Research

Social Cognition in Early Multiple Sclerosis: Neuropsychological and Anatomical Approach

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La Cognición Social en la Esclerosis Múltiple Temprana: Enfoque neuropsicológico y anatómico

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Abstract

Cognitive impairment and deficits in Social Cognition (SC) are frequent in patients with Multiple Sclerosis (MS). The aim of the present work is to study SC in patients with early MS and to analyze its neuroanatomical correlation. Thirty-four patients with relapsing remitting MS, with ≤ 2 years of disease progression and EDSS and ≤ 2, and 30 healthy control subjects matched for age, sex, and educational level were recruited. Subjects performed a comprehensive neuropsychological assessment (Rao BRB). SC was assessed using the International Affective Picture System IAPS, The Eyes in the Mind Test, the Empathy Quotient, and the Faux Pas Test. The anatomical correlation of patients with deficits in social cognition was studied through brain MRI and voxel-based morphometric for which cortical reconstruction and volumetric segmentation were performed using Freesurfer processing software. Patients showed significant deficits in executive functions, verbal memory and language tests. SC assessment showed that patients presented greater difficulties in the Faux Pas Test ($p = 0.023$), The Mind in the Eyes Test ($p = 0.014$), and presented a positive bias in the interpretation of neutral images of the IAPS ($P = 0.023$). Furthermore, patients with CS deficits presented less cortical thickness in areas of the right supramarginal gyrus, pars opercularis, and anterior cingulum.

Keywords: Cognitive Dysfunction; Social Cognition; Multiple Sclerosis; Neuropsychological Test; Disease Progression

Resumen

El deterioro cognitivo y los déficits en la cognición Social (CS) son frecuentes en pacientes con Esclerosis Múltiple (EM). El objetivo del presente trabajo es estudiar la CS en pacientes con EM temprana y analizar su correlación neuroanatómica. Se reclutaron 34 pacientes con EM remitente recidivante, con ≤ 2 años de progresión de la enfermedad y EDSS y ≤ 2, y 30 sujetos control sanos emparejados por edad, sexo y nivel educativo. Los sujetos realizaron una evaluación neuropsicológica completa (Rao BRB). La CS se evaluó mediante el Sistema Internacional de Imágenes Afectivas IAPS, el Test de la Mirada, el Cociente de Empatía y el Test de Faux Pas. La correlación anatómica de los pacientes con los déficits en cognición social se estudió mediante resonancia magnética cerebral y morfometría basada en vóxeles, para lo cual se realizó la reconstrucción cortical y la segmentación volumétrica mediante el software de procesamiento Freesurfer. Los pacientes mostraron déficits significativos en las funciones ejecutivas, la memoria verbal y las pruebas de lenguaje. La evaluación de la CS mostró que los pacientes presentaban mayores dificultades en el Faux Pas Test ($p = 0.023$), el Test de la Mirada ($p = 0.014$), y presentaban un sesgo positivo en la interpretación de imágenes neutras del IAPS ($P = 0.023$). Además, los pacientes con déficits de CS presentaron un menor grosor cortical en áreas del giro supramarginal derecho, la pars opercularis y el cíngulo anterior.

Palabras clave: Disfunción cognitiva; Cognición social; Esclerosis múltiple; Test neuropsicológico; Progresión de la enfermedad

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Introduction

Multiple sclerosis (MS) is a persistent, neuroinflammatory disease of the central nervous system affecting young adults with physical, emotional and cognitive symptoms. Cognitive impairment is present in 40-70% of MS cases and different subtypes and stages of the disease have been reported (Langdon, 2011). Related difficulties mainly affect attention, memory, language, executive functions, orientation and visuospatial abilities (Chiaravalloti / DeLuca, 2008).

Social cognition (SC) is the skill to process, store and use information about social situations. SC includes several subcomponents such as theory of mind, emotion recognition, emotional reactivity, and empathy.

MS patients are likely to have some level of compromised social cognition in the specific subcomponents of the theory of mind (the skill to infer the mental state, thoughts, and intentions of others) and emotion recognition (Ouellet et al., 2010; Banati et al., 2010). A recent study also found diminished emotional reactivity to negative stimuli in MS patients (Di Bitonto et al., 2011).

Although CS in MS patients has begun to be studied in recent years, there is still little knowledge about the impact of MS on CS in the early stages of the disease, when the burden of injury is low and physical disability is not yet present.

In times where new treatments have modified the motor impact of the disease, clinical attention moves towards other symptoms that compromise these patients' quality of life. In this framework, CS plays a predominant role, as appropriate social interaction requires preserved social cognition; CS impairment can lead to interpersonal conflicts and misunderstandings. These conflicts can affect multiple areas of exchange, such as family, friends, and work spheres (Cotter et al., 2016) . This study aims to assess social cognition's level of compromise in the early stages of multiple sclerosis, even when the physical impact is not yet present. We also intend to investigate the association between CS and general cognitive functioning, neuropsychiatric symptoms, and life quality. Finally, we will look for the relationship between these symptoms and the structural damage that the disease may generate by studying magnetic resonance imaging and voxel-based morphometry techniques.

Materials and methods

Subjects

According to the McDonald et al. (2001) criteria thirty-four patients with MS in relapse and remission were recruited. Patients were classified through the neuroimmunology service of our institution. Inclusion criteria for the study: patients had to have less than two years of disease duration and a score of less than 2 points on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Patients with significant upper extremity motor impairment, visual acuity or visual field deficits, history of alcohol or drug abuse, head trauma, major psychiatric disorders, other neurological disorders or systemic diseases were excluded.

All patients were evaluated after 90 days recovery from the last relapse or discontinuation of steroid treatment. Of thirty-four patients, seven received interferonß, eight-dimethyl fumarate, thirteen fingolimod, two natalizumab, three glatiramer acetate and one teriflunomide.

Thirty healthy controls were recruited from a local volunteer pool, matched for age, gender, and educational level.

Both groups underwent a complete neuropsychological evaluation, with tests of social cognition. Patients with brain imaging less than one month before the assessment were included in the structural sub-study.

All subjects signed an informed consent form prior to the evaluations. Prior to this, the local ethics committee approved the protocol.

Cognitive assessment

Subjects' cognition was evaluated with the Spanish version of the Brief Repeatable Neuropsychological Test Battery (BRB) (Cáceres, Vanotti, Rao & RECONEM Workgroup, 2011). This battery includes tests of verbal memory (selective recall test), visual memory (7/24 test), language (FAS), attention (oral version of the digit-symbol test), and executive functions (PASAT 3 sec. and PASAT 2 sec.). Fatigue and neuropsychiatric scales assessing anxiety and depression (FSS and HADS) were also administered. The MusiQoL scale sets the quality of life.

Assessment of social cognition

CS was assessed with an extensive battery that included tests of several of its components. Theory of mind (ToM) was assessed with the Eyes Test and the Faux Pas Test. Emotional processing was assessed using the International Affective Imagery System. Empathy was assessed with the Empathy Quotient.

- *Eyes Test*

Task consists of describing a person's emotional/mental state based solely on their eyes' image in a fixed-choice context (Baron-Cohen & Wheelwright, 2001). Subjects were presented with the Spanish version of the task in which 36 stimuli are presented (Román et al., 2012). Subjects must identify the emotional/mental state of the image by choosing one of the four options presented.

- *Faux Pas Test*

This test consists of 10 short stories containing "faux pas" situations (someone who mistakenly says something they should not) (Stone, Baron-Cohen & Knight, 1998). These are read to the person and displayed on a screen; then, subjects are asked questions to determine whether they recognize the error. Different types of errors are computed.

- *Empathy Quotient*

The Empathy Quotient (Baron-Cohen & Wheelwrights, 2004) is a self-administered questionnaire of 60-item designed to measure empathy in adults.

- *International Affective Picture System (IAPS)*

IAPS (Lang, Bradley & Cuthbert, 2008) is a set of static imagery stimuli based on the dimensional model of emotions. The collection contains several types of images that can be scored on three main dimensions: arousal, valence, and dominance. Our work followed the integrated model that states that the first two dimensions (arousal and valence) capture the global and essential emotion elements. The stimuli consisted of 38 color images from the International Affective Imagery System, two of which were used as practice images, and the other 36 were used as target stimuli. The images were selected following the paradigm designed by Louwerse, Tulen, van der Geest, van der Ende & Verhulst (2014). This design discriminates between social content (social vs. non social) and pleasantness (pleasant, neutral, or unpleasant).

Six categories were constructed, each containing six images:

1. Social - pleasant (Valence index> 6, arousal index> 4).
2. Social - neutral (Valence index 4-6, arousal index 0-4).
3. Social - unpleasant (Valence index 0-4, arousal index > 4).
4. Non-social-pleasant (Valence index> 6, arousal index> 4).
5. Non-social: neutral (Valence index 4-6, arousal index 0-4).
6. Non-social: unpleasant (Valence index 0-4, arousal index > 4).

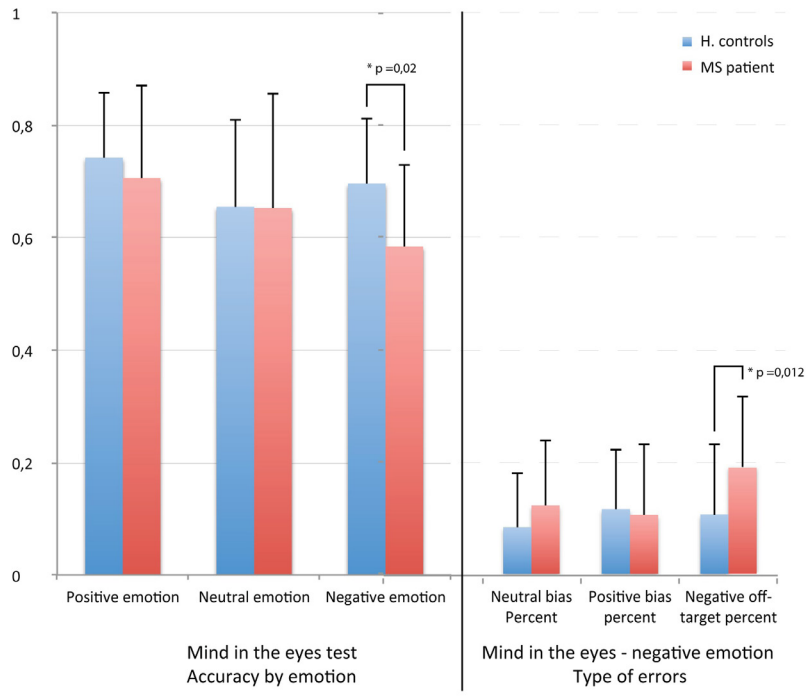

Figure 1. Eyes test.
Source: Authors.

Subjects were presented with the images on a screen and had to rate each photo using the Mannequin Self-Assessment System (Figure 1) (Bradley & Lang, 1994).

The left block shows the performance of both groups by emotion group. The adjacent graph quantifies the number of errors in detecting negative emotions. The error was to classify the image as neutral bias or optimistic bias. Despite identifying the group as unfavorable, the emotion could not be correctly identified (negative off-target).

MRI and voxel-based morphometry

The patient group was evaluated with brain MRI with volumetric sequences. Voxel-based morphometry was performed. This was followed by cortical reconstruction and volumetric segmentation using Freesurfer processing software. In previous publication technical details of these procedures are described.

- *Statistical analysis.*

Statistical analysis was performed using R version 3.6.1. For the study of the psychometric results, a T-test was used to compare means when the assumption of normality made it possible; when it was not possible, the Mann-Whitney U-test was used. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the distribution.

Images were subjected after processing in Freesurfer to a group surface analysis using a general linear model with the Qdec platform. For the analysis, the group was divided into two groups, one with poor eye test performance and one with good performance. For this, the control group was used as a cut-off point for normality. The surface analysis was performed on a model of covariance with the age of the patients, and clusters of differences between the groups were obtained. For the creation of clusters, a statistical significance limit was set at 0.01, and a sensitivity threshold was set at surfaces deviating beyond 1.5 standard deviations from normalization towards both extremes.

Results

Demographic, cognitive, and neuropsychiatric outcomes

The clinical and demographic data of the participants are shown in Table 1. No significant differences were found in age, gender, educational level or neuropsychiatric scales assessing depression, anxiety and fatigue. However, patients showed significant impairment in cognitive tests of verbal memory (SRT-A $p = 0.002$, SRT-R $p = 0.029$, SRT-D $p = 0.002$), executive functions (PASAT 3 $p = 0.038$, PASAT 2 $p = 0.023$, Digits Back $p = 0.027$.) and language (FAS $p = 0.0001$). Differences were also found in quality of life (MusiQuol $p = 0.005$). There were no differences in-group performances on measures of attention (DSMT and Digit Forwards; Table 2).

Table 1.
Demographic Results.

	CS	MS	
	Mean (SD)	Mean (SD)	p
Age	33.79 (7.69)	34.71 (8.17)	0.652
Education (years)	17.1 (1.39)	16.44 (2.16)	0.162
Sex (% men)	46.70%	41.20%	0.659
Duration of illness (months)	-	17.28 (6.33)	-
MMSE	29.97 (0.18)	29.5 (0.75)	0.001

Source: Authors.

Table 2.
Cognitive Assessment.

	CS	MS	
	Mean (SD)	Mean (SD)	p
TSM-A	55.37 (9.77)	45.65 (14.04)	0.002
TSM-R	46.53 (12.96)	38.09 (16.65)	0.029
TSM-D	10.77 (1.59)	8.88 (2.79)	0.002
PASAT 3	50.13 (8.28)	44.65 (11.85)	0.038
PASAT 2	43.8 (9.36)	38.38 (9.01)	0.023
FAS	49.57 (10.50)	37.97 (11.39)	0.0001
7/24 1-5	33.2 (2.58)	31.44 (4.24)	0.053
7/24 dis	4.3 (2.15)	4.93 (1.94)	0.249
7/24 imm	6.5 (1.38)	6.47 (1.08)	0.924
7/24 diff	6.5 (1.38)	6.29 (1.22)	0.529
Dig Fow	6.6 (0.77)	6.32 (0.94)	0.208
Dig Back	5.31 (1.00)	4.65 (1.28)	0.027
Boston Naming Test	28.87 (1.38)	27.5 (2.90)	0.022
TDS	64 (9.40)	59.24 (11.89)	0.083
MusiQol	72.66 (11.11)	81.13 (11.99)	0.005
HADS- Anxiety	7.87 (2.54)	9.33 (3.40)	0.059
HADS- Depression	2.77 (2.67)	4.06 (3.49)	0.1
Fatigue Severity Scale	30.30 (10.81)	30.38 (14.22)	0.98

Source: Authors.

Social cognition outcomes

The CS and QoL results are shown in Table 3. The ToM assessment showed that patients presented more significant difficulties in identifying mental states when confronted with negative stimuli in the Eyes Test ($p = 0.014$), evidencing deficits in inferring others' states (Figure 1).

In addition, the stories score on the Faux Pas task was significantly lower in the MS group, showing ToM deficits in detecting socially inappropriate behavior (p = 0.009). In this test, the groups did not differ in control stories or memory scores, revealing no memory or comprehension biases in their response.

With respect to IAPS performance, a significant positive bias was observed in the interpretation of neutral images in the emotional reactivity test (Non-neutral social images p = 0.023). As shown in Figure 2, patients tended to assign a more positive valence to non-social imagery than normal controls. No differences were observed in empathy quotient performance.

TABLE 3.
Social Cognition Outcomes.

	CS	MS	
	Mean (SD)	Mean (SD)	p
Eye Test			
Total Score	25.23 (3.07)	24.18 (4.15)	0.257
Positive emotion	10.00 (1.49)	9.65(2.21)	0.463
Negative Emotion	9.93 (1.76)	8.68 (2.17)	0.014
Emotion Neutral	5.30 (1.42)	6.03 (1.93)	0.094
Test Faux Pas			
Faux pas stories	27.28 (4.04)	24.21 (4.91)	0.003
Control stories	9.93 (0.37)	9.59 (0.96)	0.074
Stories Memory	19.79 (0.49)	19.26 (1.33)	0.0548
Faux pas Total Score	35.97 (7.86)	33.79 (5.02)	0.005
International Affective Picture System (IAPS)			
Valence			
Non-social pleasant	6.86 (1.23)	7.16 (1.21)	0.329
Non-social unpleasant	1.85 (0.97)	1.72 (0.81)	0.563
Non-social neutral	5.12 (0.80)	5.59 (0.80)	0.023
Socially pleasant	7.38 (1.23)	7.92 (0.92)	0.050
Socially unpleasant	1.65 (0.98)	1.40 (0.57)	0.201
Social neutral	5.21 (0.72)	5.62 (0.93)	0.058
Arousal			
Non-social pleasant	5.24 (0.95)	5.09 (1.71)	0.669
Non-social unpleasant	6.73 (1.20)	6.75 (1.54)	0.951
Non-social neutral	3.87 (1.12)	3.72 (0.99)	0.556
Socially pleasant	6.07 (0.96)	5.70 (1.70)	0.296
Socially unpleasant	7.16 (1.08)	7.01 (1.57)	0.670
Social neutral	4.17 (1.17)	3.98 (1.18)	0.518

Source: Authors.

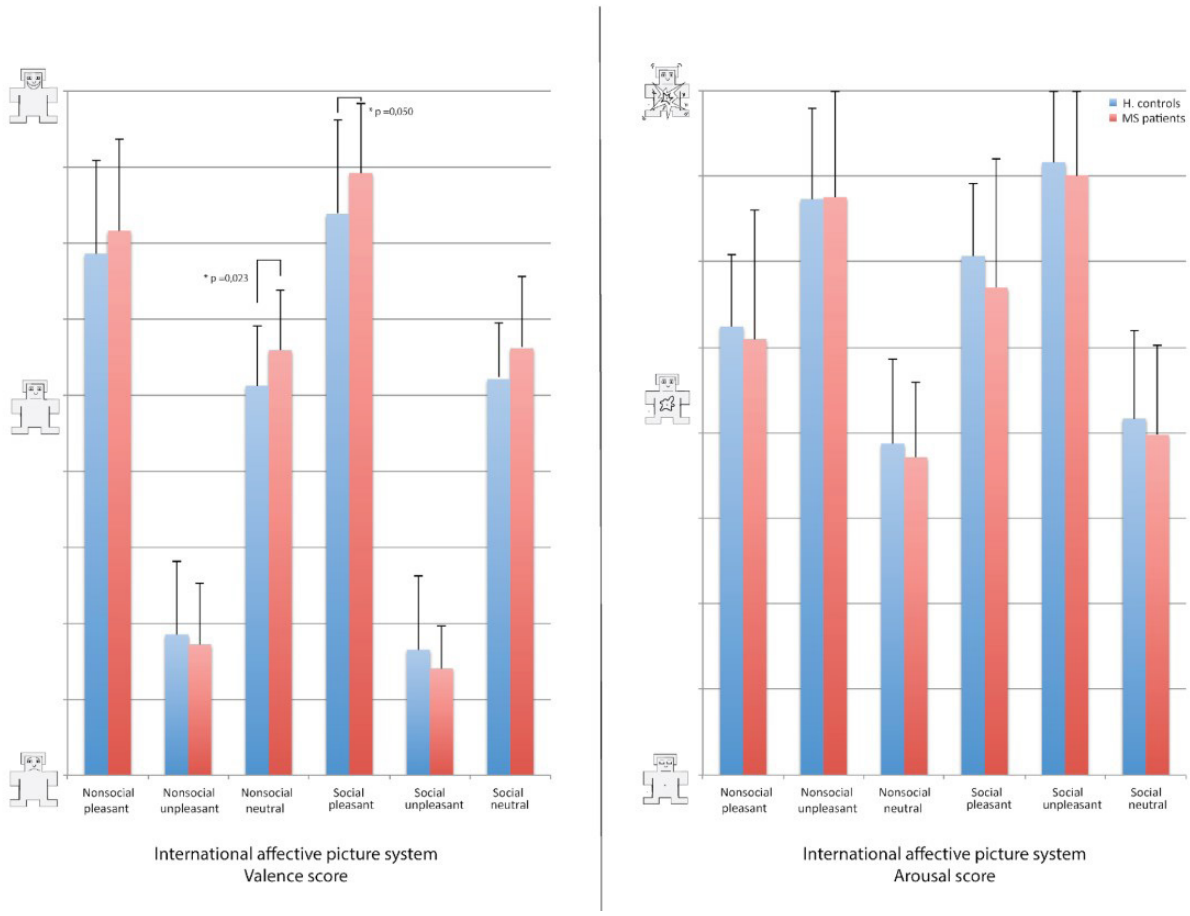

Figure 2. IAPS.
Source: Authors.

Performance of both groups in the IAPS tasks, in the left, blocks the account in detecting the valence of the perceived emotion and arousal. As a scale, the graph was constructed similar to the patient's scale score.

Influence of fatigue, depression, and anxiety on social cognition scores

Neuropsychological and social cognitive performance may be altered by fatigue and neuropsychiatric symptoms. In our study, fatigue scores assessed with the FSS showed no significant differences between groups ($p = 0.98$). Likewise, depression and anxiety, as assessed by the HADS, were not significantly different between groups ($p = 0.1$ and $p = 0.059$).

Correlation results

The correlations between neuropsychological and social cognition tests in people with MS were then assessed.

Significant correlations were found between negative emotions and PASAT 3 ($p = 0.003$, $r = 0.497$), and PASAT 2 ($p = 0.039$, $r = 0.37$). Similarly, the Faux Pas Stories score correlated with SRT storage and delayed scores ($p = 0.021$, $r = 0.39$; $p = 0.029$ $r = 0.38$). The Faux Pas total score was also correlated with SRT storage and delayed scores ($p = 0.010$, $r = 0.43$; $p = 0.029$, $r = 0.37$, respectively).

The IAPS non-social neutral total valence score showed only a positive correlation with the quality of life as measured by MusiQol ($p = 0.03$, $r = 0.27$).

Voxel-based morphometry and topographic analysis

Figure 3 summarizes the differential clusters of cortical thickness, where the comparatively lower thickness was found for the group with worse social cognition performance. The most significant differential clusters found comprise the right supramarginal gyrus, pars opercularis, and anterior cingulate. The specific extent of these areas can be visualized on the brain surface (in an inflated reconstruction of the brain to visualize gyri and sulci at the same time) on a thermal scale, regional differences, and the extent of the clusters in both hemispheres.

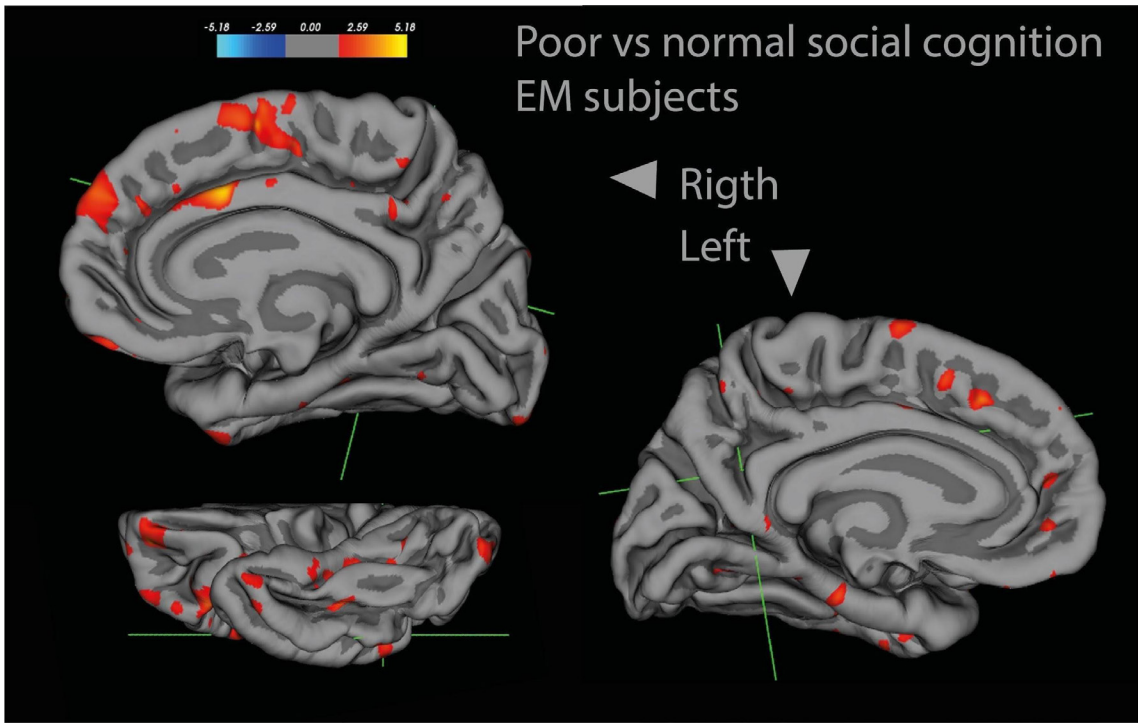

Figure 3. Reconstruction of morphometric analysis. Right brain.
Source: Authors.

Major differential clusters between patients with normal and impaired social cognition. The magnitude of the differences in standard deviations concerning the regular group is shown in the thermal scale.

Discussion

The present study assessed cognitive and CS performance in early MS and showed how patients had deficits in cognitive tests of memory, language, and executive functions. Two aspects of CS were affected: theory of mind and emotional reactivity. No difficulties were found in the self-reported empathy quotient.

There is proven evidence of cognitive difficulties in patients with MS in the early stages and CS difficulties in later stages of the disease. This suggests that there may be alterations in functional brain responses during specific emotion recognition processes (Jehna et al., 2011).

The results of the Eyes Test are consistent with previous studies in which MS patients showed difficulties in detecting facial emotions of anger and fear (Henry et al., 2009).

The two studies complement each other, as Henry's study used a task assessing emotion recognition, and our research used a task considering ToM. In our study, we specifically examined the type of emotion identified (i.e., positive, neutral, or negative) and found that consistent with Henry's results; patients did not identify negative emotions. This dissociation suggests that MS patients may have retained positive emotions and impaired recognition of negative emotions.

The literature (Calder, Keane, Lawrence & Manes, 2006) confirms dissociated neural substrates for the recognition of specific emotions and specific deficits in recognition of particular emotions for specific neurological conditions (Sprengelmeyer et al., 2002). It is, therefore, possible that particular difficulty in the interpretation of negative emotions is present in MS.

Furthermore, these results correlated with PASAT performance (3" and 2".). PASAT is a complex neuropsychological task that mainly involves selective attention, executive functions (working memory) and information processing speed. These cognitive functions could be involved in the Eyes Test. As the stimulus and response options are always present on the screen, the task does not pose any working memory. Information processing speed is not necessary for this task, as the subject has unlimited time to respond. Therefore, it is very likely that selective attention is the cognitive function that affects the subject's performance in this task.

Patients also failed to detect inappropriate responses in the Faux Pas task. MS patients successfully noticed that a faux pas was not present but did not recognize faux pas when they occurred. This suggests that they have difficulty reading or identifying subtle inappropriate behavior in social situations. The faux pas results correlated with the selective memory test results, assuming that the task may require storage and delays in verbal memory demand. However, it is essential to note that no significant differences were found between the groups in the Faux pas task's memory score. Therefore, patients could respond adequately to the memory demands of the Faux Pas test.

The IAPS results require a different interpretation. Differences in emotional reactivity were only present for neutral, non-social stimuli (patients tended to assign a more pleasant value to neutral images than controls). These results suggest that a neutral image may be more sensitive than pleasant or unpleasant images to subtle emotional reactivity changes. Other semantic systems processes are probably involved when processing a stimulus with a social component and a positive or negative valence.

We studied the empathy, theory of mind, and emotional reactivity in a sample of newly diagnosed MS subjects without motor impairment. We confirmed the presence of CS impairments and emotional reactivity deficits in early MS. These deficits are independent of neuropsychiatric symptoms, such as depression or anxiety. Global CS performance was not determined by other neuropsychiatric conditions, such as depression or anxiety because the differences between groups were not significant. However, changes in patients' quality of life was associated with emotional reactivity scores and is based more on psychological aspects than cognitive components.

Therefore, we can conjecture that a recent detection of illness leads individuals to reinterpret their emotional environment and to reconsider the value of life in terms of attributing positive value (or valence) to common objects, even bland ones, such as the non-neutral

IAPS Social Images. Furthermore, the patient's performance on this task did not correlate with cognitive performance, but correlated with quality of life. Thus, it can be inferred that emotional reactivity performance is associated with the patient's quality of life and is independent of cognitive functioning.

In our study, the regions of the right supramarginal gyrus, pars opercularis, and anterior cingulate cortex of the group of patients with deficits in social cognition showed less cortical thickness than the group of patients with good social cognition.

Consistent with our results, functional MRI studies were published in a comprehensive review (Schulz et al., 2009). Analyzed the areas involved in the generation of socially appropriate behaviors in emotional contexts. Appropriate social responses were associated with the par opercularis in the inferior frontal gyrus, the temporoparietal junction, the superior parietal lobe, and the parietal sensory association cortexes.

Furthermore, research (Apps, Rushworth & Chang, 2016), argues that the anterior cingulate cortex is involved in a wide range of behavioral and cognitive processes and contributes to social behavior by participating in human interaction's social-cognitive skills.

The anterior cingulate cortex is involved in cognition and decision-making, including social cognition (Mao et al, 2017) and social interaction. A recent study in MS patients (Batista et al., 2017) studied the correlation between different cortical areas and performance on the Eyes Test and found results consistent with ours: a positive correlation between social cognition and the fusiform gyrus. superior temporal gyrus. superior parietal gyrus. supramarginal gyrus, entorhinal cortex, medial orbitofrontal cortex and anterior gyrus cortex.

Against this background, our work sheds light on controversial issues in the disease, a critical point of contention being early grey matter involvement. The evidence for measurable participation of a cortical symptom such as social cognition with an objective parallel in the cortex's thickness merely proves the point. New questions arise from this analysis, for example, whether this structural abnormality is the result of the disease or is a predisposition (a sort of lower brain reserve) to the disease manifesting such involvement.

This study is the first to assess emotional reactivity in early MS. Di Bitonto et al. (2011) reported deficits in emotional reactivity stimuli using the IAPS, although her study was conducted with a small sample of women and did not consider time since diagnosis. In addition, IAPS images and sound were not classified into social and non-social stimuli. Therefore, these results cannot be compared with our findings.

In our study we bring a novel approach to the well-known phenomenon of social cognition deficits in MS. To this end, we apply a multidimensional approach in which we consider both the specific biological aspects (neuroimaging) and the psychological impact of the disease on patients with early MS. Our findings emphasise the importance of assessing CS in the early stages of the disease in order to intervene before these difficulties worsen and interfere with social functioning. Therefore, these results may also be relevant for the design of appropriate patient counselling strategies.

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References

Apps, M. A.; Rushworth, M. F. & Chang, S. W. (2016). The Anterior Cingulate Gyrus and Social Cognition: Tracking the Motivation of Others. *Neuron,* 90(4), 692–707. https://doi.org/10.1016/j.neuron.2016.04.018

Banati, M.; Sandor, J.; Mike A.; Illes, E.; Bors, L.; Feldmann, A.; Herold, R. & Illes, Z. (2010). Social cognition and Theory of Mind in patients with relapsing-remitting multiple sclerosis. *Europena Journal of Neurology*, 17(3), 426–433. https://doi.org/10.1111/j.1468-1331.2009.02836.x

Baron-Cohen, S. & Wheelwright, S. (2004). The Empathy Quotient: An Investigation Of Adults With Asperger Syndrome Or High Functioning Autism, And NormalSex Differences, *Journal of Autism and Developmental Disorders*, 34(2), 163–175. https://doi.org/10.1023/b:jadd.0000022607.19833.00

Batista, S.; D'Almeida, O. C.; Afonso, A.; Freitas, S.; Macário, C.; Sousa, L.; Castelo-Branco, M.; Santana, I. & Cunha, L. (2017). Impairment of social cognition in multiple sclerosis: Amygdala atrophy is the main predictor. *Multiple Sclerosis Journal*, 23(10), 1358–1366. https://doi.org/10.1177/1352458516680750

Bradley, M. & Lang, P. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry*, 25(1), 49–59. https://doi.org/10.1016/0005-7916(94)90063-9

Cáceres, F.; Vanotti, S.; Rao, S. & RECONEM Workgroup. (2011). Epidemiological characteristics of cognitive impairment of multiple sclerosis patients in a Latin American country. *Journal of Clinical and Experimental Neuropsychology*, 33(10), 1094–1098. https://doi.org/10.1080/13803395.2011.603690

Calder, A. J.; Keane, J.; Lawrence, A. D. & Manes F. (2004). Impaired recognition of anger following damage to the ventral striatum. *Brain: a journal of Neulogy*, 127(Pt 9), 1958–1969. https://doi.org/10.1093/brain/awh214

Chiaravalloti, N. D. & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurol,* 7(12), 1139–1151. https://doi.org/10.1016/s1474-4422(08)70259-x

Cotter J.; Firth, J.; Enzinger, C.; Kontopantelis, E.; Yung, A. R.; Elliott, R. & Drake, R. J. (2016). Social cognition in multiple sclerosis: A systematic review and meta-analysis. *Neurology,* 87(16), 1727–1736. https://doi.org/10.1212/wnl.0000000000003236

Di Bitonto, L.; Longato, N.; Jung, B.; Fleury, M.; Marcel, C.; Collongues, N.; de Seze, J. & Blanc, F. (2011). Reduced emotional reactivity to negative stimuli in multiple sclerosis, preliminary results. *Revue Neurolique (Paris)*, 167(11), 820–826. https://doi.org/10.1016/j.neurol.2011.01.024

Henry, J. D.; Phillips, L. H.; Beatty, W. W.; McDonald, S.; Longley, W. A.; Joscelyne, A. & Rendell, P. G. (2009). Evidence for deficits in facial affect recognition and theory of mind in multiple sclerosis. *Journal of the International Neuropsychological Society*, 15(2), 277–285. https://doi.org/10.1017/s1355617709090195

Jehna, M.; Langkammer, C.; Wallner-Blazek, M.; Neuper, Ch.; Loitfelder, M.; Ropele, S.; Fuchs, S.; Khalil, M.; Pluta-Fuerst, A.; Fazekas, F. & Enzinger, Ch. (2011). Cognitively preserved MS patients demonstrate functional differences in processing neutral and emotional faces. *Brain Imaging and Behavior*, 5(4), 241–251. https://doi.org/10.1007/s11682-011-9128-1

Kurtzke J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, 33(11), 1444–1452. https://doi.org/10.1212/wnl.33.11.1444

Lang, P. J.; Bradley, M. M. & Cuthbert, B. N. (2008). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. [*Technical Report A-8*]. Gainesville: University of Florida. Available from https://www2.unifesp.br/dpsicobio/adap/instructions.pdf

Langdon, D. W. (2011). Cognition in Multiple Sclerosis. *Current Opinion in Neurology*, 24(3), 244–249. https://doi.org/10.1097/wco.0b013e328346a43b

Louwerse, A.; Tulen, J. H.; van der Geest, J. N.; van der Ende, J. & Verhulst, F. C. (2014). Greaves-Lord K. Autonomic responses to social and nonsocial pictures in adolescents with autism spectrum disorder. *Autism Research*, 7(1), 17–27. https://doi.org/10.1002/aur.1327

Mao, C. V.; Araujo, M. F.; Nishimaru, H.; Matsumoto, J.; Tran, A. H.; Hori, E.; Ono, T. & Nishijo, H. (2017). Pregenual Anterior Cingulate Gyrus Involvement in Spontaneous Social Interactions in Primates-Evidence from Behavioral, Pharmacological, Neuropsychiatric, and Neurophysiological Findings. *Frontiers in Neuroscience*, 11, 1–10. https://dx.doi.org/10.3389%2Ffnins.2017.00034

McDonald, W. I.; Compston, A.; Edan, G.; Goodkin, D.; Hartung, H. P.; Lublin, F. D.; McFarland, H. F.; Paty, D. W.; Polman, C. H.; Reingold, S. C.; Sandberg-Wollheim, M.; Sibley, W.; Thompson, A.; Van den Noort, S.; Weinshenker, B. Y.; Wolinsky, J. S. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology*, 50(1), 121–127. https://doi.org/10.1002/ana.1032

Ouellet, J.; Scherzer, P. B.; Rouleau, I.; Métras, P.; Bertrand-Gauvin, C.; Djerroud, N.; Boisseau E. & Duquette, P. (2010). Assessment of social cognition in patients with multiple sclerosis. *Journal of the IntNeuropsychological Society*, 16(2), 287–296. https://doi.org/10.1017/s1355617709991329

Román, F.; Rojas, Galeno; N. R., Iturry, M.; Blanco, R.; Leis, A.; Bartoloni, L. & Allegri , R. F. (2012). Baremos del Test de la Mirada en español en adultos normales de Buenos Aires. *Revista Neuropsicología Latinoamericana*, 4(3), 1–5. Disponible en https://www.neuropsicolatina.org/index.php/Neuropsicologia_Latinoamericana/article/view/108

Schulz, K. P.; Clerkin, S. M.; Halperin, J. M.; Newcorn, J. H.; Tang, C. Y. & Fan, J. (2009). Dissociable neural effects of stimulus valence and preceding context during the inhibition of responses to emotional faces. *Hum Brain Mapp*, 30(9), 2821–2833. https://doi.org/10.1002/hbm.20706

Sprengelmeyer, R.; Young, A. W., Calder, A. J., Karnat, A.; Lange, H.; Hömberg, V.; Perrett, D. I. & Rowland, D. (1996). Loss of disgust. Perception of faces and emotions in Huntington's disease. *Brain: a journal of Neulogy*, 119(Pt 5), 1647–1665. https://doi.org/10.1093/brain/119.5.1647

Stone, V. E.; Baron-Cohen, S. & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience*, 10(5), 640–656. https://doi.org/10.1162/089892998562942