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ORIGINAL ARTICLE

Grey matter damage in progressive multiple sclerosis versus amyotrophic lateral sclerosis: a voxel-based morphometry MRI study

Eleonora Tavazzi · Maria Marcella Laganà · Niels Bergsland · Paola Tortorella · Giovanna Pinardi · Christian Lunetta · Massimo Corbo · Marco Rovaris

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Abstract Primary progressive multiple sclerosis (PPMS) and amyotrophic lateral sclerosis (ALS) seem to share some clinical and pathological features. MRI studies revealed the presence of grey matter (GM) atrophy in both diseases, but no comparative data are available. The objective was to compare the regional patterns of GM tissue loss in PPMS and ALS with voxel-based morphometry (VBM). Eighteen PPMS patients, 20 ALS patients, and 31 healthy controls (HC) were studied with a 1.5 Tesla scanner. VBM was performed to assess volumetric GM differences with age and sex as covariates. Threshold-free cluster enhancement analysis was used to obtain significant clusters. Group comparisons were tested with family-wise error correction for multiple comparisons ($p < 0.05$) except for HC versus MND which was tested at a level of $p < 0.001$ uncorrected and a cluster threshold of 20 contiguous voxels. Compared to HC, ALS patients showed GM tissue reduction in selected frontal and temporal areas, while PPMS patients showed a widespread bilateral GM volume decrease, involving both deep and cortical regions. Compared to ALS, PPMS patients showed tissue volume reductions in both deep and cortical GM areas. This preliminary study confirms that PPMS is characterized by a more diffuse cortical and subcortical GM atrophy than ALS and that, in the latter condition, brain damage is present outside the motor system. These results suggest that PPMS and ALS may share pathological features leading to GM tissue loss.

Keywords Multiple sclerosis · Amyotrophic lateral sclerosis · Grey matter · MRI · Voxel-based morphometry

M. M. Laganà and N. Bergsland equally contributed to the project.

E. Tavazzi · P. Tortorella · G. Pinardi · M. Rovaris (✉)
Unit of Motor Neurorehabilitation, Multiple Sclerosis Center, Scientific Institute Santa Maria Nascente, Fondazione Don Gnocchi, via Capecelatro 66, 20148 Milan, Italy
e-mail: mrovaris@dongnocchi.it

M. M. Laganà · N. Bergsland
MR Research Laboratory, IRCCS Santa Maria Nascente, Fondazione Don Gnocchi, Milan, Italy

N. Bergsland
Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy

N. Bergsland
Buffalo Neuroimaging Analysis Center, Department of Neurology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

C. Lunetta · M. Corbo
NEuroMuscular Omnicentre (NEMO), Niguarda Hospital, Milan, Italy

Introduction

A growing body of evidence shows that in multiple sclerosis (MS), both inflammation and neurodegeneration play a fundamental role from the early stages in determining tissue damage and disability accrual [1]. This is more evident in the primary progressive (PP) form, characterized by a scarce inflammatory activity at MRI and a progressive accumulation of clinical disability [2]. Contrarily, motor neuron disorders (MND), including amyotrophic lateral sclerosis (ALS), have always been classified as neurodegenerative diseases selectively affecting the motor system [3], but it is now clear that inflammation plays a role in driving tissue damage [4]. In both MS and ALS, however,

the relationship between inflammation and neurodegeneration and their relative contribution to the progression of the diseases remain partially unknown. Epidemiological studies have shown a possible association between MS and ALS [5–8], although not confirmed by others [9, 10]. Few case reports have also described comorbidities between MS and ALS [6, 11, 12]. Thus, it is conceivable that comparative studies may be helpful to improve our understanding of MS and ALS.

Advanced MRI has been applied to describe white matter (WM) and grey matter (GM) involvement in MS and ALS. In particular, published data report a significant cortico-spinal WM involvement in both diseases, although, in ALS, axonal pathology seems to be purely responsible for the damage [13] whereas in MS both demyelination and axonal degeneration seem to play a role [14]. As regards GM, several studies have shown that tissue loss is more widespread in secondary progressive than in relapsing-remitting and PPMS [15]. ALS shows cortical thinning [16] and regional GM loss in motor [17] and extra-motor areas [18], especially when cognitive impairment is present.

Against this background, the present voxel-based morphometry (VBM) MRI study was performed to compare the regional patterns of GM tissue loss in PPMS and ALS. The aim was to further investigate the determinants of the progressive neurological dysfunction characterizing both these conditions.

Materials and methods

Subjects

Patients with PPMS and with ALS, diagnosed according to international consensus criteria [3, 20], were consecutively recruited from the Motor Neurorehabilitation Unit—Multiple Sclerosis Center, IRCCS Santa Maria Nascente, Fondazione Don Gnocchi, and the NEmo Clinical Center, Niguarda Ca' Granda Hospital. To be included, MS patients had to be steroid-free for at least 3 months. All patients underwent neurological examination. Clinical disability was quantified by the expanded disability status scale (EDSS) in MS and by the ALS Functional Rating Scale (ALSFRS) in ALS. Healthy controls (HC) with no history of neurological, cardiovascular or metabolic disorders, and a normal neurological examination were also studied.

The study was approved by the "Don Carlo Gnocchi Foundation" ethics committee, Milan, and a written informed consent was obtained from all subjects prior to study entry.

MRI acquisition

For all subjects, brain MRI was acquired at the Radiology Service of Fondazione Don Carlo Gnocchi, using a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany) with a 12-channel head matrix coil. After the acquisition of a low-resolution T1-weighted localizer sequence, the following two anatomical sequences were obtained: (1) dual-echo turbo spin echo [repetition time (TR) = 2,650 ms; echo time (TE) = 28/113 ms; echo train length = 5; flip angle = 150; 50 contiguous 2.5-mm thick axial slices; matrix size = 256 × 256, interpolated to 512 × 512, and field of view (FOV) = 250 × 250 mm^2]; (2) 3-dimensional T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) [TR = 1,900 ms; TE = 3.37 ms; inversion time (TI) = 1.100 ms; flip angle = 15; 176 contiguous, 1-mm thick axial slices; matrix size = 192 × 256; FOV = 192 × 256 mm^2]. For both sequences, all slices were acquired parallel to the subcallosal plane.

MRI processing and analysis

MRI data were transferred to a workstation with Centos (Linux) operating system, where all processing were performed. WM lesions were segmented by an expert neurologist on the proton density-weighted scans, using the corresponding T2-weighted images to increase confidence in lesion identification, with Jim software (Jim 5.0, Xinapse Systems,Leicester, UK). Using a semi-automated local thresholding technique, brain lesion load (LL) was then computed. 3D T1 images were corrected for intensity inhomogeneity using the N3 tool [19]. To avoid T1 hypointensities misclassification during segmentation, 3D T1 images were preprocessed using the "lesion_filling" tool from FSL [21].

The next steps were performed with the scripts of the FSL-VBM protocol [22]. The brain of each lesion-filled 3D T1 images was GM segmented before being non-linearly registered to the MNI 152 standard space. A study-specific GM template was constructed from GM images of 18 subjects from each group. Native GM images were then non-linearly registered to the template and modulated with the Jacobian of the warp field [23] and smoothed with a Gaussian kernel of sigma = 3 mm (FWHM ≈ 6.9 mm).

Local maxima were mapped using atlases provided as part of the FSL distribution (Harvard-Oxford Structural Cortical and MNI Structural).

Statistical analysis

We used Kruskal–Wallis and Chi squared tests for assessing age and sex group differences, respectively. GM

Table 1 Clinical features of HC, ALS and PPMS patients

	HC	ALS	PPMS	*p*
Number of subjects	31	20	18	–
Age	47.9 ± 14.5	54.5 ± 9.1	46.9 ± 8.1	0.052
Gender [M/F (%M)]	11/20 (35 %)	11/9 (55 %)	12/6 (67 %)	0.09
Disease duration		30.6 ± 18.3	149.3 ± 92.8	<0.001
EDSS	–	–	6.0 (3–8)	–
ALSFRS	–	34.5 (17–40)	–	–

Age is expressed in years, disease duration in months. Age and disease duration are reported as mean ± standard deviation. EDSS and ALSFRS are reported as median (range), gender is reported as number of males (M), females (F) and male percentage

volume topographic statistical differences among the groups were assessed with general linear model (GLM), including age and sex as covariates. The threshold-free cluster enhancement (TFCE) analysis was used to obtain significant clusters. The TFCE images were then turned into voxel-wise p-values via permutation non-parametric testing (5,000 permutations). Family-wise Error (FWE) correction across space with $p < 0.05$ was used for handling multiple comparisons, with the exception of HC vs. ALS, which was tested at a significance level of $p < 0.001$ (uncorrected) and a cluster threshold of 20 contiguous voxels. Contrasts surviving the initial FWE correction were further investigated after applying Bonferroni correction.

Results

Clinical characteristics of the subjects are summarized in the Table 1. As expected, disease duration was significantly longer in PPMS than in ALS patients. ALS patients were older than PPMS patients, but the difference was not statistically significant. Clinical disability was, on average, moderate in ALS patients, as indicated by the ALSFLS score. Mean brain LL in MS patients was 11.1 ml (standard deviation: 9.2 ml). No T2-hyperintense MRI lesions were detected in healthy control subjects and in ALS patients, whose LL was, therefore, not computed. VBM findings are presented in Table 2 and detailed hereafter.

VBM analysis: ALS patients vs. HC

The clusters of significant GM loss in ALS patients compared to HC, corrected for age and sex, are shown in Fig. 1a, b. MND showed GM atrophy in left superior temporal gyrus (Brodmann area (BA) 22, part of Wernicke's area involved in auditory processing and language

Table 2 Clusters of significant GM differences between subjects' groups at VBM analysis

ALS patients vs. healthy controls*				
Anatomical regions	MNI coordinates			*p* values
	x	*y*	*z*	
Cluster 1 (181 voxels)				
R precentral gyrus	**34**	**−18**	**42**	**<0.001**
R precentral gyrus	28	−14	50	<0.001
Cluster 2 (59 voxels)				
L precentral gyrus	−54	6	8	**<0.001**
L inferior frontal gyrus	−54	10	8	<0.001
Cluster 3 (49 voxels)				
L superior temporal gyrus	**−60**	**−8**	**−6**	**<0.001**
L precentral gyrus	−54	−14	−8	<0.001
Cluster 4 (24 voxels)				
R superior frontal gyrus	10	50	22	<0.001
PPMS patients vs. healthy controls				
Cluster 1 (7818 voxels)				
R parahippocampal gyrus	**18**	**−18**	**−26**	**<0.001**
R thalamus	22	−18	−2	<0.001
L thalamus	−10	−18	−2	<0.001
L insula	−34	4	6	<0.001
L putamen	−24	16	−2	<0.001
Cluster 2 (660 voxels)				
R precentral gyrus	**48**	**2**	**18**	**0.002**
R insular cortex	32	−10	14	0.004
R inferior frontal gyrus	48	12	20	0.002
Cluster 3 (548 voxels)				
L parietal operculum cortex	**−58**	**−28**	**14**	**<0.001**
L parietal operculum cortex	−52	−30	20	<0.001
L supramarginal gyrus	−56	−24	28	0.004
L postcentral gyrus	−60	−20	28	0.008
Cluster 4 (129 voxels)				
L cingulate gyrus	**−8**	**−44**	**16**	**0.005**
R posterior cingulate gyrus	10	−36	26	0.005
Cluster 5 (54 voxels)				
R superior temporal gyrus	**62**	**−6**	**2**	**0.007**
Cluster 6 (20 voxels)				
L superior frontal gyrus	−22	30	34	0.008
Cluster 7 (14 voxels)				
L paracingulate gyrus	**0**	**40**	**22**	**0.007**
PPMS vs. ALS patients				
Cluster 1 (2233 voxels)				
L thalamus	**−2**	**−6**	**8**	**<0.001**
L thalamus	−12	−10	4	<0.001
R thalamus	4	−8	0	<0.001
R caudate nucleus	4	16	6	0.007

Global maxima are reported in bold

L left, *R* right, *ALS* amyotrophic lateral sclerosis, *PPMS* primary progressive multiple sclerosis

* Clusters for the ALS < healthy controls comparison were obtained using $p < 0.0001$ (uncorrected) with at least 20 contiguous voxels

reception), left inferior frontal gyrus (BA44, Broca's area, involved in language production) right superior frontal gyrus (BA10, executive functions) and right pre-central gyrus (frontal lobe, BA6, supplementary motor area involved in movement planning and execution).

VBM analysis: PPMS patients vs. HC

MS patients showed a widespread and bilateral GM tissue loss, involving both supratentorial and infratentorial (right cerebellar vermis) regions (Fig. 2a, b). In details, supratentorial areas of GM loss were both deep (basal ganglia, thalamus, claustrum) and cortical; among the latter ones there were the following: superior and inferior frontal gyri (BA9,10,11, frontal pole; executive functions and in particular working memory and decision-making processes), pre-central gyrus (frontal lobe, BA4, primary motor cortex), post-central gyrus (parietal lobe, BA1,2,3; primary somatosensory cortex), posterior cingulated and parahippocampal gyri (limbic system, BA23,24,33; emotion formation and processing, learning, and memory) supramarginal gyrus (inferior parietal lobe, BA 40; spatial orientation and semantic representation), superior temporal gyrus (BA22, part of Wernicke's area involved in auditory processing and language reception), middle occipital gyrus (secondary visual cortex, BA18; visual and visuo-emotional processing, visual imagery), inferior occipital gyrus (secondary visual cortex, BA19; visual association area), and insular cortex (decision making, emotion experiencing, memory procedures). Applying Bonferroni correction yielded comparable results, with the exception of the differences in the occipital gyri, which were not retained as significant.

VBM analysis: PPMS vs. ALS patients

Compared to ALS patients, PPMS patients showed reduced GM volume in both deep (bilateral thalamus, caudate nucleus, globus pallidus, putamen, claustrum) and cortical areas (Fig. 3a, b). Among the latter ones, there were the left precentral gyrus, bilateral cingulate gyrus, bilateral occipital cortex, left supramarginal gyrus, and left middle temporal gyrus, as well as the precuneus (superior parietal lobule, BA7; visuo-spatial processing, self-reflection, episodic memory) and the left parahippocampal gyrus (entorhinal cortex, BA28; olfaction and memory processing). Applying Bonferroni correction yielded comparable results as regards findings in the thalamus and caudate nucleus, whereas globus pallidus, putamen, claustrum, and cortical differences were not retained as significant. Compared to PPMS, ALS patients did not show any area of significant GM loss.

Discussion

We have compared patients with PPMS and ALS to assess whether the irreversible neurological disability observed in these progressive diseases is associated with different patterns of GM damage. On a clinical ground, PPMS is characterized by a predominance of pyramidal signs and symptoms (progressive spastic para- or hemiparesis), which are also considered a hallmark of ALS. Our VBM analysis showed that PPMS patients have a diffuse GM involvement compared to HC, involving both deep structures, such as the thalamus, and cortical areas of the frontal,

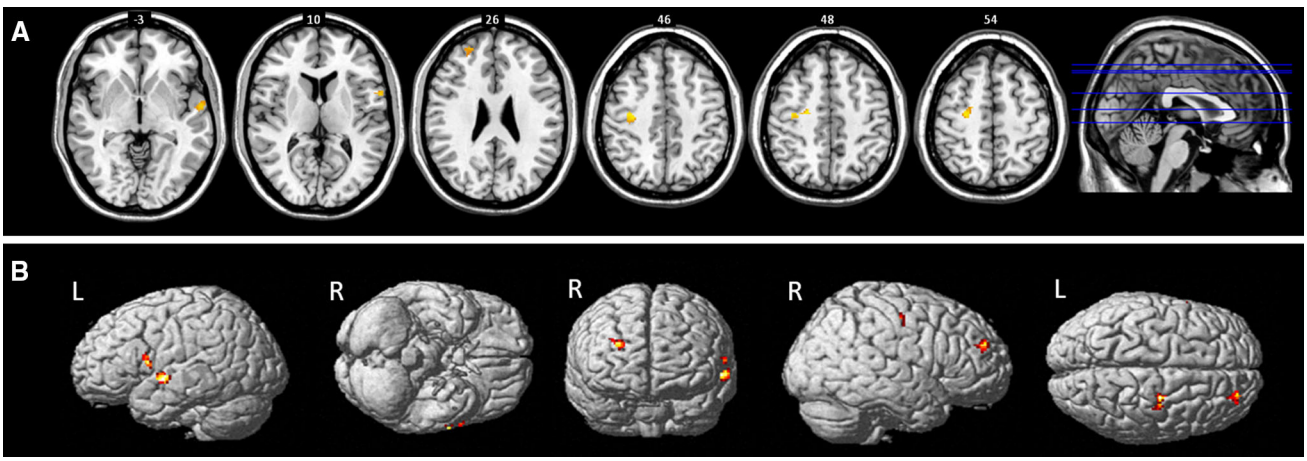

Fig. 1 Clusters of reduced GM volume in ALS patients compared to healthy controls on axial slices (**a**) and 3D reconstructions (**b**). The colored voxels, superimposed in MNI space axial slices (**a**), or on a 3D rendering of the brain (**b**) represent the areas which were significantly different between HC and ALS patients at $p_{uncorr} < 0.001$ (at least 20 contiguous voxels for each cluster). The MNI *z*-axis coordinate is shown for each slice and its position as a *line* in the sagittal image. Areas of significantly reduced GM volume for ALS vs HC are: *left* superior temporal gyrus, *left* inferior frontal gyrus, *right* superior frontal gyrus and right precentral gyrus

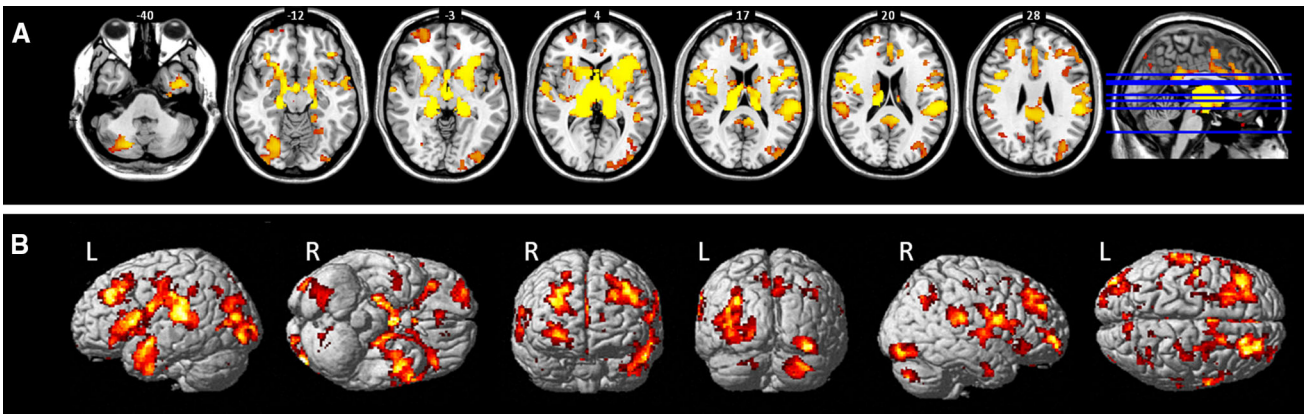

Fig. 2 Clusters of reduced GM volume in PPMS patients compared to healthy controls on axial slices (**a**) and 3D reconstructions (**b**). The colored voxels, superimposed in MNI space axial slices (**a**), or on a 3D rendering of the brain (**b**), represent the GM areas which were significantly different between HC and PPMS patients at $p_{corr} < 0.05$ (FWE). The MNI *z*-axis coordinates is shown for each slice and its position as a *line* in the sagittal image. Areas of significantly reduced GM volume for PPMS vs. HC involve bilaterally both deep GM and cortical areas of the fronto-temporo-parieto-occipital cortex

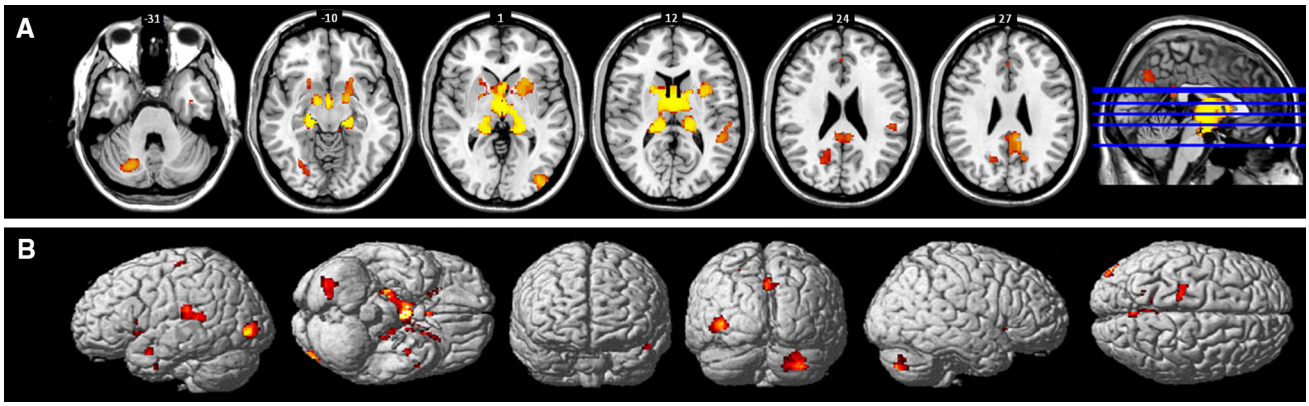

Fig. 3 Clusters of reduced GM volume in PPMS compared to ALS patients on axial slices (**a**) and 3D reconstructions (**b**). The *colored* voxels, superimposed in MNI space axial slices (**a**), or on a 3D rendering of the brain (**b**), represent the GM areas which were significantly different between ALS and MS at $p_{corr} < 0.05$ (FWE corrected). The MNI *z*-axis coordinates is shown for each slice and its position as a *line* in the sagittal image. Areas of significantly reduced GM volume for PPMS vs. ALS are: bilateral thalamus, caudate nucleus, globus pallidus, putamen, claustrum, *left* precentral gyrus, bilateral cingulate gyrus, bilateral occipital cortex, *left* supramarginal gyrus, *left* middle temporal gyrus, precuneus and *left* parahippocampal gyrus

temporal, parietal and occipital lobes, bilaterally. Other VBM studies investigating the pattern of regional GM tissue loss in PPMS [24, 25] consistently found an involvement of the thalamus, associated, only in one study, to the presence of a more widespread cortical tissue loss [24]. At any rate, a comparison between different MS phenotypes did not show a characteristic pattern of GM damage in PPMS [15]. The long disease duration of our patients may account for the more widespread GM loss than previously reported [26, 27]. It is worth remembering that, in a VBM study of early PPMS patients including magnetization transfer (MT) imaging [28], the presence of MT changes affecting GM areas where atrophy was not evident yet could be interpreted considering that changes in MT parameters reflect demyelination, which might progressively lead to axonal damage and widespread GM loss later on in the course of the disease, as reported in the present study. On the other hand, the thalamus involvement, reported since the early stages of PPMS [24, 25, 28], is consistent with several pieces of evidence supporting a crucial role of this structure in determining MS-related clinical deficits [29].

Compared to ALS, PPMS patients showed a widespread GM damage, which reflects the impairment of different functional systems characterizing MS clinical picture. In addition, our sample of ALS patients had, on average, a moderate degree of functional impairment, as assessed by the ALSFRS scale. This makes them less representative of the spectrum of the disease, but one should bear in mind that MRI scanning for research purposes requires long

acquisition times which are not tolerated by severely disabled ALS patients.

ALS patients, when compared to HC, showed GM volume decrease in motor and extra-motor areas, the latter ones involved in cognitive skills such as executive functions and language processing and production. Recently, several studies have changed the traditional belief that ALS is characterized by isolated motor deficits, showing clinical and MRI evidence of fronto-temporal involvement, as in our study [18, 30]. Notably, a correlation between cognitive deficits similar to what found in fronto-temporal dementia (FTD) and MRI tissue loss in the fronto-temporal lobes has been described in ALS, supporting the hypothesis that ALS and FTD belong to the same spectrum of neurological disorders [31, 32].

White matter (WM) changes have also been reported in ALS, involving both motor (corticospinal tract) and extra-motor (corpus callosum, associative fibers) pathways [33, 34]. These latter findings might be explained by a mechanism of retrograde axonal degeneration deriving from affected cortical areas. Nonetheless, WM damage, as well as the diffuse involvement of GM in ALS might also be viewed as signs of pathological features similar to those of PPMS.

This preliminary study suggests that PPMS is characterized by a more diffuse and pronounced GM damage than ALS and that, in the latter condition, brain damage is present outside the motor system. The results we obtained are consistent with the notion that both PPMS and ALS are characterized by GM tissue degeneration, but their interpretation is hampered by the low sample size and by the between-group difference in terms of disease duration. A further limit of the study might be represented by the fact that ALS patients were older than PPMS patients, although the difference was not statistically significant and age entered the statistical analysis as a covariate. Future comparative studies between PPMS and ALS should, therefore, be conducted in patients with shorter disease duration (i.e., "early" PPMS) and include measures of cognitive functioning to better investigate the correlation between GM damage and clinical features in both the diseases.

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References

1. Geurts JJ, Stys PK, Minagar A, Amor S, Zivadinov R (2009) Gray matter pathology in (chronic) MS: modern views on an early observation. J Neurol Sci 282(1–2):12–20
2. Thompson A (2004) Overview of primary progressive multiple sclerosis (PPMS): similarities and differences from other forms of MS, diagnostic criteria, pros and cons of progressive diagnosis. Mult Scler 10(Suppl 1):S2–S7
3. Brooks BR (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 124(Suppl):96–107
4. Agius LM (2012) Neuroinflammation as the proximate cause of signature pathogenic pattern progression in amyotrophic lateral sclerosis, AIDS, and multiple sclerosis. Patholog Res Int 2012:169270
5. Hemminki K, Li X, Sundquist J, Sundquist K (2009) Familial risks for amyotrophic lateral sclerosis and autoimmune diseases. Neurogenetics 10(2):111–116
6. Li G, Esiri MM, Ansorge O, DeLuca GC (2012) Concurrent multiple sclerosis and amyotrophic lateral sclerosis: where inflammation and neurodegeneration meet? J Neuroinflammation 9:20. doi:10.1186/1742-2094-9-20
7. Etemadifar M, Abtahi SH, Akbari M, Maghzi AH (2012) Multiple sclerosis and amyotrophic lateral sclerosis: is there a link? Mult Scler 18(6):902–904
8. Landtblom AM, Riise T, Boiko A, Söderfeldt B (2002) Distribution of multiple sclerosis in Sweden based on mortality and disability compensation statistics. Neuroepidemiology 21(4):167–179
9. Bostrom I, Riise T, Landtblom AM (2012) Mortality statistics for multiple sclerosis and amyotrophic lateral sclerosis in Sweden. Neuroepidemiology 38(4):245–249
10. van Doormaal PT, Gallo A, van Rheenen W, Veldink JH, van Es MA, van den Berg LH (2013) Amyotrophic lateral sclerosis is not linked to multiple sclerosis in a population based study. J Neurol Neurosurg Psychiatry 84(8):940–941
11. Confavreux C, Moreau T, Jouvet A, Tommasi M, Aimard G (1993) Association of amyotrophic lateral sclerosis and multiple sclerosis. Rev Neurol (Paris) 149(5):351–353
12. Hader WJ, Rpzdilsky B, Nair CP (1986) The concurrence of multiple sclerosis and amyotrophic lateral sclerosis. Can J Neurol Sci 13(1):66–69
13. Rajagopalan V, Allexandre D, Yue GH, Pioro EP (2011) Diffusion tensor imaging evaluation of corticospinal tract hyperintensity in upper motor neuron-predominant ALS patients. J Aging Res 2011:481745. doi:10.4061/2011/481745
14. Reich DS, Zackowski KM, Gordon-Lipkin EM, Smith SA, Chodkowski BA, Cutter GR et al (2008) Corticospinal tract abnormalities are associated with weakness in multiple sclerosis. AJNR Am J Neuroradiol 29(2):333–339
15. Ceccarelli A, Rocca MA, Pagani E, Colombo B, Martinelli V, Comi G et al (2008) A voxel-based morphometry study of grey matter loss in MS patients with different clinical phenotypes. Neuroimage 42(1):315–322
16. Verstraete E, Veldink JH, Hendrikse J, Schelhaas HJ, van den Heuvel MP, van den Berg LH (2012) Structural MRI reveals cortical thinning in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 83(4):383–388
17. Grosskreutz J, Kaufmann J, Fradrich J, Dengler R, Heinze HJ, Peschel T (2006) Widespread sensorimotor and frontal cortical atrophy in Amyotrophic Lateral Sclerosis. BMC Neurol 25(6):17
18. Agosta F, Pagani E, Rocca MA, Caputo D, Perini M, Salvi F et al (2007) Voxel-based morphometry study of brain volumetry and diffusivity in amyotrophic lateral sclerosis patients with mild disability. Hum Brain Mapp 28(12):1430–1438
19. Sled JG, Zijdenbos AP, Evans AC (1998) A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17(1):87–97
20. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 50(1):121–127

21. Battaglini M, Jenkinson M, De Stefano N (2012) Evaluating and reducing the impact of white matter lesions on brain volume measurements. Hum Brain Mapp 33(9):2062–2071
22. Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J et al (2007) Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain 130(Pt 9):2375–2386
23. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14(1 Pt 1):21–36
24. Bodini B, Khaleeli Z, Cercignani M, Miller DH, Thompson AJ, Ciccarelli O (2009) Exploring the relationship between white matter and gray matter damage in early primary progressive multiple sclerosis: an in vivo study with TBSS and VBM. Hum Brain Mapp 30(9):2852–2861
25. Sepulcre J, Sastre-Garriga J, Cercignani M, Ingle GT, Miller DH, Thompson AJ (2006) Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. Arch Neurol 63(8):1175–1180
26. Bergsland N, Horakova D, Dwyer MG, Dolezal O, Seidl ZK, Vaneckova M et al (2012) Subcortical and cortical gray matter atrophy in a large sample of patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol 33(8):1573–1578
27. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA et al (2008) Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol 64(3):247–254
28. Khaleeli Z, Cercignani M, Audoin B, Ciccarelli O, Miller DH, Thompson AJ (2007) Localized grey matter damage in early primary progressive multiple sclerosis contributes to disability. Neuroimage 37(1):253–261
29. Minagar A, Barnett MH, Benedict RH, Pelletier D, Pirko I, Sahraian MA et al (2013) The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. Neurology 80(2):210–219
30. Cosottini M, Cecchi P, Piazza S, Pesaresi I, Fabbri S, Diciotti S et al (2013) Mapping cortical degeneration in ALS with magnetization transfer ratio and voxel-based morphometry. PLoS One 8(7):e68279
31. Lillo P, Mioshi E, Burrell JR, Kiernan MC, Hodges JR, Hornberger M (2012) Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One 7(8):e43993
32. Mioshi E, Lillo P, Yew B, Hsieh S, Savage S, Hodges JR et al (2013) Cortical atrophy in ALS is critically associated with neuropsychiatric and cognitive changes. Neurology 80(12):1117–1123
33. Abrahams S, Goldstein LH, Suckling J, Ng V, Simmons A, Chitnis X et al (2005) Frontotemporal white matter changes in amyotrophic lateral sclerosis. J Neurol 252(3):321–331
34. Filippini N, Douaud G, Mackay CE, Knight S, Talbot K, Turner MR (2010) Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. Neurology 75(18):1645–1652