, p<0.001	r=0.28, p<0.001
Occipital	r=0.23, p<0.001	r=0.26, p<0.001	r=0.21, p=0.002	r=0.41, p<0.001
z-cortical volume				
Frontal	NS	r=0.17, p=0.012	NS	NS
Temporal	NS	r=0.18, p=0.009	NS	NS
Parietal	NS	r=0.24, p<0.001	r=0.15, p=0.032	r=0.20, p=0.003
Occipital	r=0.20, p=0.004	r=0.30, p<0.001	r=0.19, p=0.007	r=0.36, p<0.001

Table 3. Correlations between FA of the SWM and normalized brain volume, T2 lesion volume cortical thickness and volume in POMS.

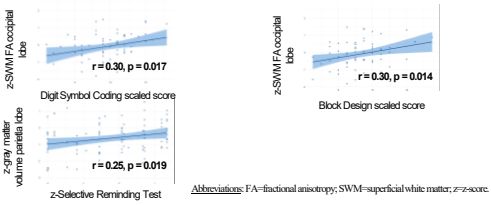
	z-SWM FA			
	Frontal	**Temporal**	**Parietal**	**Occipital**
NBV	NS	β=0.004, p=0.019	NS	NS
T2 lesion volume	NS	β=-0.66, p<0.001	β =-0.42, p=0.009	β=-0.32, p=0.024
z-cortical thickness				
Frontal	r=0.45, p<0.001	r=0.24, p=0.015	r=0.31, p=0.002	NS
Temporal	r=0.26, p=0.008	r=0.24, p=0.014	r=0.26, p=0.008	NS
Parietal	r=0.36, p<0.001	r=0.31, p<0.001	r=0.46, p<0.001	r=0.26, p=0.007
Occipital	NS	NS	NS	r=0.41 p<0.001
z-cortical volume				
Frontal	NS	NS	NS	NS
Temporal	NS	NS	NS	NS
Parietal	NS	NS	NS	NS
Occipital	NS	NS	NS	r=0.25, p=0.011

Association between z-SWM FA and NBV and logarithmic transformation of T2-lesion volume were evaluated using scanner-adjusted linear models.
Abbreviations: FA=fractional anisotropy; NBV=normalized brain volume; NS=not significant; SWM=superficial white matter.

Associations between clinical and cognitive measures and SWM. In POMS patients, no significant correlation was found between cortical thickness, cortical volume and SWM FA measures and disease duration and EDSS.

POMS patients showed unique associations not observed in HCs, including a positive correlation between verbal memory (SRT) and cortical volume of the parietal lobe and positive correlations between the FA of the SWM beneath the occipital lobe and tests of information processing speed (Digit Symbol Coding test) and visuospatial abilities (Block Design test) (**Figure 2**).

Figure 2. Scatterplots showing associations between MRI measures and cognitive outcomes in POMS patients.



Abbreviations: FA=fractional anisotropy; SWM=superficial white matter; z=z-score.

CONCLUSIONS

- **POMS is associated with impaired microstructural integrity of the SWM beneath the frontal, temporal and parietal lobe.**
- **POMS patients exhibit globally reduced cortical thickness and volume compared to age-expected values.**
- **The SWM beneath the occipital lobe appeared preserved, supporting visuospatial processing.**

REFERENCES

[1] Wu et al., Hum Brain Mapp, 2014
[2] Shaw et al., J Neurosci, 2008
[3] Colombo et al., Brain Struct Funct, 2018
[4] Buyukturkoglu et al., J Neuroimaging, 2022
[5] Walker et al., NeuroImage, 2016
[6] Kurtzke, Neurology, 1983
[7] Tedone et al., J Neurol, 2024
[8] Portaccio et al., Clin Neuropsychol, 2009
[9] Orsini & Pezzuti, 2013
[10] Orsini et al., 2012
[11] Battaglini et al., Hum Brain Mapp, 2012
[12] Desikan et al., J Neuroimage, 2006
[13] Basser et al., J Magn Reson, 1994