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Attention deficit in Multiple Sclerosis

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Abstract

Attention deficit is known to be present early in MS and may be an important indicator of cognitive decline, as it is likely to represent the early neuropsychological manifestation of the disease. The present study employs a concentrated or focused measure of attention.

We enrolled 35 MS patients and 29 controls. Attention deficit was assessed using the Toulouse Pieron Test of Concentrated Attention (TPT). The Portuguese versions of Beck Depression Inventory (BDI) and the Modified Fatigue Impact Scale (MFIS), were used to determine the influence of these variables on attention scores.

Performance differed between MS-patients and controls in work capacity of TPT, but not with regards to dispersion index. Attention deficit correlated with fatigue and unemployment but not with neurological disability as measured by EDSS.

Our results show that MS patients present an impairment of focused attention which is significantly associated with fatigue and that it seems to be an important predictor of unemployment.

Key words: multiple sclerosis, cognitive function, attention, fatigue, employment.

Introduction

It has long been known that Multiple Sclerosis (MS) has a significant impact on cognitive function [1], however its nature and importance have been overlooked. Recent studies report a 50% prevalence of a specific patterned MS-related cognitive dysfunction [2,3,4], subject to inter-patient variability, but mainly affecting memory, attention, information processing speed and executive functions [4,5]. Cognitive decline starts at an early stage of the disease and has been shown to affect social functioning and employment before classic motor deficits do [6].

Attention is the broad term used to describe the process that mediates the appropriate allocation of physiological/cognitive resources to relevant stimuli, referring these stimuli to objects, locations or moments [7]. It is a complex cognitive function that has inspired several theories on its processing.

One theory describes attention as integrating two main components, intensity and selectivity. The general level of alertness and readiness to respond to stimuli and the ability to sustain attention for a long period of time belongs to the intensity aspect. Selectivity comprises focused attention, referring to the ability to attend to only relevant stimuli, ignoring distracting ones, and divided attention, the distribution of mental resources to different sources of information [8]. Both subcomponents of selectivity were shown to rely on the same neural basis, including prefrontal structures, superior and inferior parietal cortex and anterior cingulated gyrus [9].

Another theory is that attention is carried out by three different networks that work in concert and are independent of the systems related to perception and action [10]. The anterior or executive control network is responsible for planning, decision making and detecting errors; the orienting network selectively allocates attention to a relevant area of the visual field; and the alerting network prepares the system for timely response maintaining an adequate level of cortical activation. Research shows that despite the seemingly different anatomical substrates, these networks work in concert by means of reciprocal modulation[11].

A parallel can be drawn for these two distinct theories, since they both separate the intensity or alerting aspect of attention as an internal, continuous state from the more specific task orientated selectivity, corresponding to executive and orienting networks.

Attention deficit is known to be present early in MS and may be an important indicator of cognitive decline, as it is likely to represent the early neuropsychological manifestation of the disease [16, 17]. Up to 25% of MS patients may suffer from attention deficit, mainly involving selectivity aspects[9].

Attention measures in Multiple Sclerosis are often reported in terms of results on specific tests like the Paced Auditory Serial Addition Task (PASAT) [12,13,14,15] but only a single aspect of attention, mostly sustained attention, has been considered. Recent studies [9, 16] have explored selectivity aspects of attention in MS, reporting a decline in both focused and divided attention of MS patients, though with a considerably smaller sample of patients [9].

The present study employs a concentrated or focused measure of attention, the Toulouse Pieron Test of Concentrated Attention (TPT). This should provide a consistent although not exhaustive model for testing the involvement of selectivity aspect of attention in MS.

Materials and methods

Participants

We enrolled 35 consecutive MS patients who are regularly evaluated in the neurology department of CHUC, and 28 healthy volunteers that served as normal controls (NC), aged between 18 and 45. All participants provided written informed consent to participate in the study, which was approved by the local Ethics Committee.

The demographic data of all the subjects and the clinical data of MS patients were collected, namely the disease course subtype, the disease duration and the neurological disability measured by Expanded Disability Status Scale (EDSS).

Exclusion criteria for participants were current or past history of head trauma, psychiatric or neurological disorder (other than MS in patient group), previous or current alcohol or substance abuse, severe visual or auditory impairment, current or prior use of antipsychotic medication and conditions that would preclude MRI. MS patients with history of relapse or steroid pulse treatment within 8 weeks preceding evaluation were excluded.

Neuropsychological testing

The same battery of tests was administered to all subjects in an equal fixed order. For the purposes of this study, it comprised Toulouse Pieron Test of Concentrated Attention for visual processing and error detection through sustained attention, validated for the Portuguese population by Baeta (2003) [18]. The test consists in an A3 sheet with 25 rows of 40 items. Each row contains 15 target symbols, which the subject must correctly identify. The duration of the test is 10 minutes.

Correctly identified targets (C), false positives (FP) and false negatives (FN) are calculated. Test results are expressed through dispersion index (DI=(FP+FN)) and work capacity (WC=C-(FP+FN)). Impaired performance affecting each or both of these scores has different implications. A deficit in WC can imply both inattention and delayed response. DI reflects distractibility. Information processing speed and motor integration affect both scores. To rank the degree of attention deficit, we did not employ raw data of each assessment but instead the number of abnormal assessments calculated from normative data for the Portuguese population to exclude the effects of age and education [18].

Depression, fatigue and mild cognitive impairment

The Portuguese versions of Beck Depression Inventory (BDI) [19, 20] and the Modified Fatigue Impact Scale (MFIS) [21], were used to determine the influence of these variables on attention scores.

The BDI is a measure of self reported depression severity consisting in 21 multiple choice questions. Results range from 0 to 63, and cut-offs are applied as follows: 0-14 indicates no depression, 15-19 dysphoria, 20-29 mild depression, 30-45 moderate depression and > 45 severe depression.

The MFIS measures the impact of fatigue in quality of live as perceived by the subject. The test contains 21 items and comprises 3 levels of fatigue: physical, cognitive and psychological. Results range from 0 to 63.

The Montreal Cognitive Assessment (MoCA©) [21] was used to perform a global cognitive assessment in order to detect mild cognitive impairment (MCI) in patients.

Statistical analysis

We performed a characterization of the sample of sixty-three individuals, of which twenty-eight are NC and thirty-five are MS patients. The parameters observed in all participants were: gender, age, education, professional status, BDI, MFIS-Physical, MFIS-

Cognitive, MFIS-Psychological, MFIS-Total, WC Test and DI Test. In MS patients EDSS, subtype course disease and disease duration was also analysed.

Categorical variables were characterized by absolute and relative frequencies, and continuous variables were characterized using mean, standard deviation, quartiles, minimum and maximum.

The NC and MS patients were compared for each parameter mentioned above. For categorical variables, differences between proportions were evaluated using the chi-square test or Fisher exact test. For the continuous variables, the T test was used to compare means between groups and the Mann-Whitney test was used to compare the distribution of the continuous variables, whenever the assumptions for the T test were not satisfied. The normal distribution of continuous variables and the equality of variances were tested using the Kolmogorov-Smirnov and the Levene test, respectively.

The classifications of the two tests, WC and DI, for the presence of attention deficit were compared using the Test McNemars and the degree of concordance was determined by the kappa coefficient.

The association between the presence of attention deficit (according to test DI, the test WC or the combination of these two tests) and categorical variables was evaluated using the chi-square test or the Fisher exact test. The group of patients with attention deficit was compared to the group of patients without attention deficit using the T test or the Mann-Whitney test, as appropriate.

The attention deficit predictors were determined by a logistic regression model. The stepwise forward method with Likelihood ratio test was used to select the variables among the following: EDSS, BDI-FS, MFIS-Physical, MFIS-Cognitive, MFIS-Total and fatigue. For each variable included in the regression model, the respective coefficient was tested using Wald test, and the adjusted OR with 95% Confidence interval were estimated.

The significance level used was 5% and the statistical software used was SPSS v19.0.0.2.

Results

Descriptive statistics

Participants (n=63) included 35 patients and 28 controls. Aged varied between 21 and 44 years. Level of education ranged from 4 to 19 years. Groups matched for sex and education, but not for age (**Table 1**).

Table 1 Characterization of the sample

Participants	**MSpatients**	**NC**	***p*-value**
Number	35	29	
Sex	78%[a]	68%[a]	0.374
Age[c]	36±5	31±7	0.005*
Education[c]	14 ± 4	15 ± 3	0.184
Disease duration[c]	11±6		
EDSS	2.0[b]± 1		

*p-value<0.05,values are means ± standard deviation [a] percentage female, [b] median, [c] years.

The majority of the patients (92%) presented with a relapsing-remitting clinical course (RRMS) and only 3 patients presented with a secondary progressive form of the disease (SPMS). MoCA © scores in the clinical group ranged from 20 to 29, with an average of 25 (**Table 2**). Cognitive assessment in MS patients was within normality.

Table 2 Test scores of MS patients and normal controls in the neuropsychological tests

Neuropsychological tests	**MS-patients**	**NC**	***p*-value**
MoCA©	25[a]±2	28±2	0.003*
BDI-FS	9 ± 7	4 ± 3	< 0.001**
MFIS			
physical	16 ± 9	6 ± 7	< 0.001**
cognitive	13 ± 8	8 ± 8	0.009**
psychological	2 ± 2	2 ± 2	0.112
Total	32 ± 18	16 ± 16	< 0.001**
Toulouse Pieron Test			
RT-Zscore	-1.46 ± 1.62	-0.76 ± 1.33	0.046*
ID-Zscore	2.34 ± 4.60	0.98 ± 2.07	0.383

**p*-value < 0.05, ***p*-value < 0.01, [a]median, values are means ± SDs, MS indicates multiple sclerosis

Attention

Performance differed between MS-patients and controls in work capacity of TPT, but not with regards to dispersion index (**Table 2**). Attention deficit as defined by individual work capacity or dispersion index <1.5 SD below the mean of calibration sample was present in 48,6% of the patients and only 21.4% of the controls. The degree of concordance as to the presence of attention deficit according to both parameters of TPT was acceptable, with a p-value of 0,549 for the McNemars test and a kappa coefficient of 0.613.

Relation between attention deficit and EDSS and professional status are reported on **Table 4**. Professional status and attention deficit showed significant correlation. EDSS correlated with neither.

Out of the 5 parameters analyzed in logistic regression (EDSS, BDI-FS, MFIS-Physical, MFIS-Cognitive, MFIS-Total and fatigue), only fatigue was identified as a predictor of attention deficit, regarding work capacity (p=0.032), with odds ratio of 5.0. No predictor was found for deficit in dispersion index nor for a combination of both scores.

Depression

Depression scores obtained from BDI proved higher in MS-patients than controls (**Table 2**). Dysphoria and mild depression were present in 11.4% and 8.6% of patients, respectively, and absent in controls. However, depression was not associated with lower performance in the attention task (**Table 3**).

Fatigue

Mean scores in MFIS were significantly higher in patients than controls mainly at cognitive and physical levels (**Table 2**). Higher scores in both cognitive, physical and total MFIS were associated with attention deficit (**Table3**).

Table 3 Comparison between MS patients with attention deficit and normal performance

	Attention deficit	**Normal**	***p*-value**
BDI-FS	7 ± 5	6± 6	0.156
MFIS			
physical	18± 9	9± 8	< 0.001**
cognitive	15 ± 9	9± 8	< 0.016*
psychological	2 ± 2	23± 2	0.095
Total	32 ± 18	16 ± 16	0.006**
EDSS[a]	3±1.8	2 ±0.6	0,126

**p*-value < 0.05 ***p*-value < 0.01, values are means ± SDs. [a] Patients' group only.

Table 4 Neurological disability, attention and employment status

Professional status	***Employed***	***Unemployed***	***p*-value**
EDSS	2.0[a]	2.5[a]	0,068[b]
TPT[d] (attention deficit)			
WC	34,8%	75%	0.024[c]*
ID	30,9%	41,7%	0.709[c]
Total score (DI or WC)	39,1%	75%	0,044[c]*

**p*-value < 0.05;[a] median; [b]p-value of Mann Whitney test; [c]p-value of chi-square test, [d] number of patients.

Discussion

Patients had lower performance in the attention task regarding only work capacity. A similar pattern of delayed responsiveness preserving its accuracy has been described during a visual attention task [22]. Lengthened reaction time for a simple and focused attention task has also been reported [16].

On the contrary, when attention deficit was defined by impaired performance in one or both scores, patients had similar performances to controls. This discrepancy could be an expression of neural plasticity, suggested by compensatory cortical activation that has been described during an attention task [23]. Patients achieve similar results and accuracy of response in detriment of processing speed. The role of fatigue in this scenario is controversial. Whereas it is known to be a major symptom of MS, affecting up to 90% of patients[24], its relation to cognitive impairment has been recognized by some researchers [24] and discarded by others [25]. This study shows a significant correlation between fatigue and attention impairment in patients and controls.

Delayed responsiveness and increased inattention (WC), the domains affected by fatigue, were also the ones reduced in MS patients. Moreover, fatigue was identified as a predictor of impaired performance, which in our opinion places it at the root of attention deficit in MS.

The hypotheses that activation of compensatory pathways enables patients to maintain an adequate cognitive performance but also accounts for high levels of fatigue and lengthened reaction time has already been put forward [26]. In a recent study, patients whose performance during a selective attention task were unimpaired showed no compensatory activity in structures related to attention [9], which seems to imply that other areas of the brain are being used. On the other hand, patients with specific attention deficits showed reduced cortical activity in these areas. The topic of neural correlates of attention deficit in MS is addressed in supplemental material.

Depression is a common feature in MS, present in up to 50% of the patients [27]. It was shown to affect mainly subjective perceived cognitive performance, leaving objective performance unimpaired [25]. Along the same line, our findings suggest that mild depression and dysphoria bear no relation to attention deficit.

Cognitive impairment has been associated to physical disability [14, 28] more often than not [29]. Nonetheless, where it concerns neurological disability, results suggest it to be poorly related to attention. Functional impairment as measured by EDSS also failed to establish a consistent relation to employment status. On the other hand, significant correlation between attention deficit and professional status was found. Patients presenting with attention deficit were more likely to be unemployed than the ones with normal performance. Unemployment has been related to attention deficit in early stages of the disease [16, 6]. From this point of view decreased attention is more likely to be responsible for social exclusion than physical disability. One can either argue that decreased attention forced patients to withdraw from employment, that maintaining an occupation had positive effects on the mental agility of patients, or, most probably, a combination of these.

Different courses of the disease are associated with different cognitive profiles [30]. Chronic progressive MS patients are more likely than RRMS patients to suffer from attention deficit, in particular reduced speed of information processing, executive dysfunctions, verbal intelligence and abstraction deficits. In this study, the number of SPMS patients was too small to extract reliable conclusions, although it was registered that all patients with this form of the disease suffered from attention deficit.

There are limitations to this study to be considered. The age difference between groups, although minimal, could induce an overestimate of attention deficit in the elder MS patients. However, as all statistics were performed on values normalized for age and education, this was at least partially overcome. Due to the cross-sectional design of this study, it is not possible to determine the nature of the association reported between attention deficit and fatigue, namely if is the attention deficit that firstly causes fatigue, by producing activation of compensatory pathways, or inversely if is fatigue that is contributing for the attention impairment. Moreover, the limited sample size might have prevented to fully examine the influence of other covariates on attention deficit. Prospective observational studies, adequately powered, are required to properly assess this issue.

Conclusions

Our results show that MS patients present an impairment of focused attention and then further the previous knowledge about the cognitive processes underlying attention affected by the disease. In fact, we can conclude that besides the well established involvement of sustained attention, there is also an impairment of the selectivity domain. Moreover, we demonstrate that the deficit of focused attention is significantly associated with fatigue and that it seems to be an important predictor of unemployment.

Future studies with MRI techniques are required in order to explore the neural basis underlying the attention deficit in MS which ultimately may lead to the development of strategies for symptomatic treatment.

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Neural correlates of attention deficit - *Work in progress*

Proceeding the investigation on neural correlates of attention deficit, we aim to determine its relation to gray matter volume, measured by Voxel Based Morphometry (VBM) [1]. The neural substrate of attention deficit in MS has been investigated through a lesion location approach [2] and fMRI studies [3], however VBM addressed to attention-related structures in MS has not yet been performed.

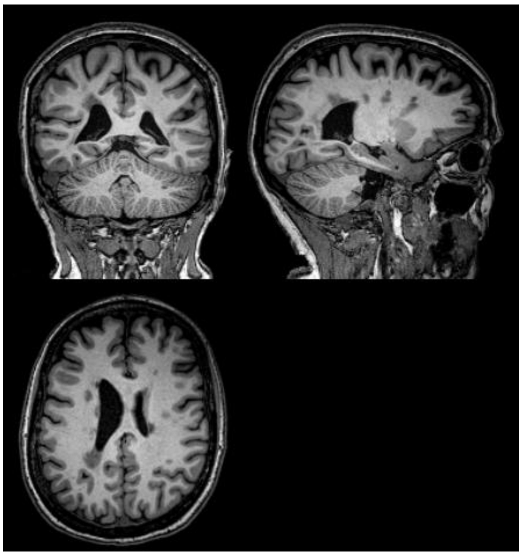
MS patients present with diffuse cortical atrophy and focal thinning in frontal and temporal regions [4]. Focused attention was shown to rely on prefrontal structures, superior and inferior parietal cortex and anterior cingulated gyrus [5]. Associations between regional cortical thickness and attentional networks showed negative correlation between attention and thickness of prefrontal, anterior cingulate and frontal areas [6]. Multiple sclerosis patients presented with reduced cortical activity in prefrontal and parietal areas during a selective attention task [3]. The cortical regions of interest in this study comprise both the ones affected by MS and those responsible for attention.

All subjects were examined on a 3Tesla Siemens TIM Trio scanner the same day neuropsychological testing took place. The following analysis is being performed:

- ✓ Conventional assessment of the lesion load
- ✓ White matter damage
- ✓ Cortical and deep gray matter volumes
- ✓ Voxel based morphometry (VBM)

VBM is a neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping. In VBM analysis, we investigate the association between regional GM volumes and each score obtained at attention tests, in an attempt to clarify those brain areas more likely to determine the deficits observed in patients and controls.

We present an example of the methodology used in this investigation through a comparison between a normal control and a patient presenting attention deficit.



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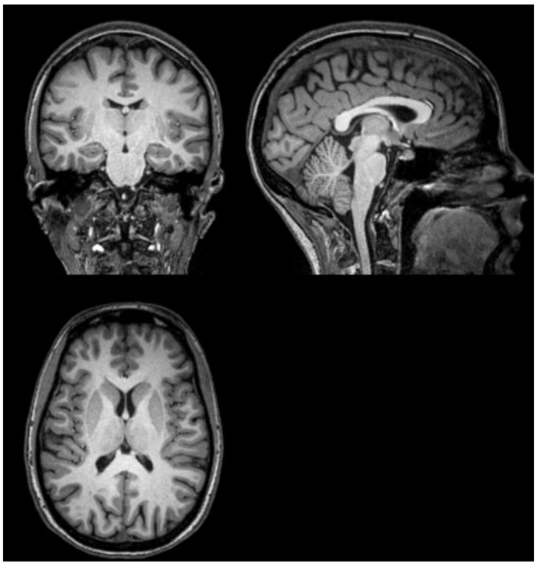

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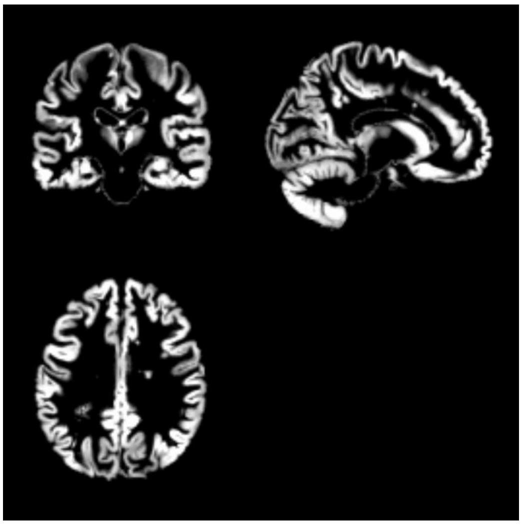

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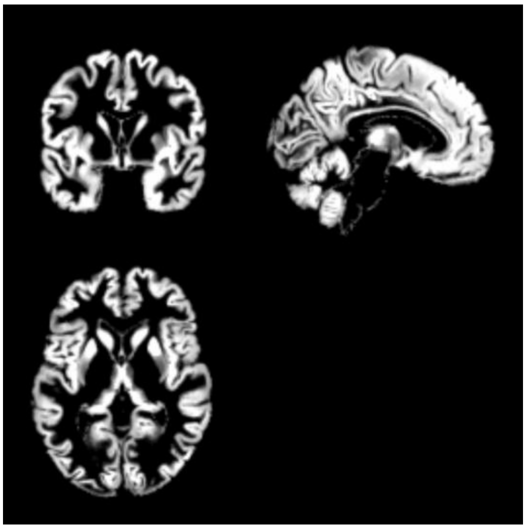

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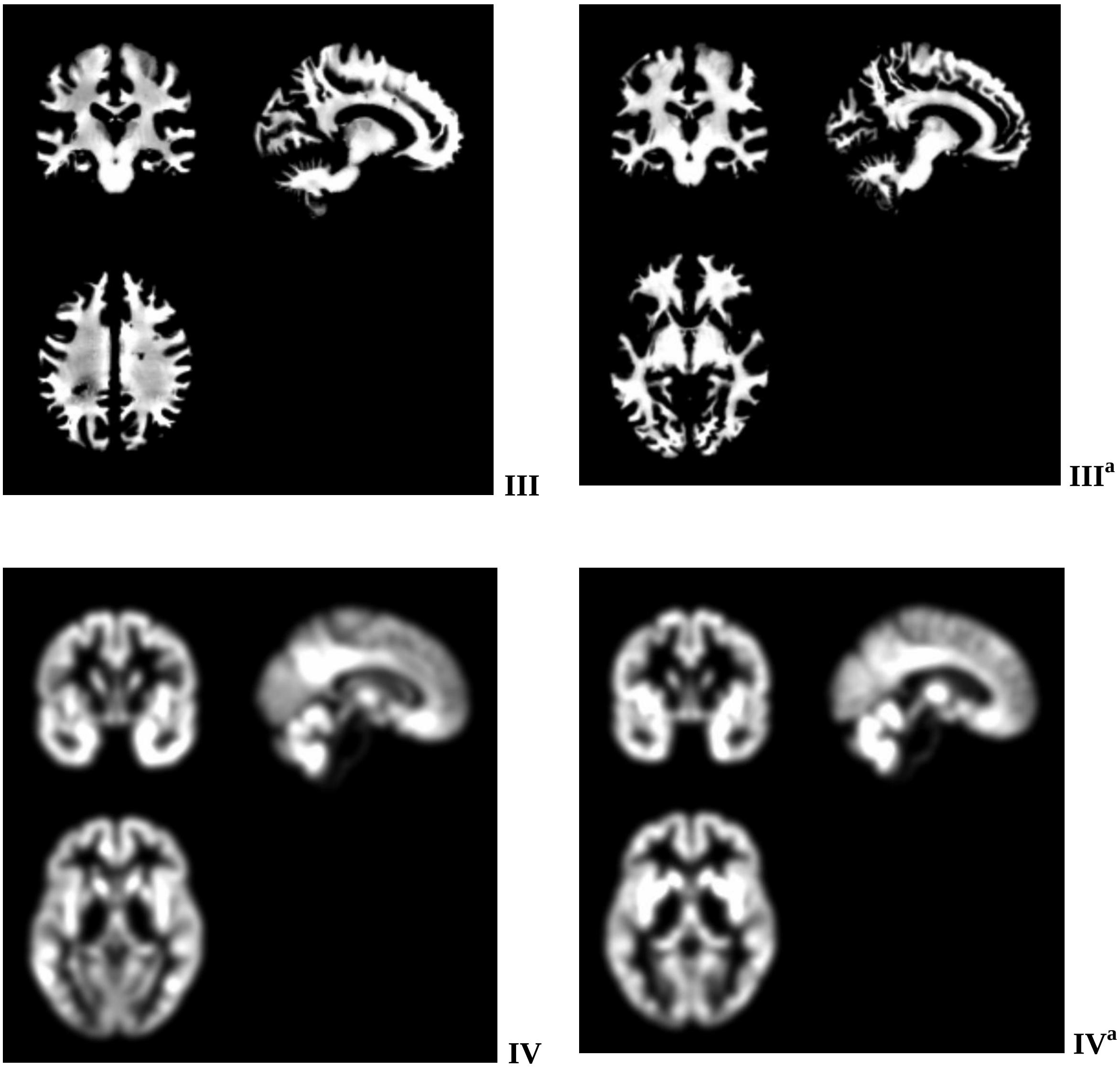

Figure 1 - Comparison MRI assessment of MS patient (left) and normal control (right)[a] **I**- T1 average acquisition **II**-Segmented grey matter analysis **III-** Segmented white matter analysis **IV-** Smoothed masked (pre-processing for VBM).

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