INFLUENCE OF COGNITIVE IMPAIRMENT AND DEPRESSION ON CORTICAL THINNING IN PATIENTS WITH MULTIPLE SCLEROSIS

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INTRODUCTION

Gray matter (GM) atrophy develops early in patients with MS, due to a combination of demyelination and neuronal loss.

Neuroimaging investigations have provided evidence of a link between the development of regional GM atrophy and the occurrence of cognitive and behavioral abnormalities in MS patients.

Voxel-Based Morphometry (VBM) studies have shown a widespread pattern of GM loss in prefrontal, parietal, cerebellar, as well as in hippocampal, insular and cingulate regions in MS patients with cognitive impairment.[1,2] Moreover, using VBM, an association has been found between depression and selective GM atrophy of the left middle frontal and right inferior frontal gyri.[3]

Cortical thickness (CT) analysis is a valid alternative technique to VBM to assess regional GM volume.[4] Compared to VBM, CT presents some advantages: it is not influenced by potential confounds represented by folding morphology and partial volume effects[5] and it may provide a more specific estimation of neuronal density and size, thus contributing to describe more accurately disease-related neuronal changes.

Previous CT studies detected significant cortical thinning in cognitively impaired (CI) *vs* cognitively preserved (CP) MS patients in temporo-frontal[6] and temporo-parietal[7] regions.

The combined effect of depression and cognitive impairment on cortical volume in MS patients has not been investigated yet.

OBJECTIVES

To Explore the association between cortical GM volume modifications and cognitive impairment and depression in patients with MS.

To define the specificity of regional cortical volume abnormalities in relation to the presence of cognitive impairment or depression.

METHODS

High-resolution T1-weighted scans were acquired from 126 MS patients and 59 matched healthy controls (HC). Exclusion and inclusion criteria are explained in **Table 1.**

Differences of cortical thickness between HC and MS patients and between patient subgroups were assessed using FreeSurfer. The following corrections were performed: intensity correction to enhance the contrast between WM and GM with a custom-made script written in Matlab; removal of extra-cerebral structures with watershed algorithms and deformable surface models; segmentation of GM, WM and CSF, estimation of GM/WM and GM/CSF boundaries; surface inflation and registration to spherical atlas, parcellation of cortex into 34 regions per hemisphere [8].

Table 1. Exclusion and inclusion criteria, clinical evaluation and MRI acquisition.

Study population	Clinical evaluation	MRI acquisition
Exclusion criteria (MS and HC) No significant medical illnesses or substance abuse, history of psychiatric, cardiovascular or neurological diseases **Inclusion criteria (MS only)** Diagnosis of MS Relapse- and steroid-free within the previous 3 months Fatigue severity scale (FSS) < 4, to avoid possible confounding effect of fatigue	**Neurological assessment** Expanded Disability Status Scale **(EDSS)** **Cognitive impairment** ≥2 abnormal tests (≥2 SD below the normative italian values)[9] in the Brief-Repeatable Battery of Neuropsychological Tests **(B-RBNT)** **Depression** Montgomery-Asberg Depression Rating Scale **(MADRS)** ≥ 9	**Structural MRI (3.0 T scanner)** Axial DE TSE Axial 3D T1-weighted FFE: TR/TE=25/4.6 ms, FA=30, FOV=230x230mm^2,matrix=256x256, slice thickness=1 mm, 220 contiguous slices **MRI analysis** Quantification of T2 lesion volume (LV) **(Jim6.0 software)** Refilling of T1-hypointense lesions,[10] quantification of normalized brain volume (NBV), GM and white (WM) matter volumes **(SIENAx software)** Cortical reconstruction and thickness estimation performed with the **Freesurfer** image analysis suite, version 5.3 (http://surfer.nmr.mgh.harvard.edu/)

Statistical analysis

Vertex-by-vertex analysis (general linear model, as implemented in Freesurfer Qdec toolbox): between-group comparisons of cortical thickness.
The following effects have been tested (all analyses adjusted by sex as nuisance covariate):

- **Main effect of disease (HC *vs* MS patients),**
- **Main effect of depression (D *vs* nD MS patients),**
- **"Pure" effect of depression (D *vs* nD in CP MS patients only),**
- **Main effect of cognitive impairment (CI *vs* CP MS patients),**
- **"Pure" effect of cognitive impairment (CI *vs* CP in nD MS patients only),**
- **Interaction between depression and cognitive impairment (conjunction analysis).**

RESULTS

65 MS patients (51%) were classified as D, while 34 MS patients (27%) were CI. 15 patients had the concomitant presence of depression and cognitive impairment (12%).

Table 1. Demographic, clinical and structural MRI characteristics of HC, MS patients, nD-MS, D-MS, CP-MS, CI-MS.

	HC (59)	MS (126)	p	nD MS (61)	D MS (65)	p	CP MS (92)	CI MS (34)	p
Men/Women	31/28	74/52	0.4$^+$	29/32	45/20	0.02$^+$	57/35	17/17	0.3$^+$
Mean age (SD)[years]	37.9 (9.6)	37.4 (11.7)	0.6*	37.1 (10.1)	37.6 (13.1)	0.9*	36.1 (11.8)	40.7 (11.1)	0.5*
Mean DD (SD) [years]	-	11.5 (0.8-36)	-	12.1 (1-26)	10.9 (0.8-36)	0.1*	10.7 (0.8-26.6)	13.5 (1.4-36)	0.6*
Median EDSS (range)	-	1.5 (0-8.0)	-	1.5 (0-7.0)	1.5 (0-8.0)	0.8*	1.5 (0-8.0)	2.0 (0-7.0)	0.2*
T2 LV (SD) [ml]	-	8.1 (9.0)	-	8.2 (9.9)	8.0 (8.2)	0.7*	6.0 (6.2)	14.0 (12.6)	<0.001*
Mean NBV (SD) [ml]	1572 (79)	1533 (98)	0.01*	1526 (103)	1540 (93)	0.4*	1551 (92)	1482 (97)	<0.001*

Main effect of disease (MS patients *vs* HC)

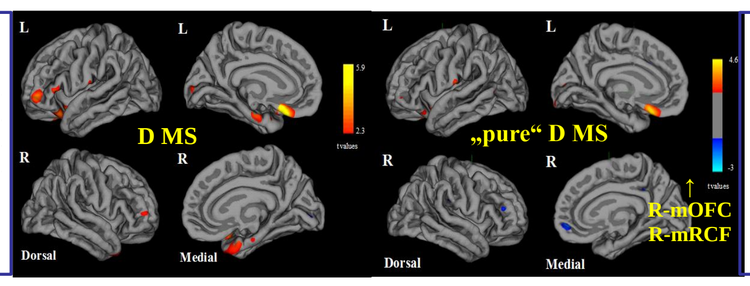
Compared with controls, MS patients had a widespread bilateral cortical thinning involving all brain lobes.

Main (D *vs* nD in MS patients) and "pure" (D *vs* nD in CP MS patients) effects of depression

Compared with nD, D MS patients had cortical thinning of the frontal and temporal lobes (B)
D MS patients also experienced increased cortical thickness in the right medial orbito-frontal and rostral middle-frontal cortex (**Figure 1**).

Figure 1. Main effect of depression (D MS *vs* nD MS and D *vs* nD in CP MS patients).

Thinning of B-OFC, B-rostral MFC, L-insula, L-IFG, L-PHG, L-pericalcarine cortex, L-enthorinal cortex).



Thinning of L-medial OFC, L-post-central gyrus, L-lateral occipital cortex.

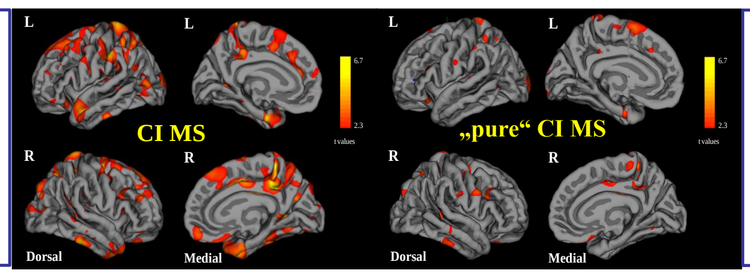
Thickening of R-medial OFC and rostral MFC in "pure" D MS.

Main (CI vs CP MS patients) and "pure" (CI vs CP in nD MS patients) effect of cognitive impairment

Compared with CP, CI MS patients had decreased cortical thickness in several bilateral regions of the frontal, temporal and parietal lobes.
Cognitive impairment had a selective effect on cortical thinning of the bilateral superior frontal gyrus, bilateral superior parietal lobule, left entorhinal cortex and right precuneus (**Figure 2**).

Figure 2. Main effect of cognitive impairment (CI MS *vs* CP MS and CI *vs* CP in nD MS patients).

Thinning of B-SFG, B-MFG, B-OFC, L-STG, B-ITG, L-supramarginal gyrus, B-SPL, B-IPL, B-PCC, R-precuneus, B pre/postcentral Gyri, L-entorhinal cortex, B-lingual gyrus, R-IFG.

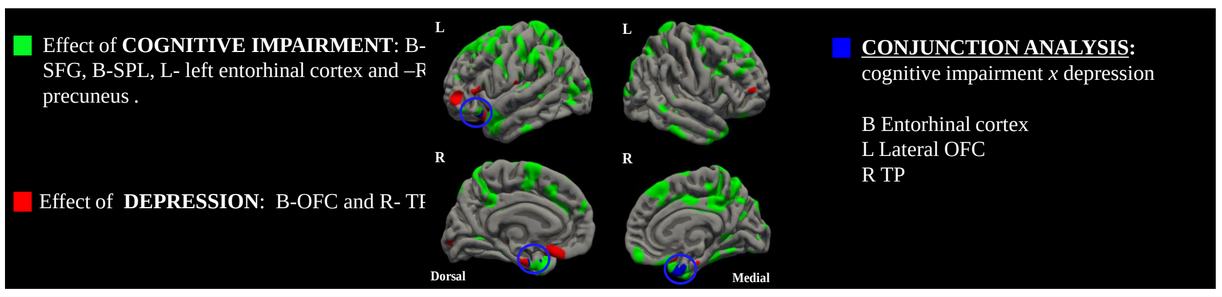


Thinning of B-SFG, R-MFG, B-OFC, BSTG, B-ITG, B-supramarginal gyrus, B-SPL, R-IPL,R-PCC, R-precuneus, B pre/postcentral Gyri, L-entorhinal cortex, L-lateral occipital cortex.

Effect of depression and cognitive impairment (conjunction analysis)

Cognitive impairment had a selective effect on cortical thinning of the bilateral superior frontal gyrus, bilateral superior parietal lobule, left entorhinal cortex and right precuneus, whereas depression affected cortical thinning of the bilateral orbitofrontal cortex and right temporal pole (**Figure 3**).

Figure 3. Interaction between depression and cognitive impairment (conjunction analysis).



CONCLUSIONS

Effect of depression: D MS patients showed GM loss in lateral orbitofrontal, middle and inferior frontal regions. In D MS patients, increased thickness of the medial OFC and rostral MFC was also found. These regions are known to be involved in introspective mental activity and regulation of negative emotions.
Effect of cognitive impairment: a widespread pattern of cortical GM loss was found in CI *vs* CP MS patients, mainly involving the posterior parietal, cingulate, superior and orbital frontal, anterior temporal and entorhinal cortices. All these regions are known to take part in a wide range of cognitive functions, including executive control, working memory, verbal fluency and problem solving, which are frequently hit by MS.
Interaction between depression and cognitive impairment: depression and cognitive impairment were both related to atrophy of the bilateral entorhinal cortex, left lateral orbitofrontal cortex and temporal pole. These regions are known to be interconnected and play a key role in introspective functions, emotional and stimulus-reinforcement association learning, and social cognition

REFERENCES

[1]Morgen et al., 2005; [2]Riccitelli et al., 2011; [3]Gobbi et al., 2014; [4]Fischl et al., 2000; [5]Hutton et al., 2009; [6]Calabrese et al., 2010; [7]Tillema et al., 2015; [8]Desikan et al., 2006; [9]Amato et al., 2006; [10]Chard et al., 2010.

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