

Increased regional gray matter atrophy and enhanced functional connectivity in male multiple sclerosis patients

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Abstract

Evidence suggests that sex/gender is an important factor for understanding multiple sclerosis (MS) and that some of its neuropathological consequences might manifest earlier in males. In the present study, we assessed gray matter (GM) volume and functional connectivity (FC) in a sample of female and male MS patients (MSp) and female and male healthy controls (HCs). As compared to female MSp, male MSp showed decreased GM volume in the bilateral frontal areas and increased FC between different brain regions. Because both sets of changes correlated significantly and no differences in cognitive performance were observed, we suggest that the FC increase observed in male MSp acts as a compensatory mechanism for their more extensive GM loss and that it promotes a functional convergence between male- and female-MSp.

Keywords

Multiple sclerosis, gender, cognition, magnetic resonance imaging, voxel-based morphometry, functional connectivity

Introduction

There is growing evidence that sex and/or gender might be relevant factors that affect the prevalence, course, disability and treatment response of multiple sclerosis (MS) patients. Indeed MS incidence and prevalence are higher in females than in males [1]. Although MS onset commences at earlier ages in females than in males [2], once the disease is established, its progression seems faster and results into a higher degree of physical disability in males than in females [3,4].

The possible effects of sex and/or gender on neurocognitive MS alterations are less clear. Although being male has been proposed as a risk factor for cognitive impairment in MS patients [5], the results on brain neuropathological MS indices are conflicting, some studies have suggested a higher degree of brain damage in males [6–8], while others have failed to replicate these findings [9,10]. As these conflicting results might derive from gender interacting with other relevant demographic and clinical variables, we explored whether female and male MS patients, carefully matched for age, years of disease, level of education, intelligence quotient (IQ), neuropsychological performance and physical disability, differed in two indices of MS progression: gray matter (GM) atrophy and resting state functional connectivity (FC) changes.

Materials and Methods

Participants

From the MS population of the Hospital General of Castellón, 34 female and 22 male relapsing-remitting (RR) right-handed patients were selected to make up two experimental subgroups (Female-and-Male MSp), who were matched for several demographical and clinical variables (see Table 1). All the MS patients were relapse- and steroid-free for at least 2 months prior to this study. Patients were neuropsychologically assessed using the Brief Repeatable Battery Neuropsychology test (BRB-N), from which Z-scores for four attentional domains (attentional/ executive; visual memory; verbal memory and fluency) were calculated as previously described [11]. The healthy control subgroups (Female-and-Male HC) included 28 females and 35

males that were right-handed, with no presence or history of psychiatric or neurologic diseases.

The study was approved by the Ethics Standards Committees of the Hospital General and the Universitat Jaume I, both of Castellón. All the participants gave informed written consent prior to participating.

MRI acquisition and preprocessing

Anatomical and resting-state functional images were acquired with a 1.5 T scanner (Siemens Avanto, Erlangen, Germany). An optimized VBM protocol using the Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL), included in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK), was performed to explore regional GM volume differences. Resting-state fMRI scans were pre-processed using the DPARSFA tool as previously described (see Supplementary Methods for MRI acquisition and preprocessing details). FC was assessed by computing pair-wise Pearson correlations among the average time series of all the 90 regions of interest selected for the present study (see Supplementary Figure 1 A).

Statistical Analyses

T-tests were run to assess dyadic differences between groups for all the demographical and clinical variables. While no differences among them were found for any variable, both male- and female-MSp differed from their respective HC subgroups in age, years of education and BPF terms (See Table 1). Therefore, these three variables were used as nuisance variables in all the subsequent statistical analyses.

Regional GM volume differences were assessed by a SPM8 full-factorial design ($p < 0.05$ FWE cluster-corrected for the multiple comparisons; cluster extent of $k=50$ voxels). For the FC analysis, individual pair-wise correlation connectivity matrices were entered into a GLM model and t-tests were performed to compare the four groups of interest ($p < 0.05$ FDR corrected for the multiple comparisons with 100 000 permutations using the Network-based statistic toolbox, NBC). The relationship between the FC changes and GM volume in MS patients was assessed by Pearson correlation indices and the relationship between these two variables and cognitive

performance were assessed by means of linear regression analyses (significance level: $p < 0.05$).

Results

Volumetric Analysis

Compared to Female-HC, Female-MSp showed GM atrophy in both thalami and in the left calcarine sulcus and the left precuneus. Compared to Male-HC, male Male-MSp showed GM loss in the same areas as the female patients did, but also in two additional regions: the left lingual and the left cerebellum (See Supplementary Figure 1B and C and Supplementary Table 1). The opposite comparisons (MS patients > HCs) gave no statistically significant differences for either gender.

Gender-related differences in GM volume were only observed between the MSp subgroups, with Male-MSp exhibited a bilateral reduction of GM in several divisions of the frontal lobe compared to Female-MSp (See Figure 1A and Supplementary Table 1). The inverse contrasts, as well as the Female-HC vs. Male-HC comparisons, yielded no significant results.

Seed-based Functional Connectivity

Although gender-related FC differences were found in the HC and MS groups, they differed in both location and direction. While the gender-related differences in the MS group were found on three intra-hemispheric pathways (right Olfactory Cortex -right Amygdala; right Middle Temporal Pole - right Inferior Frontal Gyrus; and left Parahippocampal Gyrus - left Inferior Frontal Gyrus; Figure 1B and Supplementary Table 2), with males exhibiting greater FC in all cases, the gender differences in the HC group were found on inter- and intra-hemispheric pathways, and females exhibited greater FC on one (of four) of these pathways (see Supplementary Figure 1D and E and Supplementary Table 2). No further comparisons yielded statistical significance.

Relationship between GM loss and increased Functional Connectivity in MS patients

As previous studies [12,13] have suggested that increased FC is a secondary response to primary MS-related neuropathological changes in GM, we explored the relationship between both variables. We found that the FC scores on the three pathways, where we observed gender differences within MS patients (Figure 1B), were inversely related to the GM volume in the two frontal areas, where the Male- and Female-MS subgroups also differed (Figure 1A). This inverse relationship was statistically significant in five (of six) pair-wise correlations (Figure 1C), whereas the FC scores on these pathways did not correlate with global atrophy as estimated by BPF or TLV (data not shown). Finally, to further support a possible functional relationship between GM loss and increased FC in MS patients, we found that the gender differences previously observed in FC faded when GM volume measurements were used as covariates in all these dyadic comparisons.

Functional-cognitive significance

Increased FC resulting from GM atrophy in MS patients has been interpreted in two different ways: Either as maladaptive and, as such, a sign of MS neuropathological progression [14] or, to the contrary, as a compensatory mechanism promoting normal cognitive competence of MS patients at initial stages of the disease [12,13]. To find out which of these two alternatives applies to our observations, we analyzed the relationship between FC, GM volume and cognitive performance in Male- and Female-MSp.

Male- and female-MSp did not significantly differ in any test of the BRNB (table 1) and scores of both groups were ranged within normality boundaries. However, their attentional Z scores were differentially related to GM volume and FC in the brain areas for which gender-differences had been previously identified (figure 1). More specifically, linear regression analyses revealed that attentional Z scores of Male- but not of Female-MSp could be satisfactorily predicted from these two sets of parameters ($r=0.72$; $p<0.05$ and $r=0.53$, $p=0.11$, respectively) and that remaining GM volume in frontal areas and FC values between the left Parahippocampal Gyrus and the left Inferior Frontal Gyrus were positively associated to cognitive performance (see supplementary Table 3 for details). Taken together, our results suggest that the increased FC observed in Male-MSp in this neuroanatomical pathway acts as a compensatory mechanism that allows them to retain similar cognitive performance to that observed in Female-MSp despite having a higher degree of GM atrophy.

Discussion

The findings of the present study show that, even when matched for age, years of disease, level of education, IQ, neuropsychological performance and physical disability, Male-MSp display a higher degree of GM atrophy than Female-MSp. These results confirm those of previous studies which have suggested that males are more prone to MS brain damage [7,8] and/or that they show faster MS progression than females [3,4]. On the other hand, according to the recently proposed classification of sex/ gender differences [15], this first observation should be considered as a contingent (e.g. MS – dependent) average divergence.

We also showed that Male-MSp exhibit more FC between temporal and inferior frontal areas, and between the right amygdala and the right olfactory cortex than Female-MSp. Increased FC has previously been understood as a secondary neuropathological sign of MS progression [14] or as a compensatory mechanism for early MS neuropathological changes [12,13]. Only the later interpretation would be coherent with several additional findings of our study: 1) the direct correlation found between FC and GM atrophy; 2) the fading gender-related differences in FC when GM volume was introduced as a covariate; 3) lack of differences in neurological and neuropsychological performance (see Table 1) between Male- and Female-MSp despite their different degrees of GM atrophy in several brain regions; 4) the positive association of remaining GM volume and FC scores with attentional capabilities in Male- but not in Female-MSp. Therefore, in our study increased FC seems to act as a compensatory mechanism for GM atrophy that allows Male-MSp to retain normal cognitive performance. Further, it should be noted that the gender-related differences in FC and GM atrophy observed in this study functionally compensate each other and, following a recently proposed classification of sex/ gender differences [15], they are better described as a contingent average convergence between Male- and Female-MSp.

Taken together, the present results and previous ones highlight the importance of taking into account sex/gender in MS research. Additional studies are needed to clarify whether these differences are primarily related to progression speed or to the extent of MS neuropathology, and whether sex (i.e. chromosomic complement, steroid hormone levels, etc.), gender (i.e. behavioral and sociological factors askew distributed in males

and females), or both are responsible for these differences between Female- and Male-MSp.

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Figure 1: Male MSp display enhanced GM atrophy and FC as compared to Female MSp. **A)** Male-MSp exhibited a reduction of GM volume in several frontal lobe regions forming two clusters, one at each hemisphere. Thus, gender-related differences in the left cluster affected the left Superior Frontal Gyrus (Orbital Part), Middle Frontal Gyrus (Orbital Part), Medial Orbitofrontal Cortex, whereas gender-related differences in the right cluster were observed at the right Rectus Gyrus, Superior Frontal Gyrus (Orbital Part) and Medial Orbitofrontal Cortex (see Supplementary Table 1 for further details). Results are presented at $p < 0.05$ FWE cluster-corrected for multiple comparisons and a cluster extent of $k = 50$ voxels. **B)** Male MSp exhibited enhanced FC between right Olfactory Cortex and right amygdala (R Olf – R Amyg), between right Middle Temporal Pole and right Inferior Frontal Gyrus (R MTP – R IFG (Orb) and between left Parahippocampal Gyrus and left Inferior Frontal Gyrus (L PHG – L IFG (Orb -see Supplementary Table 2 for further details-). **C)** GM volume and FC are inversely related in MS patients. GM volume scores at the areas displayed in panel A were plotted against FC scores displayed in panel B and the extent of co-variation between them was assessed by means of Pearson's correlation index (significance level was set at $p < 0.05$). Note that the covariance between the GM volume at the left frontal cluster and the FC between Inferior Frontal Gyrus- right Middle Temporal Pole scores did not yield significance and it is not displayed.

Supplementary Figure 1: **A)** Different slices showing Automated Anatomical Labeling (AAL) 90 regions of interest (ROIs). Note that cerebellar ROIs were excluded due to limited field of view of functional scans. **B)** Areas showing GM volume loss in female MS patients compared to female HC. Compared to Female-HC, Female-MSp showed GM atrophy in both thalami and in the left calcarine sulcus and the left precuneus; see supplementary table 1 for details. Results are presented at $p < 0.05$ FWE cluster-corrected for multiple comparisons and a cluster extent of $k = 50$ voxels. **C)** Areas showing GM volume loss in male MS patients compared to male HCs. Compared to Male-HC, male Male-MSp showed GM loss in the same areas as the female patients did (both thalami and in the left calcarine sulcus and the left precuneus), but also in two additional regions: the left lingual and the left cerebellum; see supplementary table 1 for details. Results are presented at $p < 0.05$ FWE cluster-corrected for multiple comparisons and a cluster extent of $k = 50$ voxels. **D)** Regions with increased Functional Connectivity (FC) in male HCs compared to female HCs. Results were

assessed at $p < 0.05$ FDR corrected for the multiple comparisons with 100.000 permutations; see supplementary table 2 for details. **E)** Regions with increased FC in female HCs compared to male HCs. Results were assessed at $p < 0.05$ FDR corrected for the multiple comparisons with 100.000 permutations; see supplementary table 2 for details. Abbreviations: L: left, R: right, IPL: inferior parietal lobule, IFG (Oper): inferior frontal gyrus (pars opercularis), Calc: calcarine sulcus, MOC: medial orbitofrontal cortex, SPL: superior parietal lobule, STG: superior temporal gyrus, PCG: posterior cingulate gyrus.

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Table 1: Main demographic, clinical, MRI and neuropsychological characteristics of all participants, including mean, standard deviation (SD) and range. (*: Significantly different $p < 0.05$, as compared to the corresponding same gender group)

	Female HC (n=28)	Male HC (n=35)	Female MS patients (n=34)	Male MS patients (n=22)
Age (years)	27.96 (7.85) [18-44]	25.54 (5.35) 18-38]	40.85 (10.18) * [20-60]	38.68 (8.72) * [23-60]
Median education level categorical [range]	1 [1-5]	1 [1-6]	4 [1-6] *	5 [1-6] *
EDSS	-	-	2.38 (1.41) [0-6.5]	2.5 (1.62) [0-6.5]
Disease duration (years)	-	-	8.82 (7.47) [1-29]	6.45 (5.53) [1-20]
BPF	0.87 (0.16)	0.86 (0.14)	0.83 (0.27)*	0.83 (0.33)*
TLV (ml)	-	-	4.55 (5.97)	2.96 (3.61)
FSS	-	-	31.48 (17.25)	37.18 (14.91)
Manipulative IQ WAIS III (Matrix)	-	-	101.91 (11.93)	98.41 (8.78)
SDMT	-	-	48.41 (14.66)	46 (15.23)
PASAT 3	-	-	33.35 (23.04)	35.23 (20.01)
SRT Long-Term Storage	-	-	41.24 (14.07)	41.32 (14.06)
SRT Consistent Long-Term Retrieval	-	-	31.85 (13.8)	30.86 (14.3)
SRT Delayed Recall	-	-	7.76 (2.61)	7.59 (2.34)
10/36 SPART Long-Term Storage	-	-	18.74 (5.62)	19.77 (6.03)
10/36 SPART Delayed Recall	-	-	6.53 (2.32)	6.73 (2.37)
Semantic Fluency (animal naming)	-	-	19.91 (5.72)	20.64 (6.5)

Abbreviations: MRI: magnetic resonance imaging; EDSS: Expanded Disability Status Scale; BPF: brain parenchymal fraction; TLV: Total Lesion Volume; FSS: Fatigue Severity Scale; IQ: Intellectual quotient; SDMT: Symbol Digit Modalities Test; SRT: Selective Reminding Test; SPART: Spatial Recall Test; PASAT: Paced Auditory Serial Addition Test;

Supplementary Table 1: Areas showing reductions in gray matter volume (GM) in male and female MS patients compared to male and female HCs as well as between them. Results are presented at $p < 0.05$ FWE cluster-corrected for multiple comparisons and a cluster extent of $k=50$ voxels. Cohen's d is provided to quantify the effect size of the observed differences (a positive d signals that mean was bigger in the first arbitrarily listed group towards than in the second)

Comparison	Brain region	Cluster size (k)	t-value	Cohen's d	MNI coordinates		
					x	y	z
<i>Female MS patients vs. Female HCs</i>	L Thalamus	232	6.01	-1.56	-7	-25	10
	R Thalamus		5.41	-1.40	4	-7	12
	L Calcarine Sulcus	825	5.51	-1.43	-3	-66	16
	L Precuneus		5.37	-1.39	-10	-72	31
<i>Male MS patients vs. Male HCs</i>	LThalamus	250	5.10	-1.41	-6	-25	10
	R Thalamus		5.76	-1.56	6	-12	15
	L Calcarine Sulcus	333	5.24	-1.45	-15	-55	10
	L Precuneus		4.93	-1.36	-6	-55	15
	L Lingual Gyrus	235	5.35	-1.48	-7	-72	-10
	L Cerebellum		4.95	-1.37	-12	-72	-13
<i>Male MS patients vs. Female MS patients</i>	L Superior Frontal Gyrus (Orbital Part)	326	5.26	1.47	-12	60	-18
	L Middle Frontal Gyrus (Orbital Part)		4.71	1.31	-19	61	-10
	L Medial Orbitofrontal Cortex		4.90	1.36	-10	59	-12
	L Rectus Gyrus		5.01	1.40	-7	58	-18
	R Rectus Gyrus	84	5.43	1,51	10	58	-18
	R Superior Frontal Gyrus (Orbital Part)		5.29	1.47	9	60	-18
	R Medial Orbitofrontal Cortex		4.60	1,28	4	58	-19

Abbreviations: MNI: Montreal Neurological Institute; R: right; L: left.

Supplementary Table 2: Areas showing functional connectivity differences between experimental groups of the 90 AAL brain regions of interest. Results are presented using a threshold of $p < 0.05$ FDR corrected for the multiple comparisons with 100,000 permutations. Cohen's d is provided to quantify the effect size of the observed differences (a positive d signals that mean was bigger in the first arbitrarily listed group towards than in the second).

Sex effect	t-value	Cohen's d	AAL brain regions
Male HC > Female HC	4.93	1.27	L Inferior Parietal Lobule - L Inferior Frontal Gyrus (Pars Opercularis)
	4.31	1.11	R Inferior Parietal Lobule - R Inferior Frontal Gyrus (Pars Opercularis)
	4.35	1.12	L Superior Parietal Lobule - R Superior Temporal Gyrus
	4.33	1.12	R Calcarine Sulcus – R Medial Orbitofrontal Cortex
Male HC < Female HC	4.43	-1.14	L Posterior Cingulate Gyrus- L Superior Parietal Lobule
Male MS patients > Female MS patients	5.26	1.47	R Olfactory Cortex – R Amygdala
	5.09	1.42	R Middle Temporal Pole – R Inferior Frontal Gyrus (Pars Orbitalis)
	4.35	1.21	L Parahippocampal Gyrus – L Inferior Frontal Gyrus (Pars Orbitalis)

Abbreviations: AAL: automated anatomical labeling; HC: healthy controls; MS: multiple sclerosis; L: left; R: right.

Attentional Z score	MALE-MSp			FEMALE-MSp		
	Beta	t	P	Beta	t	p
R Olfactory Cortex – R Amygdala	-0.065	-0.285	0.779	0.376	1.784	0.086
R Middle Temporal Pole – R Inferior Frontal Gyrus	0.081	0.326	0.749	-0.126	-0.661	0.514
L Parahippocampal Gyrus – L Inferior Frontal Gyrus	0.417	1.860	0.081	0.198	0.969	0.342
Left frontal GM volume	0.388	1.148	0.268	0.083	0.389	0.701
Right frontal GM volume	0.295	1.052	0.368	0.280	1.188	0.246
			r=0.722, p<0.05			
				r=0.531, p= 0.105		

Supplementary Table 3: Linear regression analyses showing the relationship between GM volume, functional connectivity (FC) and cognitive performance in Male- and Female-MSp. FC scores on the three pathways where we observed gender differences within MS patients (Figure 1B, supplementary table 2) and GM volume in the two frontal areas where the Male- and Female-MS subgroups also differed (Figure 1A, supplementary table 1) were used as predictors of attentional Z scores. Only in Male-MSp these neuroanatomical and neurofunctional parameters allowed a statistically significant prediction of cognitive performance, with both GM volume and FC in frontal lobe regions being positively associated to attentional/ executive capabilities. Performance in other cognitive domains could not be satisfactorily predicted in any of these two MS patients' groups.