Multiple Sclerosis and Related Disorders 20 (2018) 122–128

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Relationship between Social Cognition and traditional cognitive impairment in Progressive Multiple Sclerosis and possible implicated neuroanatomical regions

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ARTICLE INFO

Keywords:
Multiple Sclerosis
Social Cognition
MRI
Quality of life
Cognitive impairment
Neuropsychology

ABSTRACT

Background: Cognitive impairment is a relevant contributor of the medical and social burden in Progressive MS. Social Cognition, the neurocognitive processes underlying social interaction, has been explored mainly in European and North American cohorts, influencing social aspects of quality of life (QOL) of early MS patients and families. Few studies have studied Social Cognition in Progressive MS and the literature on its neuroanatomical bases or brain atrophy measurements is still scarce.

Objectives: To explore the relationship between Social Cognition performance and its correlations with traditional cognitive domains, brain atrophy and QOL in primary and secondary Progressive MS patients.

Methods: Cross-sectional analysis including: mini-Social-Cognition-and-Emotional-Assessment (mini-SEA), neuropsychological battery, disability, depression, fatigue, QOL, and brain volume.

Results: Forty-three MS patients, 23 primary and 20 secondary Progressive, 65% women, mean age and disease duration of 57.2 and 15.7 years, respectively, with high levels of disability (median EDSS 6.0) and a widespread impairment in traditional domains (mostly episodic verbal/visual and working memories) were assessed. The Mini-SEA score was correlated with executive functions (cognitive shifts Rho:0.55; $p = 0.001$) analyzing the whole group, and with visual episodic memory (Rho:0.58, $p = 0.009$) in the primary Progressive MS group. Mini-SEA score was also correlated with total normalized grey matter volume (Rho:0.48; $p = 0.004$). Particularly, atrophy within bilateral cortical regions of orbitofrontal, insula and cerebellum, and right regions of fusiform gyrus and precuneus were significantly associated with higher Social Cognition impairment. In this cohort, QOL was not correlated with Social Cognition, but with EDSS, fatigue and depression.

Conclusions: In Progressive MS, Social Cognition is directly correlated with traditional cognitive domains such as executive function and episodic memory. It is also associated with global grey matter atrophy and regional atrophy within associative visual and executive cortical areas, but no correlations with QOL were found in this cohort. These findings may contribute to the understanding of the pathological bases behind Social Cognition in Progressive MS.

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https://doi.org/10.1016/j.msard.2018.01.013
Received 7 July 2017; Received in revised form 16 November 2017; Accepted 16 January 2018

1. Introduction

Progressive Multiple Sclerosis (MS) patients represent a population with a high medical and social burden. Cognitive impairment is a relevant contributor to this burden, including a wide range of traditional cognitive domains, such as working memory, processing speed, episodic memory and attention (Ruano et al., 2016).

Social Cognition is other relevant cognitive domain, which refers to the neurocognitive processes underlying social interaction, including the ability to attribute a mental state to others, empathy and emotional processing, enabling interpersonal relationships. It has been studied in neurodevelopmental, neurodegenerative and psychiatric disorders such as autism, schizophrenia and dementia (Bertoux et al., 2012), and interest has arisen the last few years in different subtypes of MS and in pediatric onset MS (Charvet et al., 2014), because of its influence on social aspects of quality of life of patients and families (Phillips et al., 2011). Although the severity of social cognitive deficits have been found to be related with the presence of deficits in other traditional cognitive domains, such as processing speed and executive function (Bora et al., 2016; Dulau et al., 2017) or episodic and working memory (Dulau et al., 2017), a specific cognitive pattern has not been consistently associated with Social Cognition (Cotter et al., 2016). Even less is known about the possible differences between primary and secondary Progressive patients, with studies including traditional domains varying from slightly different performance, to demonstrating worse performance in either of the two phenotypes (D'Amico et al., 2016).

The specific neural basis behind Social Cognition impairment in MS is still unknown. Although brain atrophy, including measures of global and regional grey matter volume, cortical thickness or structures such as the corpus callosum have been widely reported as being correlated with traditional cognitive performance (Filippi et al., 2010; Yaldizli et al., 2014), only few recent studies have begun to explore this clinical-radiological relationship in Social Cognition, including involvement of the amygdala, associative frontal/temporal/parietal areas (Batista et al., 2017a; Chalah et al., 2017) and diffuse patterns of white matter damage (Batista et al., 2017b), with a possible underrepresentation of the Progressive MS population.

In this article, our primary aim was to study Social Cognition in a cohort of inactive Progressive MS patients, and its correlations with clinical characteristics, cognitive impairment in traditional domains with an emphasis on information processing and executive function, imaging studies including global and regional brain atrophy, and quality of life. Then, taking into account the contradictory evidence assessing differences in cognitive performance between primary and secondary Progressive MS patients, as secondary aim, we compared both phenotypes, assuming *a priori* a similar performance between the groups.

2. Materials and methods

The study was conducted at the Multiple Sclerosis Program UC of the Pontifical Catholic University of Chile. This study was approved by the local Ethics Committee and all patients signed an informed consent.

2.1. Subjects

A prospective cohort of inactive primary and secondary Progressive MS patients was consecutively recruited from November 2014 to March 2015, including the baseline evaluation of a phase II clinical trial (NCT02273635). Inclusion criteria considered patients ≥ 18 years old, not receiving any disease modifying treatment, immunosuppression or corticosteroids for at least 6 months, and a Mini Mental State Examination > 24 (González-Hernández et al., 2009), according to a local regulatory law of individuals participating in clinical trials (Ley de Derechos y Deberes de las Personas en Atención de Salud). Exclusion criteria also considered any severe or decompensated chronic systemic or neuropsychiatric illness determined under revision of medical history, medical reports from treating physicians, and structured interviews and medical evaluation performed by a trained neurologist (EC, RUSM, CC) and neuropsychologist (MV, ART). Other chronic medications, including antidepressants, were permitted as long as they were being prescribed by a physician, and at stable dosage for the last 6 months. All evaluations were performed in an outpatient clinic of our MS program.

2.2. Disability measures

Disability was assessed using Expanded Disability Status Score (EDSS) (Kurtzke, 1983) and Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999), performed by a trained neurologist.

2.3. Social Cognition assessment

Social Cognition was evaluated using the mini-Social Cognition and Emotional Assessment (mini-SEA) (Bertoux et al., 2012, 2014), a 30 min composite battery which is the reduced version of the Social Emotional Assessment test (Funkiewiez et al., 2012). It consists of two different tests including a shortened version of the Faux-Pas (FP) and the Face Emotion Recognition (FER). FP includes ten narrative vignettes or short stories in which a character inadvertently hurts or offends another, using Theory of the Mind tasks to infer another's mental state making attributions to their knowledge, beliefs and emotions. Half of the vignettes are control stories and the other half include a principal character who inadvertently hurts or offends another, the “victim of the FP”. The subject is expected to recognize the situations in which a FP is committed, why the leading character did it (cognitive theory of mind, he didn’t mean it) and how the victim of the FP must have felt (affective theory of mind, we expect him to recognize that the victim must have had a negative emotion). FER consists in 35 pictures for face affect recognition of basic emotions among a list presented at the bottom of the screen including happiness, sadness, anger, surprise, fear, disgust and neutral. The implementation of the Spanish version of the mini-SEA was done at the Cognitive Neurosciences Laboratory of the CIAE, property of Universidad de Chile (AS, ART), with the permission of its author (Bertoux M). The official Spanish translation of the Faux Pas Recognition Test done by Serrano and Allegri (2006), and the same pictures of faces corresponding to the Ekman faces for the FER were used.

2.4. Neuropsychological battery

Cognitive evaluations were based on the Brief International Cognitive Assessment for MS (BICAMS) (Benedict et al., 2012), a short form of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006) including: 1) Processing speed with Symbol Digit Modality Test (SDMT) (Smith, 2002) 2) Verbal and Visual Episodic memory: including the Spanish version of the California Verbal Learning Test, Spanish version (CVLT)(Ponton et al., 1996) and the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1997) and 3) Executive functions: including working memory with Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977), inhibitory control with Stroop test Spanish version (Golden, 1994) and cognitive shifts with flexibility categorical and lexical fluency and control of interference (FAS) from the D-KEFS (Delis et al., 2001). Stroop test was included to evaluate inhibitory control and attention deficits, as it has also been performed in previous studies in MS patients (Amato et al., 2006). All the cognitive tests were performed in Spanish by a trained neuropsychologist (MV, ART). Impairment for a single test was defined as a Z score < − 1.5 and cognitive impairment was defined as a defect on two or more test measures (Benedict et al., 2006). (Differences and similarities between MACFIMS, BICAMS and the neuropsychological battery used in this study are shown in

Supplementary Table 1).

2.5. Other scales

Depression (Spanish Beck Depression Inventory II) (Sanz and Navarro, 2003; Melipillán et al., 2008), fatigue (Spanish Fatigue Severity Scale-FSS) (Krupp et al., 1995) and quality of life (Spanish Multiple Sclerosis Impact Scale 29-MSIS29) (Hobart et al., 2001) were also assessed.

2.6. Brain atrophy measurements

2.6.1. MRI acquisition

Whole brain isotropic 3D T1W MPRAGE MRI (TR: 7.52, TE: 3.44, Flip angle: 8°, FOV: 240 mm, 180 sagittal slices, slice thickness 1 mm, Matrix 240 × 223, Voxel size reconstruction 1 × 1 × 1 mm; Acquisition time 4:13) were acquired in a Philips Ingenia 1.5 T device with an 8-channel head coil.

2.7. Corpus callosum index

Corpus callosum index (CCI) was obtained on a conventional best mid-sagittal T1W image, by drawing a straight line at greatest anteroposterior diameter of CC and a perpendicular at its midline, owing to points a, b and c. Anterior (aa′), medium (bb′) and posterior (cc′) segments of CC were measured and normalized to its greatest anteroposterior diameter (a c′). CCI was then calculated using: CCI = (aa′ + bb′ + cc′)/a c′; Anterior CCI = aa′/a c′; Medium CCI = bb′/a c′; Posterior CCI = cc′/a c′ (Yaldizli et al., 2014; Figueira et al., 2007)

2.8. Structural Image Evaluation using Normalization of Atrophy (SIENAX)

Brain tissue volume, normalized for subject head size, was estimated with SIENAX (Smith et al., 2002), part of FSL (Smith et al., 2004), (Fmrib, Oxford, UK available at http://www.fmrib.ox.ac.uk/). SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to MNI152 space (using the skull image to determine the registration scaling); this is primarily in order to obtain the volumetric scaling factor, to be used as normalization for head size. Next, tissue-type segmentation with partial volume estimation is carried out in order to calculate total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, peripheral grey matter and ventricular CSF).

2.9. Voxel Based Morphometry (VBM)

Lesions were segmented by the lesion growth algorithm (Schmidt et al., 2012) as implemented in the LST toolbox version 1.2.3 (www.statisticalmodelling.de/lst.html) for SPM. The algorithm first segments the T1 images into the three main tissue classes (cerebrospinal fluid-CSF, grey matter-GM and white matter-WM). This information is then combined with the co-registered FLAIR intensities in order to calculate lesion belief maps. By thresholding these maps with a pre-chosen initial threshold (k) an initial binary lesion map is obtained which is subsequently grown along voxels that appear hyperintense in the FLAIR image. The result is a lesion probability map which, once in alignment with a T1 volume creates a filled image in native space. Then, volumes based on voxel-wise comparison of grey and white matter volumes was applied to T1 filled images by using SPM8 (Statistical Parametric Mapping 8; Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2015b (Matworks, Natick, MA, USA). T1 filled images were Segmented, Replaced to a DARTEL template and then normalized to MNI space using VBM8 preprocessing in SPM8 (Ashburner and Friston; Ashburner, 2007).

2.10. Statistical analysis

For the statistical analysis, we performed our main analyses using the whole cohort, exploring any significant differences between phenotype afterwards. We assumed no differences between both groups, and a cohesive hypothesis based on the literature to date was developed to respond four questions:

1) Do older and more disabled patients have more severe Social Cognition or other traditional cognitive deficits?
2) Is Social Cognition performance correlated with information processing and executive functioning?
3) a) Is global or regional brain atrophy correlated with poor performance in Social Cognition? b) Are there any specific grey matter structures involved with Social Cognition performance?
4) What variables influence the quality of life of patients with Progressive MS?

For question one, mini-SEA score and Z score of traditional neuropsychological test were correlated with age at disease onset, age at entry to this study and disease duration using Spearman Rho. Also, correlations with EDSS, MSFC fatigue and depression were performed.

For question two, mini-SEA score was correlated with Z score of different traditional cognitive test using Spearman correlation. Then, we performed a mean comparison of mini-SEA score among each traditional domain categorized in normal or impaired (Z score < -1.5) using Kruskal-Wallis test and Dunn´s multiple comparison test.

For question three, we correlated global and regional CCI (anterior, middle, posterior) and global tissue volume provided by SIENAX (normalized brain volume, normalized white matter volume and normalized grey matter volume) with mini-SEA score using Spearman Rho. For the VBM analysis a multiple regression was chosen as factorial design using mini-SEA score. Significance was assessed using a family wise error (FWE) corrected of p-value < 0.05 and Cluster size > 10 voxels.

For question four, we investigated which variables could explain the quality of life of Progressive MS patients through bivariate and partial correlations.

For statistical analysis IBM SPSS Statistics 21 and GraphPad 5 for graphics were used considering significant results at two-sided $p < 0.05$.

3. Results

3.1. Characteristics of included patients

Forty-Three Progressive MS patients were recruited, 23 primary and 20 secondary Progressive, 28 women, mean age 57.2 years, mean disease duration 15.7 years, median EDSS 6.0, and median MSIS29 of 91. According to MACFIMS criteria (Benedict et al., 2006), 86.8% of the whole group were cognitively impaired (80% of the primary and 94.4% of the secondary Progressive group, $p = 0.34$). No statistically significant differences were found between demographical, clinical or cognitive performance variables between the two phenotypes. Patients characteristics and cognitive performance of the whole Progressive MS group, and categorized according to phenotype are shown in Tables 1 and 2 respectively.

1) Do older and more disabled patients have more severe Social Cognition or other traditional cognitive deficits?

We found inverse correlations between disease duration and verbal episodic memory (Rho: − 0.32; p: 0.041) when analyzing the whole Progressive MS group, and between age at disease onset and visual episodic memory in primary Progressive patients (Rho: − 0.48, p: 0.003). We found no significant correlations between Social Cognition

Table 1
Baseline demographic and clinical characteristics of included patients.

Variable	Whole Group n = 43	PP n = 23	SP n = 20	*p value**
Gender n (%) women/men	28 (65.1)/15 (34.9)	14 (60.9)/9 (39.1)	14 (70)/6 (30)	0.53
Age years mean (SD, range)	57.2 (± 10.1, 32–76)	56.2 (± 9, 36–76)	57.3 (± 12, 32–75)	0.65
DD years mean (SD, range)	15.7 (± 10.5, 2–50)	13.5 (± 9.6, 2–36)	18.6 (± 11.7, 4–50)	0.46
EDSS median (SD, range)	6.0 (± 1.3, 2.5–8.0)	6.0 (± 1.3, 3.5–8.0)	6.0 (± 1.4, 2.5–8.0)	0.62
MSFC median Z score (SD, range)	−0.6 (± 1.4, − 3.9 to 2.68)	− 0.4 (± 1.5, − 3.9 to 1.82)	− 0.4 (± 1.5, − 2.7 to 2.7)	1.0
FSS median (SD, range)	4.8 (± 1.8, 1–7)	4.5 (± 1.8, 0–7)	5.1 (± 1.8, 1–7)	0.09
BDI median (SD, range)	12 (± 9.3, 0–49)	15.7 (± 7.7, 4–30)	11.8 (± 10.7, 0–49)	0.13
MSIS29 median (SD, range)	91 (± 25, 39–146)	93.8 (± 23.5, 53–146)	84.1 (± 26.4, 39–126)	0.63
Years of Education mean (SD, range)	13.4 (± 3.3, 6–18)	14.0 (± 3.1, 6–17)	12.8 (± 3.5, 6–18)	0.22

PP: Primary Progressive; SP: Secondary Progressive; n: number; %: percentage; SD: Standard Deviation; DD: Disease Duration; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory II. MSIS29: Multiple Sclerosis Impact Scale 29.
* *p* value for Fisher's exact test (gender), or Mann-Whitney *U* test.

performance and the age of onset, age at entry to this study or disease duration.

In the whole group, there was a trend in the correlation between mini-SEA score and years of education (Rho: 0.33, $p = 0.05$), with a significant correlation only for the FER subtest (Rho: 0.46, p = 0.006). (Supplementary Table 2)

No significant correlations were found between mini-SEA score and EDSS, MSFC, depression or fatigue, in the whole sample, nor when analyzing both phenotypes separately.

2) Is Social Cognition performance correlated with information processing and executive functioning?

A direct correlation between mini-SEA score and cognitive shifts (Z score) in the whole group of Progressive MS patients' analysis was found (Rho: 0.55; *p*: 0.001; Fig. 1A). When dichotomizing patients according to cognitive shifts results (normal versus impaired), lower scores in mini-SEA were found in the impaired group than those with the preserved cognitive shifts (18.5 ± 3.6 versus 24.7 ± 2.7; *p*: 0.01; Fig. 1B).

When analyzing each phenotype of Progressive MS, a direct correlation between mini-SEA and two traditional cognitive test, cognitive shifts and visual episodic memory, was found in patients with primary Progressive MS (Rho: 0.63, *p*: 0.003 and Rho: 0.58, *p*: 0.009, Fig. 1C and D respectively).

In the subtest analysis of the whole Progressive MS group, FP was correlated with cognitive shifts (Rho: 0.49, $p = 0.002$), and FER was correlated with both cognitive shifts (Rho: 0.48, $p = 0.002$) and visual episodic memory (Rho: 0.38, $p = 0.02$).

We found no other correlations or differences of means between the mini-SEA scores and the different traditional neuropsychological tests. In the sub analysis of the FER per emotion, no statistically significant differences were observed between Progressive MS Phenotypes (Supplementary Table 3).

3a) Is global or regional brain atrophy correlated with poor performance in Social Cognition?

In the whole Progressive MS group, Mini-SEA score was correlated with total normalized grey matter volume (Rho: 0.48, $p = 0.004$). No correlations were observed between mini-SEA and normalized brain volume, normalized white matter volume or corpus callosum index, nor when categorizing according to phenotype. (Correlations of each brain volume measure and the Mini-SEA score and divided by subtest are shown in Supplementary Table 2)

3b) Are there any specific grey matter structures involved with Social Cognition poor performance?

In the whole Progressive MS group, bilateral cortical regions of orbitofrontal, insula and cerebellar, and right regions of fusiform gyrus and precuneus were significantly associated with higher Social Cognition impairment (Fig. 2).

4) What variables are associated with the quality of life of patients with Progressive MS?

Quality of life was correlated with EDSS (Rho: 0.46, $p = 0.002$;

Table 2
Cognitive performance across Progressive MS phenotypes.

Test	mean Z score ± SD	% impaired (cut-off Z < − 1.5)	PP	SP	*p value
Processing Speed					
Processing speed (SDMT)	− 0.68 ± 1.1	19.5	− 0.65 ± 1.2	− 0.71 ± 1.1	0.85
Episodic memory					
Verbal (CVLT delayed)	− 3.22 ± 1.2	87.8	− 2.91 ± 1.7	− 3.7 ± 1.5	0.13
Visual (BMVT-R delayed)	− 1.85 ± 1.3	75.0	− 1.81 ± 1.5	− 1.91 ± 1.2	0.22
Executive Functions					
Working memory (PASAT)	− 2.07 ± 1.3	63.4	− 2.01 ± 1.4	− 2.2 ± 2.5	0.81
Inhibitory control (Stroop)	− 1.08 ± 1.1	30.8	− 1.31 ± 0.98	− 0.82 ± 1.3	0.44
Cognitive shifts (FAS)	− 0.45 ± 1.2	26.8	− 0.45 ± 1.4	− 0.46 ± 1.1	0.77
Social Cognition					
– Mini-SEA	23.0 ± 4.0	–	23.4 ± 4.5	22.5 ± 3.4	0.49
– FP	12.1 ± 2.6	–	12.3 ± 2.7	12.0 ± 2.6	0.82
– FER	10.8 ± 1.8	–	11.2 ± 2.12	10.5 ± 1.4	0.73

PP: Primary Progressive; SP: Secondary Progressive; %: percentage; SD: Standard Deviation. SDMT: Symbol Digit Modality Test; PASAT: Paced Auditory Serial Addition Test; CVLT: California Verbal Learning Test Spanish version; BMVT-R: Brief Visuospatial Memory Test Revised; FAS: flexibility categorical and lexical fluency and control of interference; Mini-SEA: Mini Social and Emotional Assessment; FP: Faux Pas; FER: Face Emotion Recognition.
* *p* value for Mann-Whitney *U* test. Impairment for a single test was defined as a Z score < − 1.5 according to MACFIMS criteria (Benedict et al., 2006).

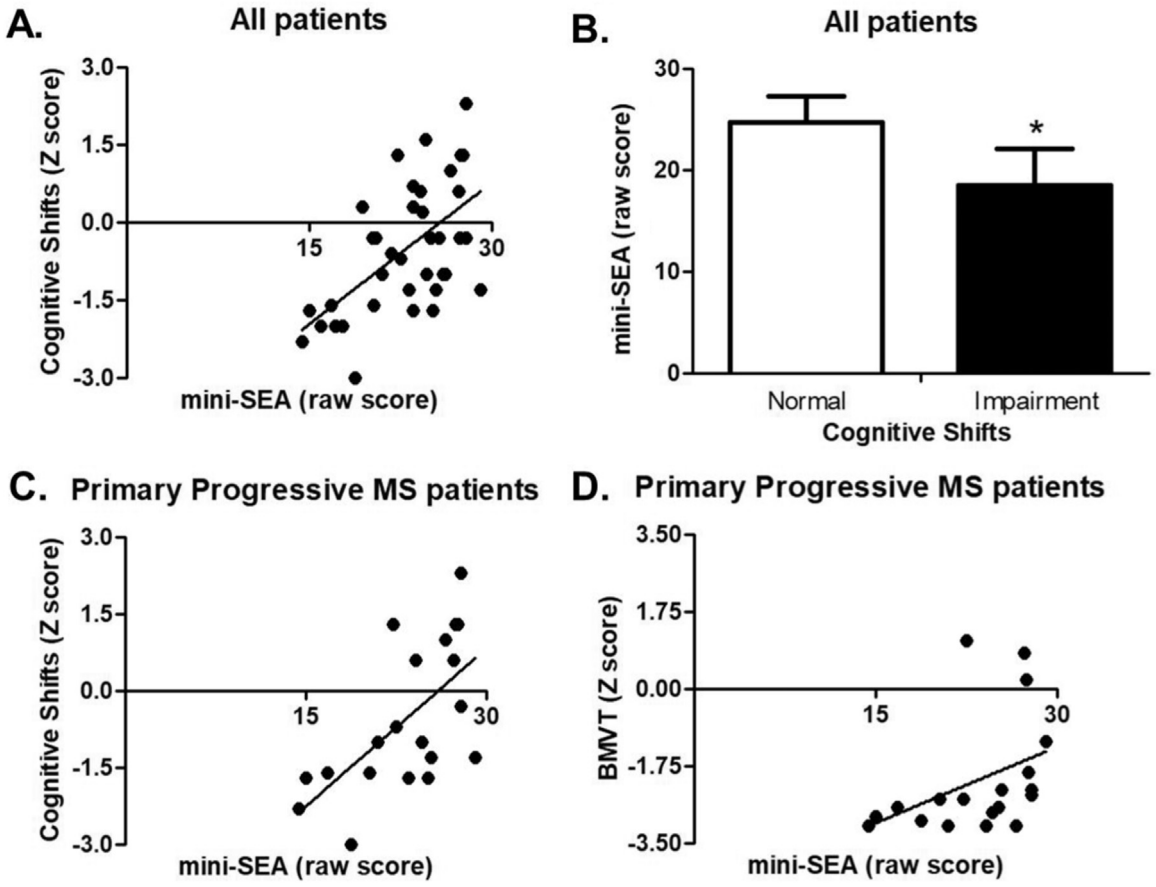

Fig. 1. Relationship between mini-SEA and traditional cognitive domains in Progressive MS phenotypes. A. Bivariate correlation between mini-SEA score and cognitive shifts (Z score) in the whole group of Progressive MS patients, Rho: 0.55; p: 0.001. B. Median and standard deviation graph of mini-SEA score and cognitive shifts categorized normal vs. impaired (Z score < − 1.5), * p value: 0.01 obtained with Kruskal Wallis and Dunn´s multiple comparisons test. C Bivariate correlation between mini-SEA and cognitive shifts in patients with primary Progressive MS, Rho: 0.63, p: 0.003. D. Bivariate correlation between mini-SEA and visual episodic memory - Brief Visuospatial Memory Test - (BVMT) in primary Progressive patients, Rho: 0.58; p: 0.009.

partial Rho: 0.32, $p = 0.047$ adjusted for fatigue and depression), fatigue (Rho: 0.61, $p < 0.001$; partial Rho: 0.47, $p = 0.002$ adjusted for EDSS and depression) and depression (Rho: 0.52, $p < 0.001$; partial Rho: 0.33, $p = 0.03$ adjusted for EDSS and fatigue). There were no significant correlations between quality of life and traditional cognitive tests or Social Cognition performance. Most of the patients were unemployed (77%), and no differences were observed in QOL or mini-SEA score between employed and unemployed patients ($p = 0.2$ and $p = 0.9$, respectively).

4. Discussion

The present study allowed us to describe a population of inactive Progressive MS patients with high levels of physical and cognitive disability, usually underrepresented in MS studies.

According to our primary aim, we found a correlation between Social Cognition performance and the executive function of cognitive shifts, and a correlation with grey matter atrophy, particularly within the orbitofrontal, temporo-parietal associative areas, cerebellum and right fusiform gyrus in the whole group. No correlation with quality of life and Social Cognition were found in this cohort. Within our secondary aim, we found a correlation of Social Cognition performance and visual episodic memory in the primary Progressive MS group, with no other significant differences between phenotypes.

We could not find any significant correlations between Social Cognition performance or its subtests, and clinical variables, such as age, disease duration, depression or EDSS, and we only found a trend in the correlation of the Mini-SEA score with years of education, with a significant correlation in the face emotion recognition subtest. This lack of association with clinical variables, including EDSS and depression has also been reported in a recent study including groups of patients with different disease phenotypes and healthy controls (Henry et al., 2017). However, a recent meta-analysis showed that older age predicted larger emotion recognition deficits (Cotter et al., 2016), and another study in a cohort including Progressive MS patients and using the Reading of the Mind in the Eyes test, found that less years of education and longer duration of the Progressive stage were associated with worse performance in this test (Chalah et al., 2017).

Some authors have suggested that all phenotypes of MS could have similar affection rates of Social Cognition impairment, in fact, we did not find differences in Social Cognition performance when comparing both Progressive phenotypes. A study that used the Bordeaux Social Cognition Assessment Protocol in 30 relapsing-remitting, 15 secondary and 15 primary Progressive MS patients, found in the overall sample, that 43.3% had at least one Social Cognition domain impairment and 20% at least two, with similar proportion of sub-test impairment between different phenotypes. However, Faux Pas scores were lower in their primary Progressive group. In this study, they also found correlations between Social Cognition, specifically Theory of the Mind, and executive function, working memory and episodic memory (Dulau et al., 2017). In another study including 31 relapsing remitting, 16 primary Progressive, 15 secondary Progressive MS patients and 33 healthy controls, they found poor performance of both Progressive MS phenotypes in face emotion recognition compared to healthy individuals and relapsing-remitting MS patients, while the secondary Progressive group differed from the healthy controls in recognition of

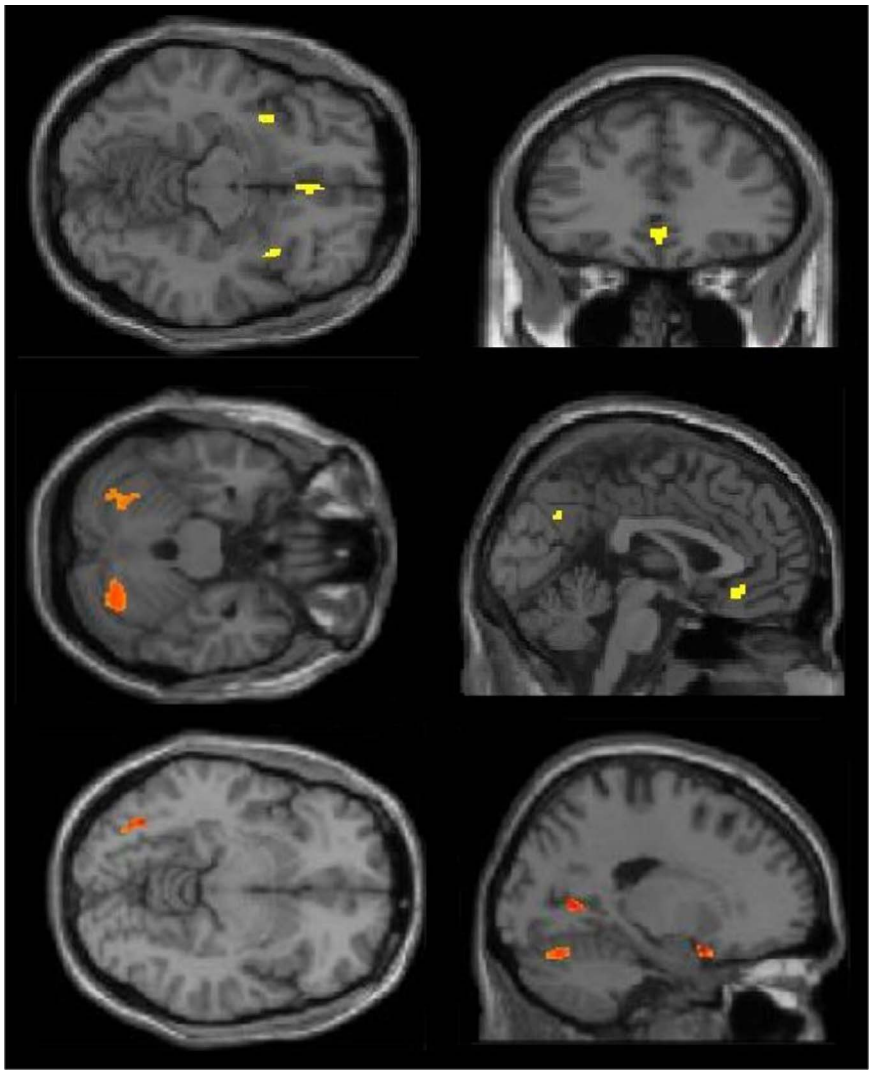

Fig. 2. Significant clusters of grey matter atrophy associated with poor Social Cognition performance. Regions of significant grey matter loss in patients with Progressive multiple sclerosis according to Social Cognition performance. Voxel Based Morphometry using Multiple Regression and Factorial design (FWE corrected $p < 0.05$, $k = 10$). Results displayed on a rendered surface (of a single subject normalized brain) including clusters within bilateral cortical regions of orbitofrontal, insula and cerebellum, and right regions of fusiform gyrus and precuneus.

sadness, and the primary Progressive group in the recognition of fear, although no statistically significant differences between both Progressive MS phenotypes were reported (Henry et al., 2017), similar to our findings.

These results reinforce the necessity of further exploring Social Cognition throughout all disease phenotypes, and probably since the beginning of the disease, as there is sufficient evidence to support the idea that changes in Social Cognition are present since the early stages of MS, with reports even in pediatric MS (28 patients, median age 17 years) presenting a lower social performance compared to healthy controls (Charvet et al., 2014).

We found that Social Cognition performance was correlated with the executive function of cognitive shifts in the whole group, as well as with visual episodic memory in patients with primary Progressive MS. Our correlations between Social Cognition and traditional cognitive tests are also in line with previous associations, supporting the role of executive function and episodic memories (Dulau et al., 2017), although we did not find a correlation with processing speed and working memory (Bora et al., 2016; Dulau et al., 2017), probably due to differences in the study populations and tests performed. Some authors even suggest that executive functions, in particular, verbal fluency, being the most sensitive test for assessing mental flexibility, might play a role in Social Cognition abilities, sharing common neuroanatomical bases between these two cognitive domains (Henry et al., 2017).

We also found that total grey matter atrophy, as well as regional grey matter atrophy of the orbitofrontal cortex and certain temporal and parietal associative areas, appear to be implicated behind the neural bases of social cognitive impairment in Progressive MS. Correlations with total normalized grey matter volume may be explained by the previously reported association of the mini-SEA test with functional and volumetric changes found in the frontal lobe, which represents about 30% of the cortical surface, especially, in rostral and dorsal medial prefrontal cortex (Bertoux et al., 2012; Bertoux et al., 2014). Regional grey matter atrophy findings using VBM, seems to be in line with those previously described in recent studies in MS patients, including orbitofrontal and temporo-parietal cortices (Batista et al., 2017a, 2017b; Chalah et al., 2017), the right fusiform gyrus, related to face recognition, and the cerebellum, although not typically reported in cognition studies, with increasing evidence of its relevance in domains as diverse as attention, language, executive function and Social Cognition (Sokolov et al., 2017).

Lastly, in contrast to our supposition, Social Cognition was not correlated with quality of life measures in this cohort. We consider that a plausible explanation could be the already poor quality of life of the group, mainly influenced by the high levels of physical and cognitive disability (median EDSS of 6.0% and 86.8% of cognitive impairment), significative fatigue and depressive symptoms, although methodological aspects of the present study could also be masking this association.

Our study has several limitations. The lack of a validated battery for Social Cognition assessment in local population and lack of a control group might have affected our results. Although, both tests included in the mini-SEA (Faux Pas and Face Emotion Recognition) have been

widely used in MS patients, with comparable results. Also, the small sample size and the lack of a healthy control group or a relapsing remitting MS group, made it difficult to assertively assess the differences and similarities with previous studies, considering the complexity of the relationship among multiple clinical variables, different neuropsychological batteries and MRI measurements performed with various techniques and unequal sample size. A more sophisticated statistical approach is then warranted, assessing interactions between the variables, larger cohorts including all the phenotypes of the disease, and hopefully longitudinal and functional MRI assessments, that are out of the scope of this small study.

5. Conclusions

Social Cognition in Progressive MS patients is correlated with traditional cognitive domains, in particular with cognitive shifts in the whole group, as well as with visual episodic memory in the primary Progressive subgroup. No other significant differences between phenotypes were found. Its neural bases seem to involve grey matter atrophy, especially within the orbitofrontal cortex, temporo-parietal associative areas, insula, cerebellum and right fusiform gyrus. No significant correlations were found between Social Cognition and quality of life in this cohort with high levels of physical and cognitive impairment.

Its awareness throughout all disease phenotypes is increasing among physicians and researchers, and standardized and validated batteries are still required to assess its real impact in MS patients and their families.

Acknowledgments

Maxime Bertoux for sharing the mini-SEA.

Juan Hancke for the support in the development of this study.

Thanks to European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) for the ECTRIMS Multiple Sclerosis Clinical Training Fellowship Programme (EC).

Funding

CONICYT-PIA-Anillo ACT1416 (JPC, CC).

CONICYT/FONDAP/15150012 (AS and PL); CONICYT/Associative Research Program/Basal Funds Grant for Centers of Excellence FB 0003 (AS and ART); CONICYT/FONDECYT regular/1160940 (PL); CONICYT/FONDECYT Regular/1140423 (AS).

CORFO Innova Chile 14PIE-26946 (EC, MV, ARD, CC).

Declaration of conflicting interests

The Authors declare no conflict of interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2018.01.013.

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