LONGITUDINAL PROGRESSION OF CORTICAL THINNING DIFFERS ACROSS MS PHENOTYPES AND IS CLINICALLY RELEVANT: A MULTICENTRE STUDY

M. Hidalgo de la Cruz[1,2], M. A. Rocca[1,3], P. Valsasina[1], C. Gobbi[4], A. Gallo[5], C. Zecca[4], A. Bisecco[5], M. Filippi[1,2,3]

[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]Vita-Salute San Raffaele University, Milan, Italy, [3]Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [4]Department of Neurology, Neurocenter of Southern Switzerland, Civic Hospital, Lugano, Switzerland; [5]Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, and MRI-Center "SUN-FISM", University of Campania "Luigi Vanvitelli", Naples, Italy.

INTRODUCTION and PURPOSE

Although MS was traditionally considered a white matter disease, the presence of widespread grey matter (GM) pathology has been recently demonstrated from the earliest stages of the disease [1]. In particular, atrophy of the cerebral cortex was found to be better correlated with clinical disability than white matter damage, and contributed to explain a variety of different clinical symptoms [2].

Cortical thickness (CTh) is a sensitive measure of cortical pathology [3], and surface-based analyses in MS patients consistently showed regional patterns of cortical thinning in frontal, temporal and parietal regions [4-11], which were correlated with clinical disability [4-6], cognitive impairment [6, 8], fatigue [7], depression [9] and the extent of white matter damage [5, 11]. Longitudinal investigations of cortical thinning in MS are still scanty [12, 13]. However, they have already demonstrated that a higher progression of CTh loss over time was associated with an earlier conversion to secondary progressive MS [13]. To date, the regional evolution of CTh abnormalities in the different disease phases has been not been fully characterized yet.

Against this background, aim of this study was to investigate the distribution and regional evolution over one year of CTh reduction in MS patients in a multicenter dataset, and to assess its relationship with concomitant progression of clinical disability.

METHODS

Subjects: **86** MS patients (75 relapsing remitting [RR] MS, 11 progressive [P] MS) and **34** healthy controls (HC), enrolled at **3 European sites** (San Raffaele Hospital, Milan, Italy; Regional Hospital of Lugano, Lugano, Switzerland; University of Campania "Luigi Vanvitelli", Naples, Italy).

Neurological assessment: at baseline and after 12 months, complete neurological assessment with rating of the EDSS score. At follow-up visit, clinical worsening defined as EDSS score increase ≥1 if baseline EDSS<6.0, ≥0.5 if baseline EDSS ≥6.

MRI acquisition (3.0 T scanners at all sites, <48h from neurological assessment): brain axial DE TSE and sagittal 3D T1-weighted MP-RAGE images.

MRI analysis: quantification of baseline and follow-up brain T2-hyperintense and T1-hypointense lesion volumes (LV) (*Jim7.0*); count of new T2-hyperintense and T1-hypointense lesions at follow-up; T1-hypointense lesion refilling of baseline and follow-up on 3D T1-weighted scans.

Baseline CTh and CTh changes over time (expressed as annualized percentage of cortical thinning compared to baseline [%]) assessed for each study subject using *Freesurfer 6.0* software and the longitudinal stream [14].

Statistical analysis: between-group comparisons of baseline CTh and CTh changes over time were calculated in MS patients *vs* HC, as well as between different MS phenotypes, using *a priori* comparisons based on disease clinical evolution. A comparison between clinically worsened and stable MS was also performed (age-corrected ANOVA models, *SPSS 22.0*).

Univariate models (Pearson's correlation coefficient, *SPSS 22.0*) were used to assess baseline correlations between clinical and CTh measures, as well as correlations between CTh changes over time and concurrent T2 LV changes.

RESULTS

Clinical and structural MRI measures: **Table 1** summarizes the main demographic, clinical and structural MRI characteristics of study participants.

Table 1.	HC (n=34)	MS (n=86)	*p*	RRMS (n=75)	PMS (n=11)	p^{Φ}	p^{Ω}
Sex (Female/Male)	19/15	51/35	0.8[a]	45/30	6/5	0.8[a]	0.8[a]
Baseline							
Mean age (SD) [years]	35.3 (9.2)	40.4 (12.4)	**<0.001[b]**	38.1 (11.7)	52.6 (9.5)	**0.001[b]**	**0.001[c]**
Median EDSS (IQR)	-	2.3 (1.0-3.5)	-	2.0 (1.0-3.0)	5.0 (3.0-6.5)	-	**<0.001[c]**
Median disease duration (IQR) [years]	-	8.7 (4.4-16.3)	-	7.3 (3.6-16)	14 (10-24)	-	**0.029[c]**
Median brain T2 LV (IQR) [ml]	-	3.1 (1.1-6.2)	-	3.3 (1.1-6.5)	2.4 (1.1-6.1)	-	0.9[c]
Median brain T1 LV [IQR] [ml]	-	2.0 (0.7-4.9)	-	2.0 (0.8-5.0)	1.7 (0.7-4.3)	-	0.7[c]
Left mean CTh (SD) [mm]	2.54 (0.12)	2.49 (0.1)	**0.014[b]**	2.49 (0.1)	2.46 (0.08)	**0.029[b]**	0.4[c]
Right mean CTh (SD) [mm]	2.54 (0.11)	2.49 (0.1)	**0.019[b]**	2.49 (0.1)	2.45 (0.09)	**0.041[b]**	0.3[c]
Month 12							
Median EDSS (IQR)	-	2.0 (1.0-3.8)	-	1.8 (1.0-3.3)	6.5 (4.0-6.5)	-	**<0.001[c]**
Median brain T2 LV (IQR) [ml]	-	2.9 (0.9-6.9)	-	3.1 (0.9-7.0)	2.1 (0.7-5.8)	-	0.4[c]
Median new T2 lesions (IQR)	-	0 (0-1)	-	0 (0-1)	0 (0-1)	-	0.9[c]
Median brain T1 LV (IQR) [ml]	-	2.0 (0.6-5.3)	-	2.3 (0.7-5.7)	0.9 (0.3-3.7)	-	0.2[c]
Mean percentage of left CTh changes *vs* baseline (SD) [%]	-0.21 (1.54)	-0.45 (1.65)	0.5[b]	-0.57 (1.62)	0.4 (1.70)	0.3[b]	**0.035[c]**
Mean percentage of right CTh changes *vs* baseline (SD) [%]	-0.04 (1.27)	-0.60 (1.81)	0.1[b]	-0.75 (1.71)	0.47 (2.2)	**0.032[b]**	**0.032[c]**

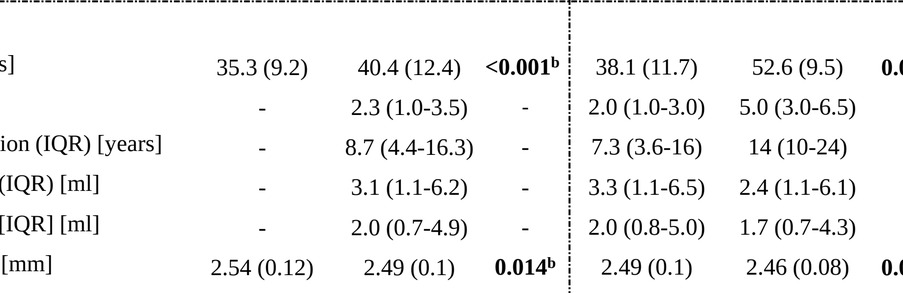
$^{\Phi}$RRMS *vs* HC; $^{\Omega}$PMS *vs* RRMS; [a]Pearson chi-square test, [b]Student's t-test, [c]Mann-Whitney-U test.

At follow-up, five RRMS patients evolved to SPMS and eight (9.3%) MS patients were clinically worsened.

CTh analysis:

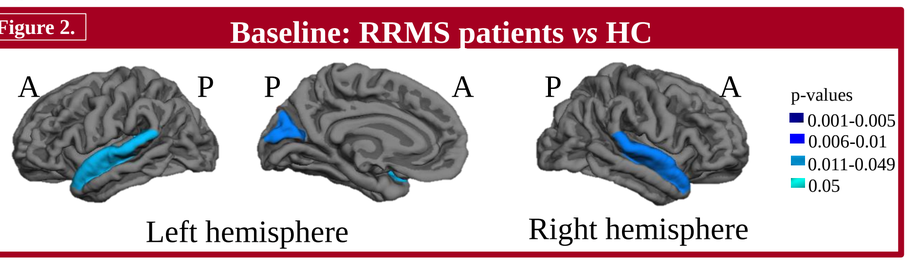
At baseline, **temporal** and **occipital** atrophy was found in **MS** patients *vs* HC (**Figure 1**).

Figure 1. Baseline: MS patients *vs* HC



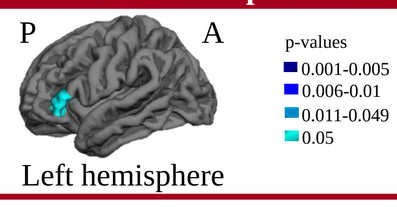
Baseline CTh loss in bilateral **superior temporal** and **occipital** regions was mainly driven by **RRMS** patients *vs* HC (**Figure 2**).

Figure 2. Baseline: RRMS patients *vs* HC



PMS patients showed additional CTh reduction in **inferior frontal** regions *vs* RRMS (**Figure 3**).

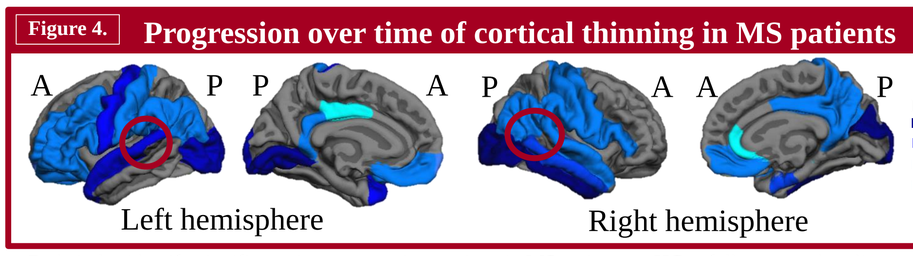
Figure 3. Baseline: PMS *vs* RRMS patients



During the follow-up, no CTh changes were observed in HC.

Significant cortical thinning over time was found in **MS** patients mainly in **frontal**, **parietal** and **temporal** areas, with significant time-by-group interactions in inferior frontal and temporal areas *vs* HC (**Figure 4**, p<0.01).

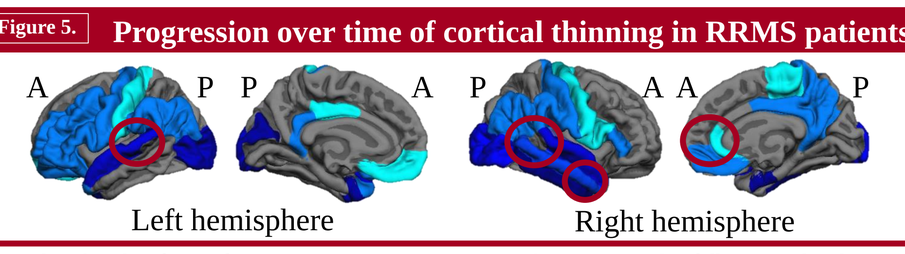
Figure 4. Progression over time of cortical thinning in MS patients



Red circles identify significant time x group interactions in MS patients *vs* HC at follow-up *vs* baseline

Significant cortical thinning over time was found in **RRMS** patients mainly in **superior frontal**, **parietal** and **occipital** cortices, with significant time-by group interactions in frontal and temporal areas *vs* HC (**Figure 5**, p<0.01).

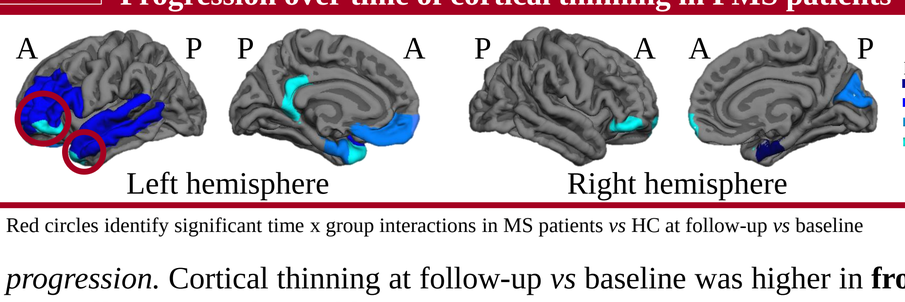
Figure 5. Progression over time of cortical thinning in RRMS patients



Red circles identify significant time x group interactions in MS patients *vs* HC at follow-up *vs* baseline

In **PMS** patients, cortical thinning mainly involved the **right occipital** and the **left inferior frontal and temporal** cortices, with a significant time-by-group interactions *vs* RRMS in these latter regions (**Figure 6**, p<0.01).

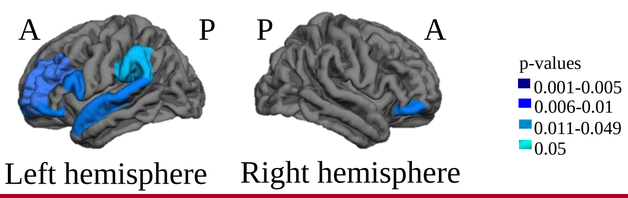
Figure 6. Progression over time of cortical thinning in PMS patients



Red circles identify significant time x group interactions in MS patients *vs* HC at follow-up *vs* baseline

Disability progression. Cortical thinning at follow-up *vs* baseline was higher in **frontal** and **temporal** regions in **clinically worsened** *vs* stable MS patients (p<0.01) (**Figure 7**).

Figure 7. Progression over time of cortical thinning in clinically worsened *vs* stable MS patients



Correlation analysis. In MS patients, a higher CTh decrease over time in the **right cuneus** correlated with a higher T2 LV at follow-up *vs* baseline (*r*=-0.27, p=0.017) (**Figure 8**).

Figure 8. Correlations between cortical thinning over time and concomitant T2 LV change

CONCLUSIONS

- The pattern of cortical atrophy highlighted a different regional susceptibility to MS-related neurodegenerative processes throughout the different phases of the disease.
- At baseline, **RRMS** patients were characterized by reduced thickness in **temporal** and **occipital** cortices, while **PMS** patients were distinguished by **inferior frontal** cortical atrophy.
- During the follow-up, one-year cortical thinning was predominant in **parietal** and **occipital** regions in **RRMS** patients, while **PMS** patients showed CTh loss mainly in **inferior frontal** and **temporal** areas.
- Notably, cortical thinning in such areas was crucial for identifying patients with more severe disability at follow-up.
- In MS patients, thinning over time in the right occipital cortex was related to a concomitant accrual of white matter lesions. Wallerian degeneration may be the predominant pathophysiological mechanism leading to cortical neurodegeneration in this region, while direct cortical damage (e.g., inflammation-mediated cortical demyelination) may be the predominant pathophysiological mechanism in the remaining cortical areas.
- One-year cortical thinning progression was variable across MS phenotypes and contributed to explain clinical worsening.

REFERENCES. [1] Filippi M, et al., *Journal of neurology*. 2015; [2] Rocca MA, et al., *Neurology*. 2017; [3] Fischl B, et al., *PNAS*. 2010; [4] Sailer M, et al., *Brain*. 2003; [5] Charil A, et al., *NeuroImage*. 2007; [6] Calabrese M, et al., *Neurology*. 2010; [7] Calabrese M, et al., *Mult Scler J*. 2010; [8] Tillema JM, et al., *Mult Scler J*. 2015; [9] Pravatà E, et al., *Mult Scler J*. 2017; [11] Jehna M, et al., *Ann Neurol*. 2015; [12] Magon S, et al., *BMC Neurosci*. 2014; [13] Scalfari A, et al., *Neurology*. 2018; [14] Reuter M, et al., *NeuroImage*. 2012.