Social cognition and executive functioning in multiple sclerosis: A cluster-analytic approach

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Short title: *Social Cognition in Multiple Sclerosis*

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Abstract:
Multiple sclerosis (MS) is associated with deficits in social cognition, the process underlying social interaction and cognitive function. However, the relationships between executive impairment and social cognition remain unclear in MS. Previous studies exclusively focused on group comparisons between healthy controls and patients with MS, treating the latter as a homogeneous population. The variability of socio- and neurocognitive profiles in this pathology therefore remains underexplored. In the present study, we used a cluster analytic approach to explore the heterogeneity of executive and social cognition skills in MS.
A total of 106 patients with MS were compared with 53 healthy matched controls on executive (e.g. working memory) and social cognition (facial emotion recognition and theory of mind) performances. A cluster analysis was then performed, focusing on the MS sample, to explore the presence of differential patterns of interaction between executive and social cognition difficulties and their links to sociodemographic, clinical, and cognitive variables.
We identified three distinct functional profiles: patients with no executive or social cognition deficits (Cluster 1); patients with difficulties in facial emotion recognition and theory of mind and, to a lesser extent, executive functioning (Cluster 2); and patients with executive functioning difficulties only (Cluster 3). Clinical characteristics (disease duration, disability, fatigue) did not differ between clusters.
Conclusions: These results suggest that there are qualitative differences in the social cognition and executive difficulties that are commonly found among patients with MS. If replicated, the identification of these profiles in clinical practice could allow for more individualized rehabilitation.

Keywords: executive functions, social cognition, facial emotion recognition, theory of mind, demyelinating diseases, cluster analysis

Social Cognition and Executive Functioning in Multiple Sclerosis: A Cluster-Analytic Approach

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, characterized by multifocal tissue damage in the brain and spinal cord (Compston & Coles, 2008; Filippi et al., 2018). It is the main cause of nontraumatic disability in young adults, and its course is highly variable and unpredictable. The disease leads to motor, sensory, and cerebellar symptoms, as well as emotional and cognitive manifestations. Cognitive symptoms affect 40-70% of patients with MS, and mainly involve attention, information processing speed, learning, memory, and executive functions (Chiaravalloti & DeLuca, 2008; Langdon, 2011; Rao, Leo, Bernardin, et al., 1991). Beyond these cognitive deficits, patients with MS also exhibit social cognition difficulties (Bora, Özakbaş, Velakoulis, & Walterfang, 2016; Chalah & Ayache, 2017).

Social cognition refers to the set of distinct cognitive processes underlying social interactions, such as the perception and interpretation of social cues (gaze, facial expressions, attitudes, etc.) and the generation of responses to the intentions, dispositions, and behaviors of others (Brothers, 1990; Frith & Frith, 2012; Happé et al., 2017). In MS, studies have mainly focused on facial emotion recognition and theory of mind (ToM), two core processes that play a crucial role in successful social interactions (e.g., Green et al., 2015). *ToM* is the ability to attribute mental states (beliefs, feelings, intentions, desires) to self and others, and to understand and predict others' behaviors. Research suggests that patients with MS have difficulty recognizing negative emotions (Beatty, Orbelo, Sorocco, & Ross, 2003; Berneiser et al., 2014; Cecchetto et al., 2014; Henry, Tourbah, Chaunu, Bakchine, & Montreuil, 2017; Henry et al., 2009; Kraemer et al., 2013) and attributing mental states to others in verbal or nonverbal ToM tasks (Banati et al., 2010; Henry et al., 2011; Pöttgen, Dziobek, Reh, Heesen,

& Gold, 2013; Roca et al., 2014). These deficits may contribute to the interpersonal and psychosocial difficulties that are frequently reported in patients with MS (Buhse, 2008; Krause et al., 2013; Langdon, 2011; Rao, Leo, Ellington, et al., 1991). Two recent meta-analyses (Bora et al., 2016; Cotter et al., 2016) confirmed the presence of significant impairments with medium effect sizes in facial emotion recognition and ToM in MS. These social cognitive deficits may be similar in magnitude to those observed in other cognitive domains (Cotter et al., 2016). In their study, Dulau et al. (2017) found that 43.3% of patients with MS were impaired on at least one social cognition test, a percentage comparable to that observed for nonsocial cognitive domains (e.g., processing speed, episodic memory, executive functions), suggesting that social cognition difficulties may be just as common as cognitive difficulties in patients with MS.

In MS, facial emotion recognition and ToM difficulties are significantly associated with nonsocial cognitive impairments, particularly executive functions. *Executive functions* refer to a set of higher-level cognitive abilities needed for planning and executing goal-directed operations. Many studies have shown positive correlations between social-cognitive and executive domains in this population (Berneiser et al., 2014; Henry et al., 2017; Henry et al., 2009; Pöttgen et al., 2013; Roca et al., 2014). There are several possible explanations for the association between emotion recognition and ToM on the one hand and executive functions on the other hand. First, when individuals attribute a mental state to others (ToM), they have to adopt another perspective, thereby engaging several executive functions: working memory (to maintain and manipulate several perspectives), flexibility (to switch from one perspective to another), and finally inhibition (to suppress irrelevant perspectives) (Apperly et al., 2004; Rowe et al., 2001; Wade et al., 2018). Second, the neuroanatomical systems underlying overall social cognition and executive functions overlap (e.g. Adolphs, 2009). However, it remains unclear whether social cognition impairments in patients with MS occur secondarily

to executive deficits, or independently of them. The relationship between overall social cognition and executive functions remains controversial for some authors, as previous studies have reported contradictory results (Bora et al., 2016; Chalah & Ayache, 2017; Cotter et al., 2016). According to Cotter et al. (2016), the statistical strength of these correlations is inconsistent, and in any case, correlations do not provide any information about the causal direction of the relationship. Moreover, some studies have highlighted facial emotion recognition and ToM impairments even after controlling for nonsocial cognitive performances, in particular executive functions (Ouellet et al., 2010; Phillips et al., 2011; Pöttgen et al., 2013). To find out whether these two skills are independent of each other, some researchers has studied the facial emotion recognition and ToM performance of patients with and without cognitive impairments (Ouellet et al., 2010; Pitteri et al., 2019). Ouellet et al. (2010) concluded that patients with MS who have mild or moderate cognitive deficits are likely to have ToM difficulties, unlike patients with no such cognitive impairment. By contrast, studies by Batista et al. (2017) and Pitteri et al. (2019) showed that deficits in facial emotion recognition and ToM may be observed even in the absence of cognitive deficits in MS.

Reliance on simple group comparisons may have hidden differential profiles, with some patients perhaps genuinely presenting strongly impaired overall social cognition and executive abilities, and others having no such impairment (Dulau et al., 2017) or presenting deficits in either one or the other. The often quite small sample sizes of earlier studies prevented any in-depth exploration of these possible variations across participants, but some contradictory results have pointed to interindividual variability in MS for overall social cognition and executive abilities. MS is a disease characterized by considerable patient heterogeneity, in terms of clinical presentation, disease course, lesion profiles, and cognitive dysfunction (DeLuca et al., 2015; Filippi et al., 2018; Katsari et al., 2016). The heterogeneity

observed in cognitive profiles might explain the apparently divergent results for the relationships between executive and social cognition deficits in MS. Different social cognition components (e.g., facial emotion recognition, ToM) or tasks may rely on specific combinations of executive abilities (e.g., inhibition, working memory, flexibility). Some of these executive abilities may be compromised in some patients but not in others, explaining the difference in impairment patterns observed across executive and social cognition tasks (Samson et al., 2007). The joint exploration of social cognition and executive functioning might help to determine the existence of such subgroups. One method that might be useful in identifying patient subtypes is cluster analysis. This provides a method of classifying individuals using a data-driven approach based on similar patterns or profiles of performances, creating the potential for more homogeneous groupings than single domains can.

The aims of the present study were to (1) identify whether patients with MS can be divided into different subgroups on the basis of similar social cognition (facial emotion recognition and ToM) and executive functioning patterns, using cluster analysis, and (2) explore whether these patient subgroups differ on clinical characteristics, cognitive variables, and psychological symptoms. We hypothesized that some patients with MS are characterized by both social cognition and executive impairments (as generally reported in studies based on group comparisons), whereas others have difficulties with only executive or social cognition skills and may even have no such impairments at all. Regarding executive functions, we explored three central executive processes, namely working memory, flexibility, and inhibition (Miyake et al., 2000). As social cognition is a broad concept comprising several processes, we decided to focus on two that have often been explored and found to be impaired in MS: facial emotion recognition and ToM. We adopted a cluster analytic approach to explore distinct profiles of patients with MS based on these five variables, as this analysis

allowed us to consider these variables as distinct processes. Understanding the extent to which the specific domains of social cognition and executive functioning are impaired in patients with MS, and assessing whether different patient profiles can be established, would be useful for identifying cognitive targets and developing intervention programs.

Method

Participants and Procedure

A total of 106 patients with clinically definite MS according to the revised McDonald criteria (Polman et al., 2011) were included in the study during their regular appointments at the Neurology Department of University Hospital (France). The exclusion criteria were (a) a history of other neurological disorders (e.g., severe head trauma, encephalitis etc.), (b) a history of major psychiatric illness (patients with major depressive or anxiety disorders were included if these disorders were controlled by medical treatment), (c) major visual or motor impairments that might interfere with psychometric testing, and (d) relapse and/or treatment with corticosteroids within the previous 6 weeks. Disease duration was measured from the time of diagnosis, and level of disability with the Expanded Disability Status Scale (EDSS; Kurtzke, 1983).

The control group included 53 healthy participants (HC) with no history of psychiatric or neurological disorders, no head trauma, and no alcohol or drug abuse. HC were recruited via advertisements. They were matched with patients for age, sex, and education level. The participants' characteristics are given in Table 1.

All participants gave their written informed consent to participate in the study, after receiving a detailed explanation of the procedures and goals. The study was conducted in accordance with the Declaration of Helsinki.

Measures

Social cognition.

The assessment of social cognition included a facial emotion recognition test and a ToM test.

The facial emotion recognition test was derived from Facial Expressions of Emotion: Stimuli and Tests (Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002). The stimuli consisted of a series of 60 black-and-white photographs of the same female face, representing the six basic emotions (anger, disgust, fear, surprise, sadness, and happiness), with 10 faces for each emotion. Faces were displayed for 5 s on a computer screen in a 4 x 3-inch format, followed by a forced-choice menu from which participants had to select the emotion they had just detected. The testing phase was preceded by a short training phase. Participants were allowed to take as much time as they needed to make their decision. The maximum score for correct identification was 10 for each emotion, and 60 for the whole task.

The ToM test consisted of six ToM cartoon stories: two assessing first-order false belief, two second-order false belief, and two faux pas detection. The stories and questions were derived from Rowe, Bullock, Polkey, and Morris (2001) and Stone, Baron-Cohen, and Knight (1998), and were adapted for a French population (for full details about the stories, questions, and scoring, see Ehrlé, Henry, Pesa, & Bakchine, 2011; Henry et al., 2011). The scores of the six cartoon stories were summed to provide an overall ToM score.

Neuropsychological Assessment

General cognitive assessment.

As processing speed and episodic verbal memory are often impaired in MS and might influence social cognition and executive performance, tests evaluating these processes were administered to patients with MS.

Processing speed was assessed with the Digit Symbol subtest of the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997).

Verbal episodic memory was assessed with the Free and Cued Selective Reminding Test (FCSRT; Grober et al., 2008; Grober & Buschke, 1987). The FCSRT begins with a study phase in which participants are asked to read a card containing four words (e.g., *grapes*) linked to a different category cue (e.g., *fruit*). Immediate recall of just these four items is then tested. If any items are not retrieved, the words are presented again, and the procedure are repeated. The search procedure is continued with three more cards until all 16 items have been identified and retrieved in immediate recall. The study procedure is followed by three recall trials, each consisting of free recall followed by cued recall for items not retrieved by free recall. The free and cued recalls for each trial are summed to obtain the total immediate recall score. The same recall procedure (free and cued) is repeated after a 30-min interval, during which participants are required to perform nonverbal tasks (delayed recall). We summed the total immediate recall score and total delayed recall score to measure learning.

Executive assessment.

The Digit Span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) was used to evaluate working memory. Participants are asked to repeat strings of numbers. The test has two conditions: (1) forward (digits repeated in the same order), and (2) backward (digits repeated in reverse order). The dependent measure was the backward digit span.

Verbal phonemic fluency (2 min to produce as many words starting with the letter *r* as possible) was then used to evaluate reactive flexibility. Fluency is one of the most sensitive measures of executive dysfunction in MS (Henry & Beatty, 2006; Zakzanis, 2000). We used the total number of responses, minus repetitions and inappropriate responses, as the dependent variable.

The Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) also served to assess several executive processes: goal-setting, set-shifting, inhibition,

and working memory. The dependent measure was the percentage of perseverative responses (inhibition).

Fatigue and Mood Scale.

In addition to social cognition and executive functions, we assessed psychological variables. Patients with MS and HC were asked to complete the French version (EMIF-SEP) of the Modified Fatigue Impact Scale (MFIS; Debouverie, Pittion-Vouyovitch, Louis, & Guillemin, 2007). The MFIS is a 40-item self-report measure of fatigue that is commonly used in MS. It comprises three subscales measuring physical, social, and cognitive fatigue on a 5-point Likert scale ranging from 0 (*No problem*) to 4 (*Extreme problem*). Total MFIS scores were standardized from 0 (*No fatigue*) to 100 (*High degree of fatigue*). All participants were also screened for depression using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), in which each item is scored on a 4-point Likert scale ranging from 0 to 3. Owing to logistical constraints, HADS could only be administered to 80 of the 106 patients with MS and 33 of the 53 HC.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 23.0 for Mac. Initial analyses were conducted to compare sociodemographic and clinical characteristics between patients with MS and HC, using *t* tests for continuous variables and χ^2 tests for categorical variables.

Patients' performances on social cognition (overall ToM score and overall facial emotion recognition score) and executive domains (dependent measures of each executive test described in the Method section: Backward Digit Span, number of responses in phonemic fluency, percentage of perseverative responses in WCST) were standardized to *z* scores, based on HC performances. For the WCST, higher perseverative scores indicate poorer

performance, so the *z* scores were reversed. The standardized scores were used to compute the cluster analysis. Regarding the cluster analysis, we relied on previous studies using this methodology to consider distinct variables in a single analysis (e.g., Devos et al., 2020; Flayelle et al., 2019) to observe whether the MS population could be described by distinct profiles (e.g., presenting high difficulties for inhibition but preserved abilities to detect emotions in others). One of the requirements of cluster analysis is that the variables selected to create the clusters are not strongly related to each other (Hair et al., 2010). This needs to be controlled to avoid multicollinearity and potential biases in the results' interpretation. In a preliminary step, we had thus computed correlations between our variables to check the reliability to include them in a single model. As cluster analysis is sensitive to multicollinearity issues, it is recommended that correlations between variables do not exceed .50, which was supported in our study. These analyses were conducted among the 106 patients with MS, combining hierarchical and nonhierarchical methods, as recommended (Hair et al., 2010). First, a hierarchical cluster analysis was carried out to identify homogeneous subgroups of patients with similar functional profiles, based on their social cognition and executive functioning scores. Similarity between cases was computed with the Euclidean distance, and the Ward linkage was selected as the agglomeration procedure. The dendrogram were visually inspected to establish the appropriate number of clusters to be retained. Second, clusters were determined using a nonhierarchical k-means analysis. The profiles of the resulting patient subgroups were compared using a one-way analysis of variance (ANOVA), with subgroup (cluster) membership as a fixed factor, and the four social cognitive and executive domains as dependent variables. Furthermore, we carried out Tukey post hoc comparisons to identify pairwise differences between subgroups when there were significant main effects. Finally, comparisons (one-way ANOVA and χ^2 applied as appropriate) between clusters were performed to examine possible differences on

sociodemographic, clinical, and neuropsychological variables. In addition, in order to know how many patients are cognitively impaired or unimpaired, we had computed the total number of MS patients by cluster who performed at or below 1.65 standard deviation of the matched HC scores for each social cognition and executive test. Patients were considered cognitively impaired for a given social cognition or executive domain if they were impaired for at least one score of this domain. A p value of 0.05 was considered statistically significant.

Results

Comparisons Between Patients with MS and Healthy Controls on Sociodemographic, Executive, and Social Cognition Measures

There were no significant differences between patients with MS and HC on age, sex, or education level (see Table 1). The EMIF-SEP score was significantly higher for patients with MS than for HC. No difference was observed between patients with MS and HC on HADS scores.

On the executive measures, patients with MS scored significantly lower than HC on verbal fluency. However, these two groups did not differ on either the Backward Digit Span or the percentage of WCST perseverative responses. Regarding social cognition measures, comparisons between groups revealed statistically significant differences in facial emotion recognition and ToM scores, with patients with MS performing more poorly. These results are summarized in Table 1.

Please Insert Table 1 here

Cluster Analysis of Patients with MS

Preliminary correlations supported the reliability to include all executive and social-cognitive processes in the same cluster analysis. The correlation between facial emotion recognition and ToM was rho = .30 ($p < .001$) and the correlations between executive tasks did not exceed rho > .33 ($p < .001$).

Cluster analysis of the MS sample ($n = 106$) indicated an optimum three-factor solution (see Fig. 1). The first cluster included 68 patients (64% of the sample), the second one 22 patients (21% of the sample), and the third one 16 patients (15% of the sample). Each cluster contained more than 10% of the sample, supporting the reliability of the analysis (Hair et al., 2010).

The three clusters were labelled *unimpaired*, *social cognition impaired* (SC-), and *executive functioning impaired* (EF-). As shown in Table 2 and Figure 2, patients in the unimpaired subgroup seemed to have similar performances to those of HC on executive and social cognition tasks. Patients in the SC- subgroup exhibited moderate-to-severe impairment of facial emotion recognition and ToM, and minor difficulties in executive functions, especially WCST perseverative responses. Finally, the EF- subgroup displayed moderate difficulties in executive functions, especially the WCST task, but no social cognition impairments. The cluster profiles on the five standardized variables are depicted in Figure 2, with respect to the baseline of 0 (i.e., HC group mean).

Please Insert Figures 1 & 2 here

Comparisons Between Three Functional Profiles on Sociodemographic, Clinical and Neuropsychological Variables

As shown in Table 2, there were no differences between the three clusters on either age ($p = .219$), disability (EDSS median score, $p = .68$), or disease duration ($p = .81$).

However, the ANOVA did reveal differences between the three subgroups on education level (p = .004). Specifically, the pairwise comparisons indicated that patients in the SC- and EF- subgroups had a lower education level than those in the unimpaired subgroup (p = .02).

Considering neurocognitive variables, the subgroups differed significantly on processing speed (p = .007), immediate recall (p = .001), and delayed recall (p < .001) (see Table 2). More specifically, pairwise comparisons indicated that the SC- and EF- subgroups scored lower on processing speed than the unimpaired subgroup. For verbal episodic memory, the SC- subgroup performed more poorly on immediate and delayed recall than both the unimpaired and EF- subgroups. The SC- subgroup performed significantly more poorly than the unimpaired group on all social cognition and executive measures. The only significant difference between the unimpaired and EF- subgroups concerned WCST perseverative responses, with the EF- subgroup performing more poorly.

Finally, regarding fatigue, anxiety and depression, no significant differences were observed.

Please Insert Table 2 here

To control for the potential influence of education level on neuropsychological performance, we conducted a series of one-way multivariate analyses of covariance. Except for the Digit Symbol subtest, which no longer reached statistical significance, $F(2, 101) = 1.967$, p = .14, $\eta^2 = 0.01$, all the cluster comparisons for the other variables remained statistically significant: WCST perseverative responses, $F(2, 101) = 74.949$, p < .001, $\eta^2 = 0.54$, immediate verbal recall, $F(2, 101) = 5.817$, p = .004, $\eta^2 = 0.07$, and delayed verbal recall, $F(2, 101) = 5.48$, p = .005, $\eta^2 = 0.07$, facial emotion recognition, $F(2, 101) = 13.76$, p < .001, $\eta^2 = 0.18$, and ToM test, $F(2, 101) = 69.55$, p < .001, $\eta^2 = 0.54$.

Comparison Between Three Clusters and Healthy Controls

ANOVAs were performed between the three clusters of patients with MS and HC. Overall, findings indicated that the unimpaired subgroup performed significantly worse than HC on the ToM tasks. The SC- and EF- subgroups performed significantly more poorly than HC on all social cognition and executive measures, although the EF- subgroup had similar performance to HC on the Backward Digit Span. These results are summarized in Table 3.

Please Insert Table 3 here

In addition, we calculated the total number of patients with MS in each cluster whose scores were at least 1.65 standard deviations below the matched HC scores for each social cognition and executive test. Table 4 showed the proportions of patients in each cluster who were impaired on the different social cognition and executive domains. None of the patients had working memory deficits. Three (4.41%) patients in the unimpaired group were impaired on both facial emotion recognition and ToM tasks, and one (1.47%) was impaired on both phonemic fluency and WCST perseverative responses. Seventeen (77.27%) patients in the SC- subgroup were impaired on both social cognition tasks, while three (13.63%) were impaired on both phonemic fluency and WCST perseverative responses. All the patients in the EF- subgroup were impaired on WCST perseverative responses, while five (31.25%) were impaired on both executive tasks and both social cognition tasks.

Commenté [SL1]: Mettre une phrase pour présenter ces analyses dans la section Statistical analysis ?

Please Insert Table 4 here

Discussion

To the best of our knowledge, this study was the first to feature a joint analysis of social cognition and executive skills in patients with MS in the form of a cluster analysis. The relationships between social cognition and executive domains remained unclear in MS, with

some researchers considering that specific SC impairment exists independently of executive deficits, and others considering that SC deficits are secondary to executive impairment. In the present study, our aims were thus to investigate (a) whether applying a cluster analytic approach to a large group of patients allowed subgroups of patients characterized by distinct executive (working memory, flexibility, and inhibition) and social cognition (especially facial emotion recognition and ToM) difficulties to be identified, and (b) whether these subgroups differed on sociodemographic, clinical, and neurocognitive characteristics.

This study shows the presence of three clusters with specific patterns of facial emotion recognition, ToM, and executive skills: unimpaired, SC-, and EF-.

The unimpaired subgroup, containing 64% of patients with MS, was characterized by executive and social cognition abilities that were relatively preserved, compared with the other two clusters. Patients belonging to this cluster did not differ from the others in terms of either clinical or psychological variables, meaning that neither disease duration nor disability severity, fatigue, anxiety or depression could explain the difference between the clusters. However, this subgroup did have a higher level of education, supporting the hypothesis that this variable is a potential moderator of cognitive deficits (e.g., Habeck et al., 2020). Importantly, even when we controlled for education level, the three subgroups remained significantly different, except on processing speed. Further research is therefore needed to properly understand the factors characterizing unimpaired patients with MS. A classic comparison between this cluster and HC revealed a slight difference between the two on one of the social cognition measures (ToM task), suggesting possible difficulty attributing intentions to others. However, these data do not allow us to conclude with certainty that there was a social cognition deficit. According to the *z* scores, ToM performances did not deviate significantly from those of HC. Furthermore, normative studies featuring batteries combining several measures of social cognition have shown that a significant proportion of healthy

participants (36.7%) have an impaired score on at least one test assessing social cognition (Etchepare et al., 2014), suggesting that an isolated deficit score does not allow us to reliably conclude that there is a social cognition impairment (Binder et al., 2009). In the same vein, we also looked at the percentage of patients in this cluster who were cognitively impaired with respect to normative data. The percentage of patients with MS who were impaired on at least one social cognition task was comparable to that reported by Etchepare et al. (2014). These elements are relevant to clinical practice and highlight the need to assess social cognition using at least two tests, as is often the case for neurocognition.

The second cluster (SC-), including 21% of the sample, was characterized by severe difficulties in both facial emotion recognition and ToM and, to a lesser extent, executive difficulties. This result confirmed those of numerous studies (e.g., Bora et al., 2016; Cotter et al., 2016) showing that social cognition deficits in MS are associated with executive function deficits. Moreover, the percentage of patients in our sample with social cognition difficulties was consistent with previous studies showing that around 28% of patients with MS have social cognition difficulties, and 20% are impaired on at least two social cognition tests (Dulau et al., 2017). In this cluster, the greatest impairments were for facial emotion recognition and ToM. We also observed less severe executive impairments, which were mainly represented by increased perseverative responses (i.e., poorer inhibitory control). This result points to a combination of emotion recognition, ToM, and inhibition difficulties in patients belonging to the SC- cluster, with apparently preserved flexibility and verbal working memory. Remarkably, previous studies had underlined that, although these three executive processes each play an important role in social cognition, inhibition is the most important process (López-Navarro, 2018; Vetter et al., 2013). By emphasizing the central role of inhibition, our results are thus totally in line with previous ones. In a sample of patients with acquired brain damage, Samson (2009, 2007) showed that ToM reasoning is underpinned by

two component processes: the ability to infer someone else's perspective (their desires, beliefs, and intentions), which recruits the temporoparietal junction; and the ability to inhibit one's own perspective in order to adopt another's perspective, which recruits the lateral prefrontal cortex. Moreover, it is worth noting that the WCST is a multifactorial test (Nyhus & Barceló, 2009; Stuss et al., 2000) that also elicits other processes, such as verbal episodic memory. The SC- cluster stood out significantly from the unimpaired cluster, with poorer performances on emotion recognition, ToM and all the executive domains we evaluated, as well as on verbal episodic memory. Again, neither sociodemographic, clinical, nor psychological variables allowed us to differentiate between these clusters.

The third subgroup (EF-), including 15% of the sample, was characterized by isolated executive difficulties, especially in inhibition processes. This cluster could be considered as an intermediate one between the unimpaired cluster with no major deficit, and the SC- cluster, with emotion recognition, ToM, executive, and memory deficits. Regarding possible difficulty recognizing facial emotions and attributing intentions, as with the unimpaired cluster, this result can be interpreted as reflecting the interindividual variability found in healthy participants. The proportion of patients with MS who were impaired on the different SC and executive domains points to the disruption of executive processes and a possible disruption of facial emotion recognition and/or ToM. Thus, inhibition-type executive difficulties may promote the emergence of difficulties in emotion recognition and ToM. However, the small size of this cluster prevented us from testing this hypothesis, which deserves to be investigated in the future. Importantly, as this cluster did not differ from the others in terms of clinical data (e.g., disease duration), these results also suggest that executive deficits do not necessarily lead to a social cognition deficit, and do not precede the onset of difficulties in social cognition. This is in line with studies that have failed to find a correlation between executive functions and ToM measures (e.g., Batista et al., 2018; Roca et

al., 2014), and more especially with studies demonstrating ToM impairments in the early stages of the disease (Kraemer et al., 2013), but no cognitive impairment. Although cognitive impairment may contribute to social cognitive impairment in MS, it was not significantly associated with more severe social cognitive deficits, as some results seemed to suggest (e.g., Bora et al., 2016).

The present study had three main limitations. First, regarding recruitment, clinical levels of psychopathological comorbidities constituted exclusion criteria, potentially creating a selection bias in our sample. Upcoming studies should therefore determine the influence of comorbid psychiatric states (anxiety, depression) on the sociocognitive and executive profiles we identified here.

Second, although the measures of social cognition and executive functions we selected for this study are valid and classically used by both academics and clinicians, they do not assess specific social cognition and executive function processes. The WCST is multifactorial and combines several executive processes, while the ToM test does not distinguish between affective and cognitive ToM, which we know can involve different executive processes (e.g., Nyhus & Barceló, 2009) and different neural circuits (Shamay-Tsoory & Aharon-Peretz, 2007). This could be addressed in future studies. In addition, social cognition is a broad construct encompassing numerous processes that may have different relationships with each other and with other cognitive processes (e.g., Happé et al., 2017). In our study, we only measured facial emotion recognition and ToM. Further studies are needed to assess other sociocognitive processes.

Third, we did not examine other characteristics that may influence the links between executive functions and emotion recognition and ToM, such as visuospatial skills or clinical variables (MS form, number of relapses, employment status). The heterogeneity we observed

here for executive and social cognition abilities may extend to these variables, and future studies should consider exploring their mutual influence and offer refined MS profiles.

Notwithstanding these limitations, the present study was, to our knowledge, the first to propose subtyping patients with MS on the basis of facial emotion recognition, ToM, and executive variables. The original results obtained here now need to be replicated and extended. We identified three distinct clusters of patients with MS, based on SC and EF performances: no impairment, executive difficulties, and combined executive and social cognition impairments. These results suggest that the MS population has heterogeneous abilities, and that the classic group comparison approach may be misleading and need to be complemented by subgroup explorations. This might explain the discrepancies between studies on the relationships between executive functioning and social cognition (e.g., Bora et al., 2016; Cotter et al., 2016). Exploring samples by means of complementary analyses, performing subgroup explorations (e.g., cluster analyses) and/or describing individual profiles (e.g., using a multiple single-case approach like the Crawford method; Crawford & Garthwaite, 2012) would allow us to refine our knowledge of possible combinations of impaired and preserved cognitive processes. The relationship between social cognition and executive functions (and, more broadly, cognitive processes) cannot be reduced to dependence, interdependence, or even causality. The cluster analysis conducted in the present study suggests that numerous combinations of preserved and impaired processes contribute to individual cognitive profiles. Thus, if there are such profiles, it seems necessary to explore these skills according to the characteristics of each individual and his/her disease. It is also crucial to identify distinct patterns in order to develop remediation programs adapted to patients' needs. More individualized approaches taking this variability or heterogeneity of functioning into consideration would contribute to targeted remediation based on patient profiles to restore or improve social cognition skills.

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Tables to be inserted

Table 1

Sociodemographic, Clinical, and Cognitive Characteristics of Patients with MS and Healthy Controls

	MS patients (n = 106)		HC (n = 53)			
	Mean	*SD*	Mean	*SD*	p value	Effect size
Demographic data						
Age in years	42.01	11.67	38.3	13.01	.08	
Sex	F: 68 (64%) M: 38 (36%)		F: 33 (62%) M: 20 (38%)		.82	
Education in years	10.97	2.6	11.45	2.63	.32	
Clinical data						
EDSS score (median)	3	2.2	_	_	_	
Disease duration in years	8.5	8.56	_	_	_	
Executive data						
Backward Digit Span	4.62	1.32	4.77	1.23	.31	r = 0.08
WCST PR (%)	12.55	9.47	9.51	4.01	.28	r = 0.38
Phonemic fluency	15.36	5.64	18.81	5.31	< .001	r = 0.29
Social cognition tasks						
FER score	50.93	7.54	55.07	3.56	.003	r = 0.24
ToM overall score	23.22	3.68	26.54	1.28	<.001	r = 0.53
Behavioral data						
EMIF-SEP (0-100)	49.95	22.58	38.37	19.28	.003	r = 0.23
	(n = 80)		(n = 33)			

Total HADS	13.66	6.64	13.18	5.6	.29	$r = 0.11$
Depression subscale	5.86	4.01	4.76	5.11	.80	$r = 0.02$
Anxiety subscale	7.8	3.54	8.42	3.76	.44	$r = 0.07$

Note. EDSS: Expanded Disability Status Scale; WCST PR: Wisconsin Card Sorting Test perseverative responses (%); FER: facial emotion recognition test; ToM: theory of mind; EMIF-SEP: Modified Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale.

Table 2

Comparisons of Sociodemographic, Clinical, and Cognitive Characteristics of the Three Functional Clusters

	Cluster 1 (*n* = 68)	Cluster 2 (*n* = 22)	Cluster 3 (*n* = 16)			Post hoc tests
	Unimpaired	SC-	EF-			
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	*p*	
Demographic data						
Age in years	40.57 (11.83)	45.27 (11.41)	43.62 (11.41)	1.54	.21	ns
Education in years	11.59 (2.77)	9.95 (1.84)	9.75 (1.73)	5.95	.004	C1 > C2 & C3*
Clinical data						
EDSS score (median)	3 (1.85)	3.55 (1.9)	3.25 (2.2)	.38	.68	ns
Disease duration in years	8.1 (7.63)	9.95 (1.84)	9.75 (1.73)	.20	.81	ns
Social cognition tasks						
FER score	53.47 (5.98)	44.22 (7.07)	49.37 (8.41)	16.72	< .001	C1 > C2*** & C3* C3 > C2*
ToM overall score	24.65 (2.1)	17.7 (3.5)	24.78 (1.3)	75.59	< .001	C1 > C2*** C3 > C2***
Executive data						
Backward Digit Span	4.94 (1.4)	3.91 (0.87)	4.25 (1.06)	6.35	.002	C1 > C2**
WCST PR in %	7.93 (4.2)	14.87 (8.28)	29.02 (7.59)	86.74	< .001	C1 > C2 & C3*** C2 > C3***
Phonemic fluency	16.62 (5.6)	12.45 (5.25)	14.06 (4.72)	5.46	.006	C1 > C2**
Cognitive data						
Digit symbol	8.62 (3.12)	6.86 (2.68)	6.44 (2.87)	5.15	.007	C1 > C2* & C3*

FCSRT Total IR	47.2 (1.43)	45.09 (3.43)	46.37 (2.18)	7.96	.001	C1 > C2***
FCSRT Total DR	15.86 (0.48)	15.13 (1.08)	15.37 (1.31)	8.53	< .001	C1 > C2***
Behavioral data						
EMIF-SEP (0-100)	50.06 (21.88)	51.8 (25.44)	46.94 (22.63)	.21	.81	ns
	(*n* = 47)	(*n* = 18)	(*n* = 15)			
Total HADS	13.79 (6.95)	12.17 (6.9)	15.07 (5.23)	.79	.45	ns
Depression subscale	5.45 (3.89)	5.89 (4.43)	7 (3.93)	.80	.45	ns
Anxiety subscale	8.3 (3.59)	6.28 (3.66)	8.07 (2.84)	2.24	.11	ns

Note. SC: social cognition; EF: executive function; EDSS: Expanded Disability Status Scale; FER: facial emotion recognition test; WCST PR = Wisconsin Card Sorting Test perseverative responses; FCSRT: Free and Cued Selective Reminding Test; IR: immediate recall; DR: delayed recall; EMIF-SEP: Modified Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3

Comparisons Between the Three Clusters and Healthy Controls on Social Cognition and Executive Measures

	Cluster 1 (*n* = 68)	Cluster 2 (*n* = 22)	Cluster 3 (*n* = 16)	Healthy controls (*n* = 53)			Post-hoc tests		
	Unimpaired	SC-	EF-	HC					
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	*p*	C1-HC	C2-HC	C3-HC
Social cognition tasks									
FER score	53.47 (5.98)	44.22 (7.07)	49.37 (8.41)	55.07 (3.56)	20.69	< .001	.13	< .001	.002
ToM global score	24.65 (2.1)	17.7 (3.5)	24.78 (1.3)	26.54 (1.28)	96.56	< .001	< .001	< .001	< .001
Executive data									
Backward digit span	4.94 (1.4)	3.91 (0.87)	4.25 (1.06)	4.77 (1.23)	4.47	.002	.81	.03	.43
WCST PR (%)	7.93 (4.2)	14.87 (8.28)	29.02 (7.59)	9.51 (4.01)	74.18	< .001	.63	< .001	< .001
Phonemic fluency	16.62 (5.6)	12.45 (5.25)	14.06 (4.72)	18.81 (5.31)	8.51	.006	.08	< .001	.009

Note. SC: social cognition; EF: executive function; EDSS: Expanded Disability Status Scale; FER: facial emotion recognition test; ToM: theory of mind; WCST PR: Wisconsin Card Sorting Test perseverative responses.

Table 4

Number and Percentage of Patients with MS Impaired on Sociocognitive and Executive Domains in Each Cluster

	Backward Digit Span	Phonemic Fluency	WCST	EF domain	Emotion Recognition	ToM	SC domain
	%(*n*)	%(*n*)	%(*n*)	%(*n*)	%(*n*)	%(*n*)	%(*n*)
Cluster 1	0	17.6 (12)	5.88 (4)	1.47 (1)	23.53 (16)	33.8(23)	4.41(3)
Cluster 2	0	40.91 (9)	36.36(8)	13.63(3)	77.27 (17)	100 (22)	77.2(17)
Cluster 3	0	31.22 (5)	100(16)	31.25(5)	43.75 (7)	43.75(7)	31.2(5)

Note: SC: Social cognition; EF: executive function; WCST: Wisconsin Card Sorting Test

Figures

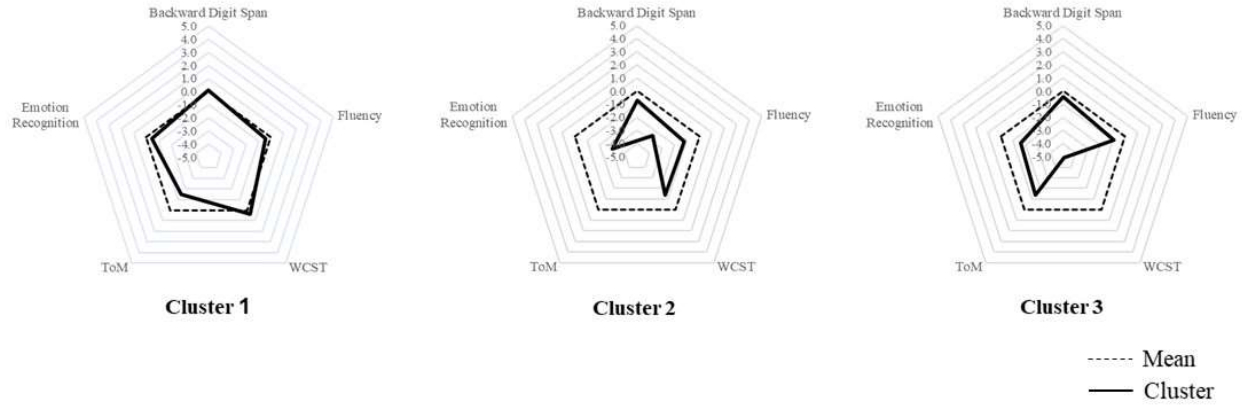

Figure 1: The three functional clusters of patients with MS. Patient subgroups determined by cluster analysis according to executive function measures (Backward Digit Span, phonemic fluency, and number of Wisconsin Card Sorting Test (WCST) perseverative responses) and social cognition measures (facial emotional recognition and theory of mind (ToM).

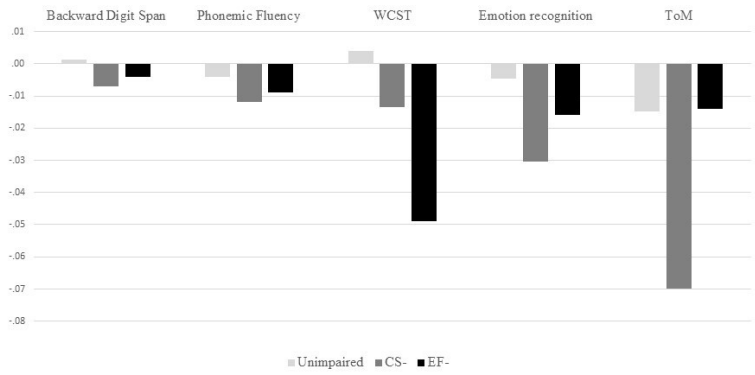

Figure 2. Comparisons between SC and EF domains according to three functional clusters. All variables were standardized with respect to the healthy sample. The baseline 0 represents the healthy sample. Values are expressed as *z* scores (i.e. in standard deviation units with respect to the healthy sample). Negative values denote poorer performance with respect to the healthy sample. WCST: number of Wisconsin Card Sorting Test perseverative responses; ToM: theory of mind.