LESION LOCATION AND FUNCTIONAL CONNECTIONS REVEAL COGNITIVE IMPAIRMENT NEWORKS IN MULTIPLE SCLEROSIS

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INTRODUCTION and PURPOSE

Cognitive impairment, fatigue, and depression are common in multiple sclerosis (MS) patients. White matter (WM) lesion accumulation in strategic brain regions may disrupt regional functional connectivity, contributing to these symptoms. By mapping the intrinsic functional brain connections disrupted by T2-hyperintense WM lesions using a large external normative connectome of the human brain [**1**], lesion network mapping (LNM) has been recently proposed to explore how lesions with heterogeneous sizes and topographies may be associated with similar clinical manifestations due to shared functional connectivities with specific brain regions [**2,3**].

Here we explored whether the location of T2-hyperintense WM lesions in strategic brain regions, and the specific involvement of brain regions functionally connected to such lesions may contribute to these manifestations.

METHODS

- **Subjects.** 596 MS patients.
- **Neurological evaluation.** Disease duration, EDSS score, MS clinical phenotype (relapsing-remitting [RR]; progressive [P]), ongoing disease modifying treatment (DMT).
- **Neuropsychological evaluation**

-Cognitive performance: Brief Repeatable Battery of Neuropsychological tests (BRB-N). Global cognitive impairment: ≥2 impaired cognitive domains (≥1 test of BRB-N assessing that domain with a score 1.5 standard deviations below normative values). Cognitive impairment in specific domains (information processing speed, verbal memory, visual memory and verbal fluency): ≥1 abnormal neuropsychological tests of BRB-N for each domain.

-Depression: Montgomery-Asberg Depression Rating Scale (MADRS) score ≥9.

-Fatigue: Modified Fatigue Impact Scale (MFIS) score ≥38.

- **Brain MRI acquisition (3.0 Tesla scanners).** Scanner 1: (a) dual-echo (DE) turbo spin-echo (TSE), (b) 3D T1-weighted fast field echo (FFE); scanner 2: (a) 3D fluid attenuated inversion recovery (FLAIR); (b) 3D T1-weighted turbo field echo (TFE).
- **Conventional MRI analysis.** Quantification of T2-hyperintense WM lesion volume (LV) [Scanner 1: semi-automatic local thresholding segmentation technique; Scanner 2 (**Figure 1A**): fully automated approach based on a cascade of two 3D patch-wise convolutional neural networks]. Normalized brain volume (NBV) was also calculated [FSL SIENAx].
- **T2-hyperintense lesion probability mapping (LPM). a)** Creation of T2-hyperintense WM lesion masks of each MS patient and **b)** co-registration to standard MNI space (**Figure 1B**); **c)** lesion masks of MS patients' groups based on presence or absence of cognitive impairment, fatigue or depression are averaged to obtain T2-hyperintense WM LPMs, colored in green for absence and in red for presence; **d)** T2 LPM are compared in a voxel-wise manner between impaired and preserved MS patients [Statistical non-Parametric Mapping (SnPM) toolbox included in SPM12, non parametric models with 5000 permutations adjusted for scanner, age, sex and EDSS score, p<0.05 cluster-wise family wise error (FWE)-corrected] (**Figure 1C**).
- **T2-hyperintense WM lesion network mapping (LNM). e)** Lesion masks of MS patients were utilized as seeds for resting state (RS) functional connectivity (FC) analysis, computed on pre-processed RS functional MRI data from a publicly available large cohort of 1000 HC acquired for the brain Genomics Superstruct Project (GSP) **[1].** RS FC maps obtained for each lesion mask from the 1000 HC are then averaged [SPM12 one-sample t test]. Corresponding T maps are LNMs, which undergo between group-comparison in a voxel-wise manner (e.g., presence *vs* absence of the symptom) using SPM12 [full factorial model adjusted for scanner, age, sex and EDSS score, p<0.05 cluster-wise FWE-corrected] (**Figure 1D**).

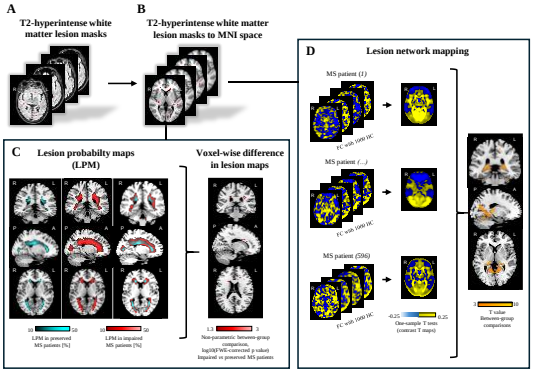

Figure 1. Schematic representation of study methodology to explore between-group differences in T2-hyperintense WM LPMs and LNM according to cognitive, fatigue and depression status.

RESULTS

Table 1 shows the main demographic, clinical and MRI features of cognitively-preserved and cognitively-impaired MS patients.

Table 1.

	Cognitively-preserved MS patients (n=434)	Cognitively-impaired MS patients (n=162)	p-value
Sex (%): Women/Men	262 (60) /172 (40)	88 (54) /74 (46)	0.182[a]
Mean age (SD) [years]	42.8 (11.3)	46.2 (11.5)	**0.001**[b]
Mean disease duration (SD) [years]	12.3 (9.6)	15.5 (9.9)	**<0.001**[b]
Median EDSS score (IQR)	2.0 (1.5;5.0)	4.5 (2.0;6.0)	**<0.001**[c]
Clinical phenotype (%): RR/P	305 (70) / 129 (30)	78 (48) / 84 (52)	**<0.001**[a]
Ongoing DMT (%): none/1st line/2nd line	85 (20) /184 (42) /165 (38)	49 (30) /58 (36) /55 (34)	**0.021**[a]
Median education (IQR) [years]	13.0 (9.3;17.8)	13.0 (8.1;17.2)	0.631[c]
Mean MFIS (SD)[e]	29.7 (16.5)	39.8 (19.1)	**<0.001**[b]
Mean MADRS (SD)[f]	9.0 (7.7)	9.9 (7.2)	0.296[b]
Median T2- hyperintense WM LV (IQR) [ml][g]	3.3 (1.2;7.2)	10.0 (3.6;19.6)	**<0.001**[b]
Estimated mean NBV (SE) [ml]	1538 (3)	1492 (5)	**<0.001**[b]

[a]Chi-square test; [b]Two sample t test; [c]Mann-Whitney U test; [d]First line = glatiramer acetate, interferon beta 1a, teriflunomide or dimethyl fumarate; Second line=fingolimod, siponimod, ozanimod, natalizumab, cladribine, anti-CD20 (ocrelizumab, rituximab, ofatumumab) and other immunosuppressants; [e]Available for 493 out of 596 MS patients. [f]Available for 495 out of 596 MS patients. [g]Comparison performed on log-scale. [h]Age-adjusted, scanner-adjusted and sex-adjusted linear regression model.

- **Global cognitive function**. **Figure 2** shows A) LPMs of cognitively impaired (in red) and preserved (in cyan) MS patients; B) difference of lesion distribution between cognitively impaired and preserved MS patients (in red); C) difference of LNMs between cognitively impaired and preserved MS patients (in orange); D) overlay of the differences in LNM (in orange) and LPM (in red) between cognitively impaired and preserved MS patients.

Global cognition

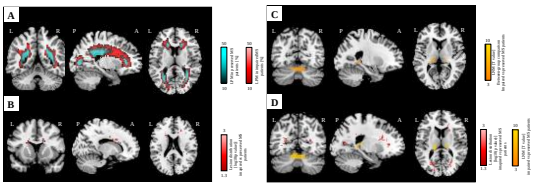

Figure 2. LPM and LNM findings according to performance in global cognitive function.

- **Between-group comparisons in information processing speed/attention and verbal memory**. **Figure 3** shows (A, E) LPM of prerserved (cyan) or impaired MS patients (red); (B and F) difference of lesion distribution between MS patients impaired and preserved (in red), (C and G) Difference of LNMs between MS patients impaired and preserved (in orange). (D-H) Overlay of the differences in LNM (in orange) and LPM (in red) between impaired and preserved MS patients.

Information processing speed/attention **Verbal memory**

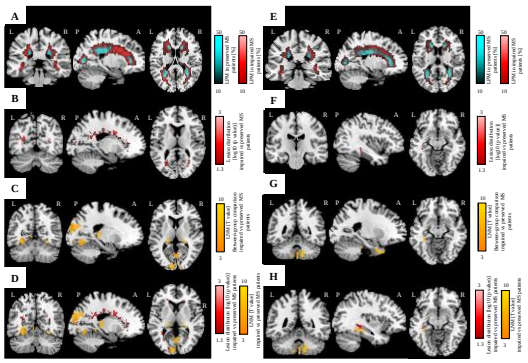

Figure 3. LPM and LNM findings according to performance in information processing speed/attention and verbal memory.

- **Between-group comparisons in verbal fluency and visual memory**. **Figure 4** shows (A and C) LPM between prerserved (cyan) and impaired (red); (B) Difference of LNMs between MS patients impaired and preserved (orange).

Verbal fluency **Visual memory**

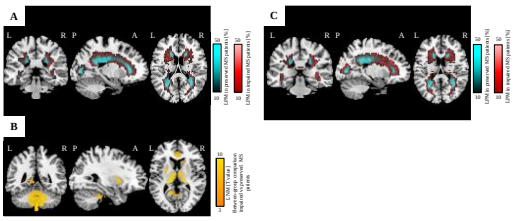

Figure 4. LPM and LNM findings according to performance in verbal fluency and visual memory.

- **Fatigue and depression**. Among MS patients, 184/493 (37.3%) patients were classified as fatigued, whereas 192/495 (38.8%) patients were classified as depressed. No difference in LPM and LNM were found according to fatigue and depression status.

CONCLUSIONS

- **Compared to those preserved, cognitively-impaired MS patients (and similar for those with impaired processing speed) had significantly higher prevalence of WM lesions in several cognitively-relevant WM tracts that were more functionally connected to bilateral hippocampi, thalami, cerebellum, and occipital cortices.**
- **MS patients impaired in verbal memory had significantly more widespread WM lesions being functionally connected to the parahippocampi, temporal pole and cerebellum than those preserved.**
- **No significant difference in regional WM lesion distribution was found based on verbal fluency performance, but WM lesions in MS patients with impaired verbal fluency were more connected to the thalami, putamen, caudate nuclei, anterior cingulate cortex and cerebellum compared to preserved patients.**
- **MS patients with impaired visuospatial memory showed no significant lesion distribution or network connectivity differences compared to preserved patients.**
- **No significant lesion distribution or network connectivity differences were found in patients with fatigue or depressive symptoms.**
- **WM lesion accumulation in specific brain regions may disrupt intrinsic connections in strategic brain regions contributing to global and specific cognitive impairment. Other pathological processes, independent from focal WM lesion accumulations, may be more relevant for fatigue and depression.**

REFERENCES

[1] Cohen A et al., GSP1000 Preprocessed Connectome. 2020. [2] Boes AD et al., Brain. 2015 [3] Fox MD et al., N Engl J Med. 2018