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CRITICAL REVIEW

Deficits in Social Cognition: An Unveiled Signature of Multiple Sclerosis

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Abstract

Background and Objectives: Multiple sclerosis (MS) is a chronic progressive inflammatory disease of the central nervous system, representing the primary cause of non-traumatic disability in young adults. Cognitive dysfunction can affect patients at any time during the disease process and might alter the six core functional domains. Social cognition is a multi-component construct that includes the theory of mind, empathy and social perception of emotions from facial, bodily and vocal cues. Deficits in this cognitive faculty might have a drastic impact on interpersonal relationships and quality of life (QoL). Although exhaustive data exist for non-social cognitive functions in MS, only a little attention has been paid for social cognition. The objectives of the present work are to reappraise the definition and anatomy of social cognition and evaluate the integrity of this domain across MS studies. We will put special emphasis on neuropsychological and neuroimaging studies concerning social cognitive performance in MS. **Methods:** Studies were selected in conformity with PRISMA guidelines. We looked for computerized databases (PubMed, Medline, and Scopus) that index peer-reviewed journals to identify published reports in English and French languages that mention social cognition and multiple sclerosis, regardless of publication year. We combined keywords as follows: (facial emotion or facial expression or emotional facial expressions or theory of mind or social cognition or empathy or affective prosody) AND multiple sclerosis AND (MRI or functional MRI or positron emission tomography or functional imaging or structural imaging). We also scanned references from articles aiming to get additional relevant studies. **Results and Conclusions:** In total, 26 studies matched the abovementioned criteria (26 neuropsychological studies including five neuroimaging studies). Available data support the presence of social cognitive deficits even at early stages of MS. The increase in disease burden along with the "multiple disconnection syndrome" resulting from gray and white matters pathology might exceed the "threshold for cerebral tolerance" and can manifest as deficits in social cognition. Admitting the impact of the latter on patients' social functioning, a thorough screening for such deficits is crucial to improving patients' QoL. (*JINS*, 2017, *23*, 266–286)

Keywords: Social cognition, Multiple sclerosis, Theory of mind, Emotions, Empathy, Prosody

INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) representing the primary cause of non-traumatic disability in young adults (Compston & Coles, 2008). Its precise etiology remains unclear and includes a constellation of mechanisms. Its most common type is the relapsing-remitting (RR) which usually shifts to a secondary progressive (SP) fate (Compston & Coles, 2008). Primary progressive (PP) MS is a third form which still does not have approved disease-modifying therapies and is considered to have a poor prognosis (Gajofatto & Benedetti, 2015; Segal & Stüve, 2016). The disease course can be very heterogeneous, through which patients may develop sensorimotor, cerebellar, emotional, and cognitive symptoms (Compston & Coles, 2008).

Cognitive decline occurs in approximately 40–65% of MS patients at some point during their life (Benedict et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991; Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006) and may involve any of the six core functional domains: are perceptual-motor functions, language, learning and memory, executive functions, complex attention, and social cognition (5th ed.; DSM–5; American Psychiatric Association, 2013). Working memory

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and information processing speed (IPS) are the most frequently impaired areas in MS, followed by learning, memory, and executive functions (Benedict et al., 2006; Rao, Leo, Bernadin, et al., 1991; Sanfilipo et al., 2006).

Although these domains have been well studied in MS (Mohr & Cox, 2001), little attention has been paid for social cognition, which defines the individual's ability to understand others' mind and feelings (Sebastian et al., 2012; Uekermann, Channon, Winkel, Schlebusch, & Daum, 2007; Uekermann & Daum, 2008; Uekermann et al., 2010; Vistoli, Brunet-Gouet, Baup-Bobin, Hardy-Bayle, & Passerieux, 2011; Wolkenstein, Schonenberg, Schirm, & Hautzinger, 2011). It is a multi-component construct that includes theory of mind (ToM) (Abdel-Hamid et al., 2009; Koelkebeck, Abdel-Hamid, Ohrmann, & Brune, 2008), empathy (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Decety & Jackson, 2004; Leslie, Johnson-Frey, & Grafton 2004; Seitz, Nickel, & Azari, 2006; Vollm et al., 2006), and social perception of emotions from prosody, facial expressions, and bodily gestures (Calder & Young, 2005; Ethofer et al., 2006; Heikkinen et al., 2010; Ross, Thompson, & Yenkosky, 1997; Wheaton, Thompson, Syngeniotis, Abbott, & Puce, 2004; Uekermann & Daum, 2008; Uekermann, Abdel-Hamid, Lehmkamper, Vollmoeller, & Daum, 2008).

The integrity of social cognitive functions is crucial for proper retrieval of information from social stimuli, to establish an appropriate social interaction and cope with chronic diseases such as MS (Montel & Bungener, 2007). In this perspective, deficits in social cognition might have a drastic impact on quality of life (QoL) and interpersonal communication. Interestingly, altered social interactions have been frequently reported in MS patients (Buhse, 2008; Kesselring & Klement, 2001; Rao, Leo, Elllington, et al., 1991) and could be reflected by high rates of divorce and unemployment (Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008; Langdon, 2011; Pfleger, Flachs, & Koch-Henriksen, 2010; Rao, Leo, Elllington, et al., 1991) and increased level of social anxiety (Poder et al., 2009).

The main objective of the present work is to review the available data concerning social cognition in MS. First, we will reappraise terms defining social cognition, particularly social perception of emotions, theory of mind and empathy. This section will also include the neuroanatomy of social cognition in healthy brain. The second section will examine neuropsychological studies regarding social cognition in MS. This will be followed by a third section that puts emphasis on neuroimaging studies of social cognition in this population. Finally, findings will be discussed in the light of the "cognitive reserve" hypothesis. The clinical assessment of social cognition is developed elsewhere (for reviews, see Henry, von Hippel, Molenberghs, Lee, & Sachdev, 2016) and is beyond the scope of this review.

NEUROANATOMICAL CORRELATES OF SOCIAL COGNITION

In the past few years, tremendous advances in neuroimaging have unveiled many cerebral hubs that take part in brain networks dedicated to social cognition. Although social cognitive domains might recruit different cerebral areas, an overlapping seems to occur among their networks.

Social Perception

Social perception of emotions from facial expressions

A chief element in social interaction is the ability to recognize facial expressions and their emotional significance (Brothers, 1990; Van Kleef, 2009). A large-scale network and a complex processing have been suggested by this skill. The first step consists of early visual processing of faces, which entails a relatively shared neural pathway for facial identity discrimination and facial emotion recognition (Calder & Young, 2005; LaBar, Crupain, Voyvodic, & McCarthy, 2003; Palermo & Rhodes, 2007; Vuilleumier & Pourtois, 2007). In the following steps, distinct cortical regions would intervene. For instance, the fusiform face area (FFA) plays a key role in recognizing invariant or neutral facial aspect that defines identity (Kanwisher & Yovel, 2006). Other areas, such as the superior temporal sulcus (STS), are more specialized in changeable facial features (i.e., perception of eyes and mouth movements; Allison, Puce, & McCarthy, 2000). The amygdala is an essential element in automatic attentional capture by emotionally relevant facial expressions (Vuilleumier & Pourtois, 2007). The orbitofrontal cortex (OFC) is crucially involved in processing non-conscious aspects of facial expressions (Adolphs, 2006; Krause et al., 2009). To note, non-conscious perception of emotional stimuli is an intrinsic property of the healthy brain. Through this process, emotionally relevant visual stimuli that are not perceived consciously can induce behavioral responses manifesting as changes in emotional states (Tamietto & de Gelder, 2010).

Of interest, observing facial emotions is known to trigger an affective reaction which subsequently leads to adaptive changes in the observer's behavior (Van Kleef, 2009). Such a reaction depends on the generation of an "emotional state" and a "motivation state." The former is mainly created by the anterior insula that integrates environmental cues with viscero-reception of internal body state (Adolphs, 2002). The latter is completed *via* the action of the anterior cingulate cortex (ACC; Critchley, 2005).

Social perception of vocal cues: *Affective* prosody

Prosody is an aspect of language represented by acoustic characters such as the pattern of intonation (i.e., timing, pitch, rhythm, stress, and pausing; Heikkinen et al., 2010; Uekermann & Daum, 2008; Uekermann, Abdel-Hamid et al., 2008). Among the subdivisions of prosody, the most relevant here are the linguistic and affective components (Ross et al., 1997; Uekermann & Daum, 2008). While processing linguistic prosody seems to involve left-sided brain regions, perception of affective prosody is a dominant function of the right hemisphere and encompasses many steps (Ethofer

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et al., 2006; Uekermann & Daum, 2008; Uekermann, Abdel-Hamid, et al., 2008; Wildgruber, Ackermann, Kreifelts, & Ethofer, 2006).

For example, primary and higher order right-hemispheric acoustic areas deal with extracting suprasegmental acoustic information whose meaningful representation mainly involves the right STS. Bilateral inferior frontal regions maintain an explicit assessment of affective prosody. Lastly, the corpus callosum (CC) participates by ensuring the inter-hemispheric integration of language functions (Ross et al., 1997); this seems crucial to understanding emotional prosody, especially when the latter is not in agreement with the linguistic component. In this situation, a proper understanding requires a successful prioritization of the affective aspect over the linguistic one (Uekermann et al., 2010).

Theory of Mind

ToM, also known as "mentalizing," suggests understanding and predicting mental states of others, based on (i) their emotions and feelings (affective ToM) and/or (ii) their intentions, thoughts, and beliefs (cognitive ToM; Stone, Baron-Cohen, & Knight, 1998; Uekermann et al., 2007; Uekermann, Channon, et al., 2008). ToM is a key aspect of social cognition and constitutes an important prerequisite for adequate social interactions. The two extremes of ToM abnormalities are known as "undermentalizing" (insufficient ToM) and "overmentalizing" (excessive ToM), which, respectively, refer to deficits commonly encountered in patients with autism (Baron-Cohen, 2000) and schizophrenia (Frith, 2004).

ToM recruits a complex neural network which includes the ACC, OFC, amygdala and many areas of the temporal lobe (i.e., posterior STS, temporal pole, and temporoparietal junction [TPJ]; Adolphs et al., 2002; Frith & Frith, 2006; Herold et al., 2009; Kuperberg et al., 2003; Schulte-Rüther et al., 2011; Stone et al., 1998; Uekermann et al., 2007, 2010). Remarkably, available data suggest that ToM sub-components be modulated by distinct frontal circuits. Saying differently, while the ventromedial prefrontal cortex (VMPFC) appears to be particularly involved in processing affective ToM (Shamay-Tsoory & Aharon-Peretz, 2007); the ventrolateral prefrontal (VLPFC) and dorsolateral prefrontal cortices (DLPFC) seem to be chiefly implicated in mediating cognitive ToM (Shamay-Tsoory & Aharon-Peretz, 2007).

Empathy

Empathy lies in the individual's ability to reason, predict the consequences of emotions, and have a compassionate response accordingly (Decety & Jackson, 2004; Ruby & Decety, 2004; Uekermann & Daum, 2008; Uekermann, Channon, et al., 2008; Uekermann et al., 2010). Such a skill consists of taking another person's perspective (other-oriented emotions), which often leads to altruistic helping behavior. In contrast, self-oriented emotions, such as personal distress, primarily focus on the empathizer's feelings in a way that it might interfere with prosocial behavior and, therefore, are not considered empathy (Davis, 1983; Tangney, Stuewig, and Mashek, 2007). The empathy network includes anterior insula and regions of the prefrontal and frontal cortices (i.e., dorsal and middle parts of the ACC, supplementary motor areas; Decety & Jackson, 2004; Fan, Duncan, de Greck, & Northoff, 2011; Gallese, Keysers, & Rizzolatti, 2004; Seitz et al., 2006; Vollm et al., 2006).

STUDY SELECTION

For the aims of this review, studies were selected in conformity with PRISMA guidelines (Moher et al., 2009). First, we searched for computerized databases that index peer-reviewed journals (PubMed, Medline, and Scopus) to identify published reports, in English and French languages, mentioning social cognition and multiple sclerosis, regardless of publication year. For the section dealing with neuropsychological studies, we combined keywords as follows: (facial emotion or facial expression or emotional facial expressions or theory of mind or social cognition or empathy or affective prosody) AND multiple sclerosis. Second, for the section dedicated to neuroimaging underpinnings of social cognitive performance in MS, our combination consisted of the previous keywords AND [MRI/functional MRI (fMRI)/positron emission tomography (PET)/functional imaging/structural imaging]. In both researches, we scanned references from articles aiming to get additional relevant studies. Twenty-six neuropsychological studies matched these criteria (25 in English, 1 in French), of which five also contained neuroimaging data.

SOCIAL COGNITION ACROSS MULTIPLE SCLEROSIS STUDIES

After defining social cognition and its neuroanatomical substrates in healthy humans, we will continue by reviewing the neuropsychological studies assessing social cognition in MS patients.

Social Perception

Social perception of facial emotions in multiple sclerosis

In the past two decades, there was a growing interest in understanding the abilities of MS patients to recognize emotional facial expressions (EFE). The earliest insight into this topic came from a pioneering study by Beatty and colleagues (1989). Patients with chronic progressive MS and age and education matched healthy controls (HCs) performed the Benton Facial Recognition Test (BFRT) for facial identity discrimination (Benton, Sivan, Hamsher, Varney, & Spreen, 1994) and an affective judgment task that evaluates the ability to recognize the six basic facial emotions (i.e., happiness, sadness, anger, fear, disgust and surprise; Ekman and Friesen, 1976).

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Compared to HCs, patients had worse cognitive performance and lower accuracy in both facial identity discrimination and facial emotion recognition. The deficits in emotion recognition were not restricted to a particular emotional state. Furthermore, correlation analysis revealed a positive correlation between scores on BFRT and those on affective judgment task. This made the authors consider the observed deficits in EFE recognition as secondary to those in facial identity discrimination which can somewhat reflect visuoperceptual deficits. Concurrently, the authors included a group of RR MS patients who, unlike their progressive counterparts, had preserved abilities to recognize EFE but were "slightly" impaired on BFRT test. Based on these findings, one would assume that clinical and demographic differences between both patient groups accounted for the observed differences in recognizing EFE. Unfortunately, the RR MS group was not included in the remaining statistical analyses.

Consistent with the first report, Parada-Fernández et al. considered a mixed cohort of RR and progressive MS patients and healthy subjects (2015). The authors used BFRT and Facially Expressed Emotion Labeling task (Kessler, Bayerl, Deighton, & Traue, 2002) which, respectively, evaluate facial identity discrimination and facial emotion recognition. To further eliminate any bias that might result from visual impairment, the authors excluded patients who had visual difficulties which disable them from reading and/or writing. This study showed that patients had difficulties in facial emotion recognition and identity discrimination. Moreover, a stepwise multiple regression analysis revealed that disease type and non-social cognitive abilities were the main contributors to the observed deficits in recognizing EFE. Facial identity discrimination did not seem to contribute to social cognitive deficits in this study.

Similarly, Berneiser et al. applied the facial affect task of Florida Affect Battery (Bowers, Blonder, & Heilman, 1991, 2001) to evaluate EFE recognition abilities in patients with different MS subtypes and HCs (2014). Compared to HCs, patients had worse performance in all subsets of the facial affect task, even after exclusively considering those with intact abilities to discriminate facial identity. This stands with what Parada-Fernández et al. stated (2015) and is against the earlier suggestion by Beatty et al. (1989). Again, Berneiser et al. found more pronounced deficits among SP MS patients compared to those suffering from RR MS. In addition, emotion recognition scores were directly correlated with cognitive performance and indirectly correlated with each of depression and fatigue scores, disease duration, and level of physical disability based on the Expanded Disability Status Scale score (EDSS).

Analogously, in the study by Cecchetto et al., patients had poorer performance than HCs on tasks assessing the recognition of all of the six basic facial emotions but had intact abilities to discriminate facial identity (2014). When patients were subdivided based on physical disability (EDSS scores), only highly disabled ones were impaired in labeling EFE. The latter was further correlated with disease characteristics (i.e., disease duration and EDSS scores) and non-social cognitive performance.

In the same perspective, Phillips et al. have assessed emotions' recognition skills using static (Ekman & Friesen, 1976) and dynamic measures (videos featuring frustration, excitement, annoyance, and boredom by Sullivan & Ruffman, 2004) (2011). Compared to HCs, patients had worse mood and cognitive scores and showed deficits in recognizing facial emotions without differences in facial identity discrimination. The deficits remained significant even after accounting for depression and cognitive decline. In addition, EFE recognition was associated with social and psychological aspects of QoL (Phillips et al., 2011).

Unlike the above-mentioned studies that brought out social cognitive deficits in all of the six basic facial emotions, others rather found an isolated pattern of impairment in recognizing EFE. For instance, two MS trials documented exclusive deficits in identifying the emotions "fear" and "anger" (Henry et al., 2009, 2011). These results are in line with those of a third study comparing HCs and two groups of MS patients with or without altered abilities to recognize EFE (Krause et al., 2009). Here, compared to HCs and the preserved MS group, affected patients had deficits in recognizing "sadness," "fear," and "anger" but were able to discern positive emotions. Moreover, in a fourth study, patients with intact abilities to discriminate facial identity had significant impairment in identifying "fear," "sadness," "anger," and "surprise" (Prochnow et al., 2011). More interestingly, when considering physical disability as a variable, severely disabled patients had worse cognitive performance and displayed an additional deficit in the emotion "disgust." Thus, higher disability levels seem to contribute to the emergence of other deficits.

The isolated involvement of negative emotions in the latter studies (Henry et al., 2009, 2011; Krause et al., 2009; Prochnow et al., 2011) might be explained as follows: One of the possibilities is that positive emotions might be relatively easier to process than negative ones and could hence be more compensated (Skowronski & Carlston, 1989). This idea is supported by one MS study in which "happiness," for example, was better recognized than "fear" or "sadness" (Cecchetto et al., 2014). Another reason is that MS patients might express low sensitivity toward aversive stimuli (Di Bitonto et al., 2011). Indeed, these patients were found to have reduced emotional reactivity to negative stimuli (i.e., sounds and pictures) compared to HCs but had normal reactivity to positive ones (Di Bitonto et al., 2011).

Functional neuroimaging data can provide a third explanation. In fact, the normal processing of each emotion seems to induce a selective pattern of brain activation (Jehna, Neuper, et al., 2011). For example, some cerebral areas (i.e., VLPFC, ACC, and superior temporal gyri) are more activated during processing of "sadness," while others (i.e., DLPFC, cingulate gyrus, inferior temporal gyrus, and cerebellum) appear to be more specific for "happiness" (Habel, Klein, Kellermann, Shah, & Schneider, 2005).

This idea can be exemplified by one fMRI study in MS where the selective deficit in recognizing negative emotions was associated with hypoactivation of cortical areas devoted to processing negative emotions (i.e., ACC, fSTS, and VLPFC) (Krause et al., 2009).

Finally, five studies found intact EFE recognition abilities in MS patients (Di Bitonto et al., 2011; Jehna et al., 2010; Jehna, Langkammer, et al., 2011; Passamonti et al., 2009; Pinto et al., 2012). This is not surprising given that four of them recruited exclusively (Passamonti et al., 2009; Jehna, Langkammer, et al., 2011; Di Bitonto et al., 2011) or predominantly (Pinto et al., 2012) RR MS patients. Once more, the cohort of the fifth study consisted mostly of preserved patients with clinically isolated syndrome and RR MS (Jehna et al., 2010). Here, the authors assessed the accuracy and reaction time during EFE recognition task. Although accuracy did not differ between both groups, patients were slower than HCs. The observed slowing might not reflect deficits in emotion recognition, but could rather hint to a general delay in IPS which is frequent in MS (Vázquez-Marrufo et al., 2014) or an age-related slowing (Knight & Mather, 2013) since HCs were significantly younger than patients.

The above-mentioned studies are summarized in Table 1. The differences in their outcomes might be explained by the disparity in clinical and demographic characteristics of their cohorts (e.g., Berneiser et al., 2014; Henry et al., 2009, 2011; Prochnow et al., 2011), differences in adopted assessment tools (dynamic *vs*. static tasks) and presence of confounding variables such as mood and affective disturbances, cognitive deficits, and MS fatigue, all of which might contribute to deficits in identifying EFE.

Starting with disease characteristics, patients with higher physical disabilities seem to be the most affected on tasks assessing EFE recognition (Cecchetto et al., 2014; Prochnow et al., 2011). In this context, some studies were for a correlation between EDSS scores (Kurtzke, 1983) and deficits in judging EFE (Cecchetto et al., 2014; Berneiser et al., 2014), while others denied it (Henry et al., 2011; Jehna et al., 2010). As for disease subtypes, progressive MS patients seem to suffer from more pronounced deficits compared to RR MS patients (Beatty et al., 1989; Jehna et al., 2010; Jehna, Langkammer, et al., 2011; Parada-Fernández et al., 2015; Passamonti et al., 2009; Pinto et al., 2012). Regarding disease duration, it was found to be associated with deficits in labeling EFE in some (Cecchetto et al., 2014; Berneiser et al., 2014) but not all studies (Henry et al., 2011; Jehna et al., 2010).

Facial identity discrimination remains the main confounding variable in the recognition of EFE (Beatty et al., 1989; Di Bitonto et al., 2011; Pinto et al., 2012) since both processes share early common neural processing pathways. Although some MS studies suggest that deficits in the former be behind those in the latter (Beatty et al., 1989; Di Bitonti et al., 2011), most of the remaining data are not in favor of this assumption (Berneiser et al., 2014; Cecchetto et al., 2014; Krause et al., 2009; Parada-Fernández et al., 2015; Phillips et al., 2011; Prochnow et al., 2011).

MS fatigue is another frequent symptom that can be defined as a reversible alteration of cognitive task performance (Chalah et al., 2015). Up until now, only a few studies evaluated its relationship with EFE recognition. While one study found it to be associated with EFE task performance (Berneiser et al., 2014), others were not able to detect any significant relationship (Cecchetto et al., 2014; Henry et al., 2011).

Importantly, an interaction was previously found among emotions, mood, and cognition (Leppanen, 2006; Pessoa, 2008). In some studies, MS patients with deficits on EFE recognition tasks had also high depression scores (Beatty et al., 1989; Berneiser et al., 2014; Henry et al., 2011; Krause et al., 2009; Parada Fernandez et al., 2015; Phillips et al., 2011; Pinto et al., 2012; Prochnow et al., 2011) and poor cognitive abilities (Beatty et al., 1989; Henry et al., 2009, 2011; Krause et al., 2009; Parada-Fernández et al., 2015; Phillips et al., 2009; Prochnow et al., 2011). However, the correlation of EFE recognition with cognitive and mood scores remains controversial. While some studies are in favor of this relationship (Berneiser et al., 2014; Cecchetto et al., 2014; Henry et al., 2009; Jehna et al., 2010; Parada-Fernández et al., 2015; Pinto et al., 2012), others failed to detect any significant association (Cecchetto et al., 2014; Henry et al., 2011; Jehna et al., 2010; Krause et al., 2009; Prochnow et al., 2011).

Alexithymia is an additional variable that might interfere here (Grynberg et al., 2012). By definition, it is a personality trait characterized by difficulties in emotional identification, understanding, and description (Franz et al., 2008). Alexithymia was tackled in two MS trials evaluating EFE recognition. Although one of them featured higher levels of alexithymia in MS patients compared to HCs (Prochnow et al., 2011), the other did not find any group difference (Cecchetto et al., 2014), and neither of them detected an association between alexithymia and deficits in EFE recognition.

All in all, deficits in facial emotion recognition might occur early during MS, and do not seem to be restricted to progressive disease subtypes. However, disease characteristics and concomitant symptoms may contribute to such deficits. Heterogeneity in MS lesions location might be behind the different patterns of EFE recognition deficits encountered in various studies. One might speculate that during disease course, clinical and radiological MS progression can also be mirrored by a shift from an intact abilities to recognize EFE (Jehna et al., 2010, Jehna, Langkammer, et al., 2011; Passamonti et al., 2009; Pinto et al., 2012), to an isolated pattern of deficits (Henry et al., 2009, 2011; Krause et al., 2009; Prochnow et al., 2011), and finally to a global deficit (Beatty et al., 1989; Berneiser et al., 2014; Parada-Fernández et al., 2015).

Social perception of affective prosody in multiple sclerosis

In advanced MS stages, visual deficits can become very pronounced, and patients might depend on the perception of affective prosody for a successful social interaction. Only two MS studies have addressed this issue. In the first one, the

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Table 1. Studies assessing facial emotion recognition in multiple sclerosis

Authors (year)	Population	Facial emotion recognition task	Facial identity discrimination task	Neuropsychological evaluation	Outcomes (patients)	Correlation and other analyses (Emotion recognition)
Beatty et al. (1989)	21 chronic progressive MS *(gender NP; age: 52.0; EDSS: 6.6; DD: 18.4)* 42 RR MS *(sociodemographic & clinical data: NP)* 19 HCs	Ekman (*Ekman and Friesen, 1976*)	BFRT (*Benton et al., 1994*)	Cognition: MMSE Mood: BDI	SP MS: - Deficit in facial emotion recognition - Deficit in facial identity discrimination. - High mood scores - Poor cognitive performance RR MS: - Intact facial emotion recognition - Slight deficit in facial identity discrimination	Correlation with facial identity discrimination (BFRT)
Henry et al. (2009)	27 MS, type NP *(18 F; age: 47.0; Disease Steps score: 1.9; DD: 7.0)* 30 HCs	Ekman (*Ekman and Friesen, 1976*)	NP	Cognition: SEFCI, measures of fluency Mood: GDS	Deficit in the recognition of anger and fear Poor cognitive performance No group difference on mood scores	Correlation with cognitive measures (only fluency)
Krause et al. (2009)	7 RR/4 SP MS patients with deficits in facial emotion recognition *(9F; age: 42.7; median EDSS: 3.5; DD: NP)* 10 RR/1 PP MS patients without deficits in facial emotion recognition *(9F; age: 36.3; median EDSS: 1.5; DD: NP)* 11 HCs	5th subset of FAB (*Bowers et al., 1991, 2001*)	1st subset of FAB (*Bowers et al., 1991, 2001*)	Cognition: PASAT Mood: BDI	Intact facial identity discrimination Deficits in the recognition of unpleasant facial emotions (sadness, fear and anger) in the impaired patients Significant difference between impaired and preserved MS patients on cognitive performance and mood scores	A trend for direct correlation with cognitive measures (PASAT) and a trend for inverse correlation with mood (BDI) and EDSS scores
Passamonti et al. (2009)	12 RR MS patients with no cognitive or affective deficits *(7 F; age: 29.3; median EDSS: 1.5; DD: 4.3)* 12 HCs	Task derived from Ekman with emotional (faces) and neutral (shapes) stimuli (*Ekman and Friesen, 1976*)	NP	Cognition: RAVLT, ROCFT, WCST-Nelson's version, Word List Generation, revised WAIS-R Mood : CMDI, HAM-A Fatigue FSS	Intact facial emotion recognition. No group difference on cognitive performance No group difference on mood scores No group difference on fatigue scores	NP
Jehna et al. (2010)	7 RR MS/12 CIS /1 SP MS *(13F; age: 36.4 ; EDSS: 1.7; DD: 0.6 for CIS, 8 for RR and 6 for SP)* 23 HCs	A computerized test (accuracy and RT) based on Ackerer and Ekman (*Ackerer, 2003*; *Ekman and Friesen, 1976*)	Task (Part 2 of emotion recognition test) to assess recognition of non-emotional faces (gender)	Cognition: FST Mood: ADS-L	Slight deficit in facial emotion recognition (Intact accuracy but long RT on test subsets) Poor cognitive performance No group difference on mood scores	Correlation with cognitive measures (FST)
Di Bitonto et al. (2011)	13 RR MS *(13F; age: 42; EDSS: 2.8; DD: NP)* 13 HCs	Ekman (*Ekman and Friesen, 1976*)	BFRT (*Benton et al., 1994*)	Cognition: Brief repeatable battery of neuropsychological tests for MS Mood: BDI, Hamilton Anxiety Scale Emotional valence and arousal: IADS and IAPS (*Lang et al., 2005*; *Bradley and Lang, 2007*)	Intact facial emotion recognition Intact facial identity discrimination No group difference on cognitive performance No group difference on mood scores No group difference on emotional valence and arousal tests	Correlation with facial identity discrimination (BFRT)
Henry et al. (2011)	64 RR MS *(50F; age: 42.4 EDSS: 2.3; DD: 9.1)* 30 HCs	FEEST (*Young et al., 2002*)	NP	Cognition (only patients): WAIS-R, Brixton Spatial Anticipation Test Mood: BDI Fatigue: MFIS	Deficits in facial emotion recognition Poor cognitive performance High mood scores High fatigue scores	No correlation
Prochnow et al. (2011)	5 RR/29 SP/1 PP MS *(12F; age 48.2; median EDSS: 6.0; DD: 9.2)* 61 HCs	Ekman and PCFAE (*Ekman and Friesen, 1976; Ingenhag et al. 2007, unpublished)*	BFRT (*Benton et al., 1994*)	Cognition: MMSE, FST Mood: BDI Alexithymia: TAS- 20 (*Bagby et al., 1994*)	Deficits in the recognition of fear, surprise, anger, sadness Deficit in the recognition of disgust only in highly disabled patients	Correlation with cognitive measures (FST), diagnosis onset, age, and education

Table 1: (*Continued*)

Authors (year)	Population	Facial emotion recognition task	Facial identity discrimination task	Neuropsychological evaluation	Outcomes (patients)	Correlation and other analyses (Emotion recognition)
					Poor cognitive performance High mood scores High alexithymia scores	
Jehna, Langkammer, et al. (2011)	15 RR MS *(10F; age: 29.5; EDSS: 1.7, DD: 7.3)* 15 HCs	BERT (*designed by the authors)*	Control task to evaluate facial identity discrimination (gender)	Cognition: BRB-N, WCST Mood: BDI	Intact facial emotion recognition Intact facial identity discrimination No group difference on cognitive performance No group difference on mood scores	NP
Phillips et al. (2011)	27 RR/3 SP/2 PP MS *(22F; age: 44.0, Disease Steps: 2.2, DD: 7.9)* 33 HCs	Ekman and Brief video clips of interpersonal interactions featuring frustration, excitement, annoyance, and boredom (*Ekman and Friesen, 1976*; *Sullivan and Ruffman, 2004*)	Control task to evaluate facial identity discrimination	Cognition: FAS letter fluency task, memory task from SEFCI and SART Mood: HADS Quality of life: WHOQoL-BREF (*Skevington et al., 2004*)	Deficits in facial emotion recognition Intact facial identity discrimination Poor cognitive performance High mood scores No group difference on quality of life	Correlation with psychological and social aspects of quality of life
Pinto et al. (2012)	48 RR/3 SP/5 PP MS *(32F; age: 38.9; EDSS: 2.5; DD: 9)* 56 HCs	Nim Set Collection (*Tottenham et al. , 2009*)	BFRT (*Benton et al., 1994*)	Cognition (only patients): MMSE, Auditory Verbal Learning Test, Corsi-Block Test, Digit Span, Letter Word Fluency, Sentence Repetition, and WCST (Nelson's version) Mood: HADS	Intact facial emotion recognition Intact facial identity discrimination No group difference on cognitive performance High mood scores	Correlation with cognitive measures, mood and EDSS scores
Berneiser et al. (2014)	47 RR/11 SP/3 PP MS *(44F; age: 42.2; EDSS: 3.6; DD: 6.1)* 53 HCs	2^{nd}–5^{th} subsets of FAB (*Bowers et al., 1991, 2001*)	1^{st} subset of FAB (*Bowers et al., 1991, 2001*)	Cognition (only patients): PASAT 3 Mood: BDI Fatigue: MS-specific fatigue scale	Deficits in facial emotion recognition Intact facial identity discrimination No group difference on cognitive performance High mood scores No group difference on fatigue scores	Correlation with cognitive measures, mood, fatigue and EDSS scores, and duration of the disease (since diagnosis)
Cecchetto et al. (2014)	30 RR MS *(21F; age 34.2; EDSS: 2.0, DD: 9.1)* 30 HCs	Nim Set Collection (*Tottenham et al. , 2009*)	BFRT (*Benton et al., 1994*)	Cognition (only patients): BRB-N, TMT, phonemic verbal fluency, verbal and spatial span Mood: BDI Fatigue: FSS Alexithymia: TAS-20 (*Bagby et al., 1994*)	Deficits in facial emotion recognition Intact facial identity discrimination. No group difference on cognitive pefromance No group difference on fatigue scores No group difference on alexithymia	Correlation with cognitive measures, EDSS score, age and disease duration
Parada-Fernández et al. (2015)	24 RR/15 PP/6 SP MS *(64.4% F; age: 49.4 ; EDSS: NP; DD: NP)* 40 HCs	FEEL (*Kessler et al., 2002*)	BFRT (*Benton et al., 1994*)	Cognition: Stroop test, TMT, SDMT, Complutense Verbal Learning Test Mood: HADS	Deficit in facial emotion recognition Deficit in facial identity discrimination Poor cognitive performance High mood scores	*Neuropsychological measures and disease subtype had main effects on emotional recognition*

Note. Demographic and clinical data were expressed as mean unless indicated otherwise. Age and disease duration were expressed in years.
ADS-L = Allgemeine Depressions-Skala; BDI = Beck Depression Inventory; BEAST = Bodily Expressive Action Stimulus Test; BERT = Behavioral Emotion Recognition Test; BFRT = Benton Facial Recognition Test; BRB-N = Brief Repeatable Battery of Neuropsychological Tests; CIS = clinically isolated syndrome; CMDI = Chicago Multiscale Depression Inventory; DD = disease duration; FAB = Florida Affect Battery; FEEL = Facially Expressed Emotion Labeling; FEEST = Facial expressions of emotions, stimuli and tests; FSS = Fatigue Severity Scale; FST = Faces Symbol Test; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton Rating Scale Anxiety; HCs = healthy controls; IADS = International Affective Digitized Sounds and Picture System; IAPS = International Affective Picture System; IPS = information processing speed; MFIS = Modified Fatigue Impact Scale; MMSE = Mini Mental Status Exam; MS = multiple sclerosis; NP = not provided; PASAT = Paced Auditory Serial Attention Test; PCFAE = Test of Perceptual Competence of Facial Affect Recognition; PP = primary progressive; RAVLT = Rey Auditory-Verbal Learning Test; ROCFT = Rey–Osterrieth Complex Figure Test; RR = relapsing remitting; RT = reaction time; SART = Sustained Attention to Response Task; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SEFCI = Screening Examination for Cognitive Impairment; SP = secondary progressive; TAS- 20 = Toronto Alexithymia Scale; TMT = Trail Making Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test;

authors used the comprehension and discrimination portions of Aprosodia battery (Ross et al., 1997) in a cohort of chronic MS patients (Beatty, Orbelo, Sorocco, & Ross, 2003). Compared to HCs, patients had worse performance on affective prosody, mood, and cognitive scales. Measures of affective prosody were positively correlated with cognitive scores but were not associated with mood disturbance, hearing loss, aphasia, treatment profile, or education. Unfortunately, patients' clinical characteristics were not provided and their impact on prosody was not assessed.

In contrast with the first study, the second one included patients with early stage of RR MS (Kraemer, Herold, Uekermann, Kis, et al., 2013). Compared to HCs, patients had higher depression scores but did not differ on most of the cognitive scores. They poorly discriminated affective prosody, had lower accuracy in matching affective prosody to the facial expression for "anger," but were able to recognize "happiness." This finding is in line with the isolated pattern of deficits seen in some EFE studies (anger and fear in Henry et al., 2009, 2011; anger, sadness, and fear in Krause et al., 2009; anger, sadness, fear, and surprise in Prochnow et al., 2011). The observed deficits were unrelated to mood, cognitive performance, or physical disability. Unlike the cohort examined by Beatty et al. (2003), patients seen here performed better than HCs on matching affective prosody to facial expression for the emotion "fear." This finding might be due to an increased sensitivity for recognizing "fear" in a population of young patients recently shocked by the diagnosis of a chronic disabling disease such as MS (Kraemer, Herold, Uekermann, Kis, et al., 2013).

ToM in MS

The majority of ToM studies in MS have adopted the Faces test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), Reading the Mind in the Eyes test and Faux Pas test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999) (for a summary, see Table 2). Faces test consists of 20 photographs of the same actress portraying different complex mental states (Banati et al., 2010; Baron-Cohen et al., 1997, 2001; Mike et al., 2013). During Reading the Mind in the Eyes test, also simply known as Eyes test, patients are asked to observe and comment on feelings or thoughts expressed in 36 face photographs depicting only the eye region (Banati et al., 2010; Baron-Cohen et al., 1999; Mike et al., 2013). Both are non-verbal tasks that evaluate "affective" ToM based on visual cues. The third one, Faux Pas test, is a verbal task that assesses "cognitive" ToM.

Some authors used exclusively verbal or non-verbal ToM tasks and found pronounced ToM deficits in their MS cohorts (Henry et al., 2009, 2011; Parada-Fernández et al., 2015; Roca et al., 2014). Others combined several tools that assess both ToM aspects (affective and cognitive) and obtained heterogeneous results. For instance, in two studies, patients were evaluated by the means of Reading the Mind in the Eyes test, Faces test, and Faux Pas test (Banati et al., 2010; Mike et al., 2013). Patients had an altered performance on the first (Banati et al., 2010; Mike et al., 2013) and second (Mike et al., 2013) tests, but had normal scores on the third one.

At a first glance, the absence of abnormality on the Faux Pas test appears surprising. However, this test seems to have low sensitivity to detect mentalization deficits as seen in some MS trials (Henry et al., 2011; Mike et al., 2013; Ouellet et al., 2010). For instance, in one study, MS patients had ToM deficits according to the Strange Stories task (Happé, Winner, & Brownell, 1998), yet they had normal performance on the Faux Pas test (Baron-Cohen et al., 1999). Such a discrepancy might be due to the fact that the Strange Stories task assesses a diversity of mental states and, unlike the Faux Past test, is not limited to detecting a "faux pas" in social interaction (Ouellet et al., 2010). Another plausible explanation is that MS patients may be more prone to mentalization deficits that depend on visual information processing than verbal processing (Mike et al., 2013). This might be due to a selective involvement of emotional networks at some point during the disease course. This assumption is supported by data from a fMRI study where verbal and non-verbal social information elicited different patterns of neural activation, respectively, in the precuneus/posterior cingulate cortex (PC/PCC) and amygdala (Kuzmanovic et al., 2012).

Besides classical static ToM tasks used in the aforementioned works, some authors used dynamic videotaped tasks presenting social interactions and obtained similar results (Genova, Cagna, Chiaravalloti, DeLuca, & Lengenfelder, 2016; Kraemer, Herold, Uekermann, Kis Wiltfang, et al., 2013; Ouellet et al., 2010; Pöttgen, Dziobek, Reh, Heesen, & Gold, 2013). Interestingly, in the study by Pöttgen et al., MS patients further exhibited insufficient mentalization abilities (2013), similar to those documented in autism (Baron-Cohen, 2000). Dynamic tests such as the one used here necessitate online complex processing abilities for an adequate interpretation of the exposed scenes. This might make of them better simulator of daily life events compared to the static written tests.

Last but not least, cognitive and affective ToM deficits in pediatric-onset MS patients have been documented by Charvet et al. (2014). The observed deficits were correlated with visuospatial attention and IPS scores (Charvet et al., 2014) and remained significant after accounting for cognitive functions.

As seen in EFE section, ToM studies enclosed several confounding factors such as MS fatigue (Henry et al., 2011), low intelligence quotient (Pöttgen et al., 2013), high mood scores (Banati et al., 2010; Henry et al., 2011; Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013; Mike et al., 2013; Parada-Fernández et al., 2015), and cognitive deficits (Banati et al., 2010; Charvet et al., 2014; Genova et al., 2016; Henry et al., 2009, 2011; Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013; Mike et al., 2013; Parada-Fernández et al., 2015; Roca et al., 2014).

While ToM scores were significantly associated with non-social cognitive performance (Charvet et al., 2014;

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Table 2. Studies reporting deficits in the theory of mind in multiple sclerosis

Authors (year)	Population	ToM task	Neuropsychological measures	Outcomes (patients)	Correlation and other analyses (ToM)
Henry et al. (2009)	27 MS, type NP *(18 F; age: 47.0; Disease Steps score: 1.9; DD: 7.0)* 30 HCs	Affective ToM: Reading the Mind in the Eyes test (*Baron-Cohen et al., 1999*)	Cognition: SEFCI, measures of fluency Mood: GDS	Deficits in affective ToM Poor cognitive performance No group difference on mood scores	Correlation with cognitive measures (only fluency)
Henry et al. (2011)	64 RR MS *(50F; age: 42.4; EDSS: 2.3; DD: 9.1)* 30 HCs	Cognitive ToM: False Belief tasks; Faux Pas test (*Baron-Cohen et al., 1985, 1999*; *Rowe et al., 2001*)	Cognition (only patients): revised WAIS, Brixton Spatial Anticipation Test Mood: BDI Fatigue: MFIS	Deficits in cognitive ToM Poor cognitive performance High mood scores High fatigue scores	No correlation
Banati et al. (2010)	37 RR/3 SP MS *(29F; age: 36.2; EDSS: 2.3; DD :NP)* 35 HCs	Cognitive and affective ToM: Faux Pas test, Reading the Mind in the Eyes test and Faces test (*Baron-Cohen et al., 1997, 1999*)	Cognition: revised WAIS Mood : BDI, STAI	Deficits in affective ToM No group difference on cognitive performance High mood scores	NP
Ouellet et al. (2010)	11 RR/2 SP/2 PP MS patients with cognitive impairment *(based on Rao et al., 1991a)* *(sociodemographic & clinical data: NP)* 11 RR/11 SP/3 PP/1 type NP MS patients without cognitive impairment *(based on Rao et al., 1991a)* *(sociodemographic & clinical data: NP)* 20 HCs	Cognitive and affective ToM: Strange Stories, Faux Pas test and C&I test (*Happé et al., 1998*; *Baron-Cohen et al., 1999*; *Ouellet et al., 2010*)	Cognition: TMT, Oral Word Association Test, Zoo Map Test, Mazes subtest of WISC-III, Stroop test, Three Minute-Reasoning Test, subsets of WAIS-III, Card Sorting Test, Bells Test, Rey's Auditory Verbal Memory Test, PASAT Mood: BDI	Deficits in cognitive and affective ToM (only in cognitively impaired patients) No group difference on cognitive performance No group difference on mood scores	Correlation with cognitive measures
Mike et al. (2013)	44 RR/5 SP MS *(31F; age: 39.8, EDSS : 2.4; DD: 9.5)* 24 HCs	Cognitive and affective ToM: Faux Pas test, Faces test, Reading the Mind in the Eyes test (*Baron-Cohen et al., 1997, 1999*)	Cognition: N/A Mood (only patients): BDI, STAI	Deficits in affective ToM No group difference on cognitive performance High mood scores	NP
Pöttgen et al. (2013)	31 RR/8 SP/6 PP MS *(31F; age: 42.4; EDSS: 3.5; DD: 8.5)* 45 HCs	Cognitive and affective ToM: MASC (*Dziobek et al., 2006*)	Cognition: SDMT, Multiple Choice Vocabulary Intelligence Test B, Verbal Learning and Memory Test, and executive function Mood: HADS	Deficits in cognitive and affective ToM (even after excluding patients with high mood scores, high physical disability and poor cognitive performance) No group difference on cognitive performance No group difference on mood scores	Correlation with cognitive measures and EDSS
Kraemer, Herold, Uekermann, Kis, et al. (2013)	25 RR MS *(15F; age: 30.9, EDSS: 1; DD: 1.2)* 25 HCs	Cognitive and affective ToM: MASC (*Dziobek et al., 2006*)	Cognition: task derived from the Letter– Number Sequencing subtest of the Wechsler Memory Scale, TMT, Stroop test Mood: BDI	Deficits in cognitive ToM Poor cognitive performance (only on Stroop test) High mood scores	Correlation with cognitive measures (only Stroop test)
Roca et al. (2014)	18 RR MS *(gender NP; age: 40.7; EDSS : 0.6; DD: 5.0)* 16 HCs	Cognitive and affective ToM: Faux Pas test designed to test separately cognitive and affective aspects (*Baron-Cohen et al., 1999*)	Cognition: PASAT, Frontal Assessment Battery, digit span forward and backward tests, verbal fluency test, WCST and TMT Mood : BDI Fatigue : MFIS	Deficits in cognitive ToM Poor cognitive performance No group difference on mood scores No group difference on fatigue scores	Correlation with cognitive measures
Charvet et al. (2014)	28 pediatric-onset MS *(19F; age: 16.3; median EDSS: 1.0; DD: 2.8)* 32 HCs	Cognitive and affective ToM: Faux Pas test, False Beliefs task and Reading the Mind in the Eyes test (*Baron-Cohen et al., 1985, 1999*; *Rowe et al., 2001*)	Cognition: SDMT, Wechsler Abbreviated Scale of Intelligence	Deficits in cognitive and affective ToM Poor cognitive performance (only on SDMT)	Correlation with cognitive measures (only SDMT)
Parada-Fernández et al. (2015)	24 RR/15 PP/6 SP MS *(64.4%F; age: 49.4; EDSS NP; DD: NP)* 40 HCs	Affective ToM: Reading the Mind in the Eyes test (*Baron-Cohen et al., 1999*)	Cognition: Stroop test, TMT, SDMT, Complutense Verbal Learning Test Mood: HADS	Deficits in affective ToM Poor cognitive performance High mood scores	NP

Genova et al. (2016)	10 RR/3 PP/2 SP MS *(11F; age: 49.5, EDSS :NP; DD : 18)* 15 HCs	Cognitive and affective ToM: Social Inference-Enriched subtest of TASIT (Dynamic video-taped social interactions featuring lies & sarcasm) *(McDonald et al.,2003, 2006)*	Cognition: Digit Span subtest of WAIS -IV, SDMT, PASAT, California Verbal Learning Test, Intelligence	Deficits in cognitive and affective ToM Poor cognitive performance (only on SDMT)	Correlation with cognitive measures

Note. Demographic and clinical data were expressed as mean unless indicated otherwise. Age and disease duration were expressed in years.
BDI = Beck Depression Inventory; C&I = Conversations and Insinuations video-taped task; DD = disease duration; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HCs = healthy controls; IPS = information processing speed; MASC = Movie for the Assessment of Social Cognition; MFIS = Modified Fatigue Impact Scale; MS = multiple sclerosis; NP = not provided; PASAT = Paced Auditory Serial Attention Test; PP = primary progressive; RR = relapsing remitting; SDMT = Symbol Digit Modalities Test; SEFCI = Screening Examination for Cognitive Impairment; SP = secondary progressive; STAI = Spielberger Trait Anxiety Inventory; TASIT = The Awareness of Social Inference Test; TMT = Trail Making Test; ToM = theory of mind; WAIS = Wechsler Adult Intelligence Scale-Revised; WCST = The Wisconsin Card Sorting Test.

Genova et al., 2016; Henry et al., 2009; Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013; Ouellet et al., 2010; Pöttgen et al., 2013; Roca et al., 2014) and clinical characteristics in some studies (EDSS scores in Pöttgen et al., 2013; progression rate in Banati et al., 2010); other studies did not detect any significant association between ToM performance and each of demographic or clinical characteristics (Charvet et al., 2014; Henry et al., 2011), cognitive profiles (Henry et al., 2011; Roca et al., 2014), and mood scores (Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013; Pöttgen et al., 2013; Roca et al., 2014), or MS fatigue (Roca et al., 2014).

Empathy in MS

Two studies reported low levels of empathy in MS patients (Gleichgerrcht, Tomashitis, & Sinay, 2015; Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013). In the first one, patients also had mood disturbance and cognitive decline (Kraemer, Herold, Uekermann, Kis, Wiltfang, et al., 2013). In the second, they had high levels of alexithymia and altered moral judgment (Gleichgerrcht et al., 2015). It is noteworthy that alexithymia could modulate empathy (Bird et al., 2010). Hence, the observed low levels of empathy and high levels of alexithymia might have contributed to an altered moral judgment (Gleichgerrcht et al., 2015).

Differently, other studies have documented high levels of empathy among MS patients. For instance, Benedict, Priore, Miller, Munschauer, and Jacobs detected a discrepancy between the levels of empathy as reported by patients and their informants (family members or friends) (2001). While informants reported low levels of empathy among patients, patients themselves generated high self-reporting. These results were substantiated by another report by Banati et al. who found higher empathy levels in patients with greater physical disability and shorter disease duration, both of which characterize a rapid disease progression (2010).

The findings of both studies might be explained by different views. For instance, severely impaired patients may exhibit more profound emotional misjudgment compared to relatively preserved patients, which can appear as high levels of empathy. Another possibility is that MS-related emotional stress might lead to a more focused emotional processing which can emerge as a higher estimate of empathy. The phenomenon of benefit finding can also account for the observed results (Pakenham & Cox, 2009). It provides an explanation on how constant challenges, such as those seen during MS course, might lead to positive learning and experiencing psychological growth (Pakenham & Cox, 2009).

Of interest, one study included a cohort of pediatric-onset MS patients and HCs but did not detect any significant group differences based on empathy questionnaires filled by parents (Charvet et al., 2014). However, one should keep in mind that parents-filled questionnaires do not necessarily reflect the patients' impression.

The papers mentioned above are summarized in Table 3.

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Table 3. Studies reporting alteration of empathy in multiple sclerosis

Authors (year)	Population	Empathy task	Neuropsychological measures	Outcomes (patients)	Correlation and other analyses (empathy)
Benedict et al. (2001)	13 RR/ 21 SP or PP MS *(21F; age: 43.9 ; EDSS mode: 4.1; DD NP)* 14 HCs	Self and informant reports on the HES (*Hogan, 1969*)	Cognition: Token test, Boston naming test, Judgment of line orientation, complex figure test, California verbal learning test, brief visuospatial memory test revised, TMT, PASAT, WCST, Booklet category test Mood: BDI Personality: NEO Personality Inventory (*Costa and McCrae, 1992*)	High self-ratings but low informant- ratings on the HES Poor cognitive performance High mood scores No group difference on personality test	*Cognition scores: significant predictors for empathy*
Banati et al. (2010)	37 RR/3 SP MS *(29F; age: 36.2; EDSS: 2.3; DD NP)* 35 HCs	Baron-Cohens Empathy Quotient (*Baron-Cohen and Wheelwright, 2004*)	Cognition: WAIS Mood : BDI, STAI	Normal empathy level No group difference on cognitive performance High mood scores	*Subgroup analysis: High empathy in patients with short disease duration and high disability*
Kraemer, Herold, Uekermann, Kis, et al. (2013)	25 RR MS *(15F; age: 30.9; EDSS: 1.0; DD: 1.2)* 25 HCs	Baron-Cohen's Empathy Quotient (*Baron-Cohen and Wheelwright, 2004*)	Cognition: task derived from the Letter– Number Sequencing subtest of the Wechsler Memory Scale, TMT, Stroop test Mood: BDI	Low empathy level No group difference on cognitive performance High mood scores	No correlation
Charvet et al. (2014)	28 pediatric-onset MS *(19F; age: 16.3; median EDSS: 1.0; DD: 2.8)* 32 HCs	Parent-reported Empathy and Systemizing Quotient Child Version (*Auyeung et al., 2009*)	Cognition: SDMT, Wechsler Abbreviated Scale of Intelligence	Normal empathy level Poor cognitive performance	NP
Gleichgerrcht et al. (2015)	38 RR MS *(87.3%F; age: 42.3; EDSS:1.7; DD: 1.6)* 38 HCs	Interpersonal Reactivity Index (*Davis, 1983*)	Alexithymia: TAS-20 (*Bagby et al., 1994*) Moral judgement: dilemmas measuring moral permissibility & relativity and emotional reactivity (*Greene et al., 2001, 2004*)	Low empathy level High alexithymia scores Altered moral judgment	Correlation between empathy and alexithymia; inverse correlation with moral judgment

Note. Demographic and clinical data were expressed as mean unless indicated otherwise. Age and disease duration were expressed in years.
BDI = Beck Depression Inventory; DD = disease duration; HCs = healthy controls; HES = Hogan Empathy Scale; MS = multiple sclerosis; NP = not provided; PASAT = Paced Auditory Serial Attention Test; RR = relapsing remitting; SDMT = Symbol Digit Modalities Test; SP = secondary progressive; STAI = Spielberger Trait Anxiety Inventory; TAS-20 = Toronto Alexithymia Scale; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WCST = The Wisconsin Card Sorting Test.

NEURAL UNDERPINNINGS OF SOCIAL COGNITIVE DEFICITS IN MULTIPLE SCLEROSIS

Five MRI studies (Table 4) investigated the neural basis of social cognitive deficits in MS (Beatty et al., 2003; Jehna, Langkammer, et al., 2011; Krause et al., 2009; Mike et al., 2013; Passamonti et al., 2009).

Structural Neuroimaging Data

Concerning facial emotion perception, Krause et al. performed voxel-based lesion symptom mapping in MS patients with or without deficits in EFE recognition (Krause et al., 2009). Although lesion volume did not statistically differ between both patient groups, poor performance on facial affect task was correlated with lesions in left temporal WM (Figure 1), an area containing several connections between the OFC and the STS (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000). Therefore, the observed impairment in EFE recognition might be due to interruption of the fibers responsible for visual processing of emotionally relevant stimuli. To note, this study also contained fMRI data that will be analyzed in the following section.

Our insight into ToM in MS arises from the study by Mike et al. who compared structural MRI data between MS patients and healthy controls (Mike et al., 2013). In addition to the observed social cognitive deficits in the patients' group, inverse correlations were found between each of the Faces and Reading the Mind in the Eyes tests and total T1 lesion volume (tT1LV). More interestingly, patients' performance on the Faces test was inversely associated with regional T1 lesion volume (rT1LV) of CC (genu and splenium) and several fasciculi (bilateral uncinated fasciculus, right inferior longitudinal and fronto-occipital fasciculi); with regional T2 lesion volume of CC (genu) and left fornix, and with cortical thinning of many areas (i.e., bilateral FFA, right entorhinal cortex).

Second, performance on Reading the Mind in the Eyes test was inversely correlated with rT1LV of the CC (splenium) and cortical thinning of left anterior inferior temporal gyrus (temporal pole), left FFA and right caudal middle frontal gyrus (right premotor frontal eye field, FEF). However, performance on the Faux Pas test did not correlate with any of the studied parameters. The multiple regression analysis also revealed several issues. For instance, rT1LV of left uncinated fasciculus was an independent predictor of the Faces test performance. Besides, performance on Reading the Mind in

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Table 4. MRI Studies evaluating social cognition in multiple sclerosis

Authors (year)	Population	MRI	Social cognitive task	Outcomes (patients)	Correlation and other analyses (MRI findings)
Beatty et al. (2003)	47 chronic MS (*41F; age: 46.6 ; mild (n = 32), moderate (n = 7) & severe disability (n = 8) on the Ambulation index; DD NP)* 19 HCs	Structural (conventional T2-weighted MRI; details NP)	Aprosodia Battery (*Ross et al., 1997*)	No group difference in CC size	No correlation between comprehension of affective prosody and CC size or extent of lesions in the left or right hemispheres
Krause et al. (2009)	7 RR/4 SP MS patients with deficits in facial emotion recognition *(9F; age: 42.7; median EDSS: 3.5)* 10 RR/1 PP MS patients without deficits in facial emotion recognition *(9F; age: 36.3; median EDSS: 1.5; DD NP)* 11 HCs	Structural (LV) and functional	Adapted version of the 5th subset of FAB (*Bowers et al., 1991, 2001*)	Structural MRI findings - No difference in lesion volume between both patient groups Functional MRI findings - Hypoactivation of fSTS, left insula and left VLPFC in impaired patients compared to preserved ones	Correlation between deficits in facial emotion recognition and left temporal WM lesions Correlation between performance on facial emotion recognition and hyperactivation in left insula and left VLPFC (analysis done on the whole patients group)
Passamonti et al. (2009)	12 RR MS patients without cognitive or affective deficits according to DSM-IV *(7 F; age: 29.3; median EDSS: 1.5; DD 4.3)* 12 HCs	Structural (LL; whole-brain, GM, and WM volumes) and functional	Negative facial emotions (fear, anger and sadness) (*Ekman and Friesen, 1976*)	Structural MRI findings - No differences in structural MRI measures Functional MRI findings - Hyperactivation of bilateral VLPFC, left posterior cortices (precuneus, superior parietal cortex) - Reduced functional connectivity between left amygdala and prefrontal regions (VLPFC and medial prefrontal cortex)	Correlation between Structural and functional MRI measures: NP
Jehna, Langkammer, et al. (2011)	15 RR MS *(10F; age: 29.5; EDSS: 1.7; DD: 7.3)* 15 HCs	Structural (LL; whole-brain, WM and GM volumes) and functional	Negative facial emotions recognition task (anger, disgust, fear) (*Jehna et al., 2011*)	Structural MRI - Decrease in whole-brain and GM volumes Functional MRI findings - Hyperactivation of PCC and precuneus for anger (left side) and disgust (right side)	No correlation between structural and functional MRI measures
Mike et al. (2013)	44 RR/5 SP MS *(31F; age: 39.8, EDSS: 2.4; DD: 9.5)* 18 HCs	Structural (total WM LV, regional WM LV in fiber bundles, cortical GM thickness)	Faces test, Reading the Mind in the Eyes test, and Faux Pas test (*Baron-Cohen et al., 1997, 1999*)	Decreased cortical thickness in the left anterior inferior temporal gyrus	Inverse correlation between total T1 LV and each of Faces and Reading the Mind in the Eyes tests No correlation between Faux pas test and any MRI parameter Following multiple regression analysis: left UF was an independent predictor of the Faces test performance; rT1LV of the splenium of CC and cortical thickness of left FFA and left temporal pole were independent predictors of Reading the Mind in the Eyes test performance

Note. Demographic and clinical data were expressed as mean unless indicated otherwise. Age and disease duration were expressed in years.
CC = corpus callosum; DD = disease duration; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders, 4th edition; FFA = fusiform facial area; fSTS = facial area of the superior temporal sulcus; GCC = genu of corpus callosum; GM = gray matter; LL = lesion load; LV = lesion volume; MS = multiple sclerosis; NP = not provided; PP = primary progressive; RR = relapsing remitting, SCC = splenium of corpus callosum; SP = secondary progressive; PCC = posterior cingulate cortex; UF = uncinated fasciculus; VLPFC = ventrolateral prefrontal cortex; WM = white matter.

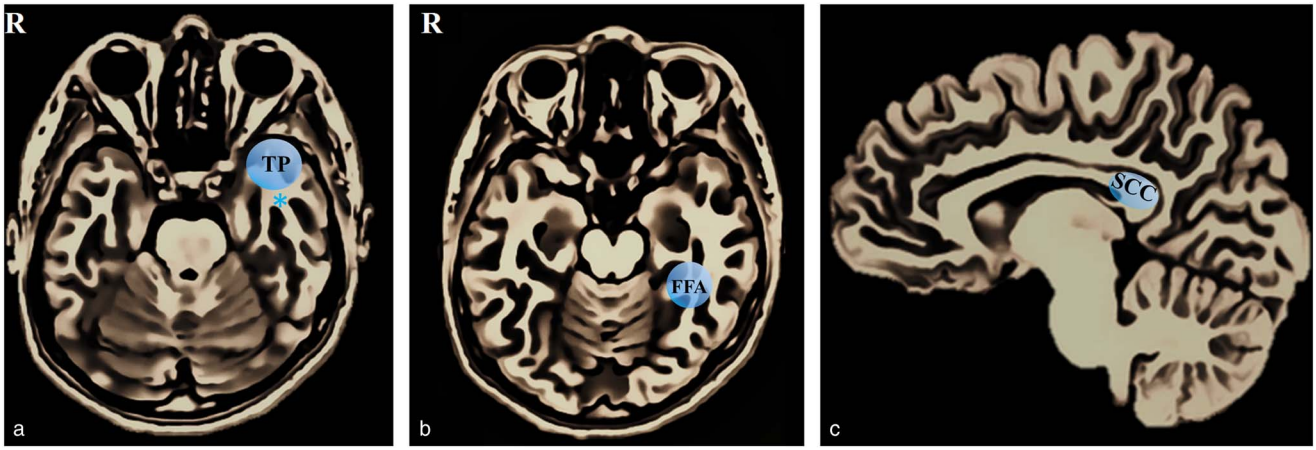

Fig. 1. (a, b) Axial and (c) sagittal brain views illustrating the structural correlates of social cognitive deficits in multiple sclerosis. FFA: left fusiform facial area; R: right; SCC: splenium of the corpus callosum; TP: left temporal pole; *: left temporal white matters lesions; left uncinated fasciculus not shown.

the Eyes test was predicted by rT1LV of the splenium of CC and cortical thickness of left FFA and left temporal pole (Figure 1).

Of interest, all of these structures are neural nodes which take parts of social cognitive networks. For instance, the genu and splenium of CC links, respectively, identical anterior (prefrontal and premotor) and posterior cortical areas (occipital, parietal, and temporal lobes) involved in emotional, cognitive, and visual processing (Park et al., 2008). The role of FFA has been already seen in facial identity discrimination and emotion recognition (Haxby, Hoffman, & Gobbini, 2000, 2002; Zaki, Hennigan, Weber, & Ochsner, 2010). The temporal pole enables the confrontation of perceived social and emotional cues (visual information) with stored general knowledge (contextual information) (Frith & Frith, 2006).

As for affective prosody, the available data are derived from only one study in which the comprehension of affective prosody did not correlate with any studied parameters, namely the CC size and the extent of right or left hemispheric lesions (Beatty et al., 2003). The absence of correlations might be due to the use of basic MRI measures which could have been different with the adoption of non-conventional MRI techniques (Rovaris, Comi, & Filippi, 2001).

Functional Neuroimaging Data

The available fMRI studies in MS patients focused on EFE recognition. The first one included early stage RR MS patients with intact social cognitive abilities and healthy controls (Passamonti et al., 2009). The imaging acquisition took place during the execution of an active task that consisted of processing facial emotions relative to neutral stimuli (geometric shapes such as circles, or horizontal and vertical ellipses) (Passamonti et al., 2009). Compared to their healthy counterparts, patients exhibited a hyperactivation within bilateral prefrontal areas (VLPFC) and left posterior cortices (PC, superior parietal cortex) (Passamonti et al., 2009). They also displayed a reduced pattern of functional connectivity between prefrontal cortices (ventrolateral and medial parts) and left amygdala (Figure 2).

It is noteworthy that a lateralization pattern of amygdalar activation exists in the normal human brain during emotional processing, with the left amygdala being more activated than the right one (Baas, Aleman, & Kahn, 2004). In fact, by communicating with posterior brain regions that are involved in visual processing, the amygdala has a pivotal role in decoding emotionally significant sensory stimuli and by doing so, it participates in the formation of emotional memory. Also, the dialogue between the amygdala and prefrontal cortex is crucial in the processing of emotional information (Ghashghaei, Hilgetag, & Barbas, 2007).

The findings of this study were supported soon after by another one in which early stages RR MS patients had normal performance on cognitive and facial affect recognition tasks compared to healthy controls (Jehna, Langkammer, et al., 2011), yet they exhibited a hyperactivation within fusiform gyri and other right cortical areas (i.e., fontral pole, ACC, and paracingulate cortex) during the performance of neutral faces (facial identity); and hyperactivation of PC and PCC during the performance of "anger" (left activation) and "disgust" (right activation) contrasted to neutral faces (Figure 2).

In addition to the above-stated role of the amygdala, PCC is implicated in mediating the interactions between emotional and memory-related processes (Maddock, Garrett, & Buonocore, 2003). More interestingly, The PC seems to be divided into two parts, an anterior one dealing with self-centered mental imagery strategies and a posterior one in charge of episodic memory retrieval (Cavanna & Trimble, 2006).

A third study by Krause et al. provides additional evidence. MS patients with or without deficits in facial affect recognition underwent functional imaging (Krause et al., 2009). Compared to the preserved MS group, the impaired group showed a hypoactivation in the facial area of STS, left VLPFC and insula, all of which are normally implicated in the social perception of EFE (Figure 2). In the whole patients

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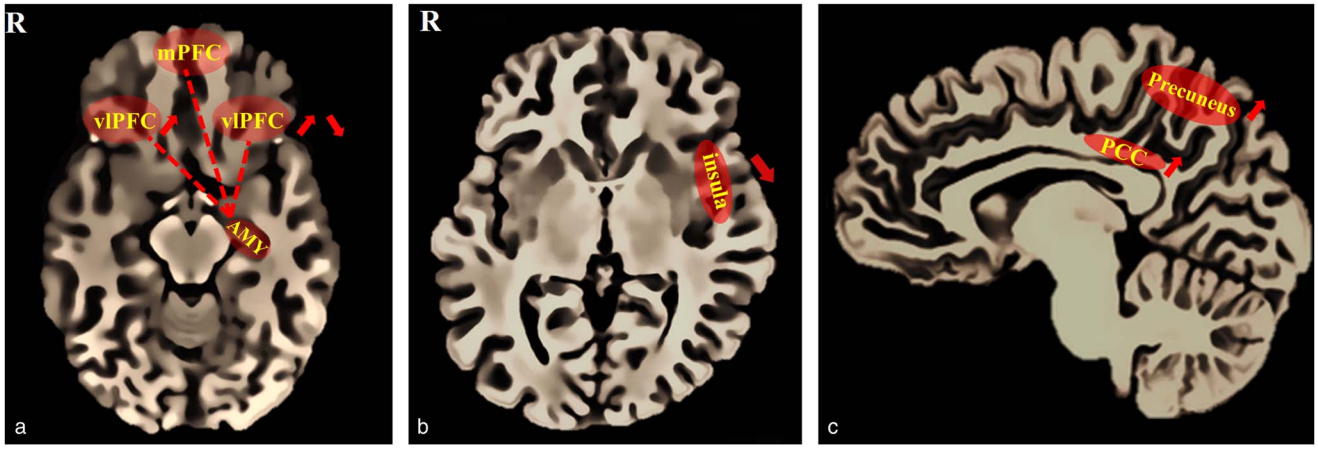

Fig. 2. (a, b) Axial and (c) sagittal brain views illustrating the functional changes during social cognitive performance in multiple sclerosis. AMY: left amygdala; mPFC: medial prefrontal cortex; R: right; SPC: superior parietal cortex; vlPFC: ventrolateral prefrontal cortex; upward arrows: hyperactivation pattern seen in multiple sclerosis patients with preserved social cognitive abilities compared to healthy controls; downward arrows: hypoactivation pattern seen in multiple sclerosis patients with social cognitive deficits compared to those with intact abilities; dashed lines: reduced functional connectivity in the tagged networks; left superior parietal cortex not shown.

group (impaired and preserved), the accuracy on facial affect task was correlated with the increased activation within the left anterior insula and left VLPFC.

To sum up, all of the three studies, featured a hyperactivation pattern in MS patients with preserved social cognitive abilities (Jehna, Langkammer, et al., 2011; Krause et al., 2009; Passamonti et al., 2009). To explain these findings, one can speculate that compensatory processes occur early in the disease course to restrain the social cognitive deficits that might arise from MS-related gray (GM) and white (WM) matter pathologies (Mainero et al., 2004; Mainero, Pantano, Caramia, & Pozzilli, 2006; Pantano et al., 2002; Rocca et al., 2009; Sumowski, Wylie, Deluca, & Chiaravalloti, 2009; Staffen et al., 2002; Sweet, Rao, Primeau, Durgerian, & Cohen, 2006; Wegner et al., 2008). These mechanisms could radiologically manifest as increased regional activation patterns (Jehna, Langkammer, et al., 2011; Passamonti et al., 2009) or reduced functional connectivity of some brain networks (Passamonti et al., 2009). Saying so, the increase in lesions load and subsequent diffuse neural disorganization might lead to reduced or maladaptive plasticity processes (Citri & Malenka, 2008; Morgen et al., 2004). This would cause poor social cognitive performance and lead to regional hypoactivation on fMRI as seen with the impaired MS group of the third study (Krause et al., 2009).

SOCIAL COGNITIVE DEFICITS IN MULTIPLE SCLEROSIS: A PRIMARY OR SECONDARY SIGNATURE

Several cognitive domains could be altered in MS patients, and this population commonly suffers from mood disturbances, fatigue, alexithymia, and sleep problems. Hence, one might ask whether social cognitive deficits in MS constitute a primary phenomenon or rather result from the previously described confounders. Although this issue is still a matter of debate, the influence of these variables on social cognition was addressed in some studies and deserves to be mentioned here.

For instance, despite the high prevalence of alexithymia in MS patients (Bodini et al., 2008; Chahraoui et al., 2008, Chahraoui, Duchene, Rollot, Bonin, & Moreau, 2014; Gay, Vrignaud, Garitte, & Meunier, 2010), only few studies controlled for this factor (Cecchetto et al., 2014; Gleichgerrcht et al., 2015; Prochnow et al., 2011). It is worth noting that patients with alexithymia were found to have social cognitive deficits (Grynberg et al., 2012) and display abnormal pattern of brain activation during EFE processing (Kano et al., 2003).

Moreover, alexithymia was associated with decreased GM volume in regions such as the ACC, amygdala, and insula (Ihme et al., 2013), which had abnormal activation pattern in fMRI studies assessing social cognition in MS (Jehna, Langkammer, et al., 2011; Krause et al., 2009; Passamonti et al., 2009). These facts altogether should prompt screening for alexithymia in future assessment of social cognition.

Depression also appears to be a frequent symptom in MS patients (Feinstein, 2011) and is linked to pathological changes in bilateral frontal regions which are key components in social cognitive processing (Gobbi, Rocca, Riccitelli, et al., 2014). Admitting the influence of mood on social cognition in MS (Berneiser et al., 2014; Pinto et al., 2012; Parada-Fernández et al., 2015) and other clinical settings (Asthana, Mandal, Khurana, & Haque-Nizamie, 1998; Leppanen, 2006; Persad & Polivy, 1993; Suslow et al., 2004), an optimal evaluation of social cognition should account for this variable.

As for MS fatigue *per se*, its underlying pathophysiology lies in the so-called "cortico-striato-thalamo-cortical loop" (for reviews, see Chalah et al., 2015), which includes pathological alterations of many cerebral tracts such as UF, CC, and IFOF (Bisecco et al., 2016; Gobbi, Rocca, Pagani, et al.,

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2014). Importantly, abnormalities in these brain structures are also documented in social cognition studies and were inversely correlated with MS patients' performance on ToM tasks (Mike et al., 2013). The fact that both fatigue and social cognitive deficits in MS share several anatomical pathologies should pave the way for a better control of MS fatigue in upcoming trials.

Furthermore, MS patients commonly suffer from cognitive symptoms (Ayache et al., 2015; Kesselring & Klement, 2001; Vázquez-Marrufo et al., 2014) and significant correlations were found in MS patients between social cognitive performance and several non-social cognitive abilities, such as attention, processing speed, working memory, learning, and executive functions (Benedict et al., 2001; Berneiser et al., 2014; Cecchetto et al., 2014; Charvet et al., 2014; Genova et al., 2016; Henry et al., 2009; Jehna et al., 2010; Kraemer, Herold, Uekermann, Kis, et al., 2013b; Ouellet et al., 2010; Pinto et al., 2012; Pöttgen et al., 2013; Roca et al., 2014). For these reasons, evaluating non-social cognitive abilities in forthcoming works might help better understand their relationship with social cognition.

Nevertheless, altered moral judgment could also co-occur with social cognitive deficits and has been related to pathological changes within the TPJ, the latter region being an important component of the ToM circuit (Samson, Apperly, Chiavarino, & Humphreys, 2004; Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010). Lastly, sleep disorders, frequently encountered in MS, might as well influence social cognition and deserve to be taken into consideration (Beattie, Kyle, Espie, & Biello, 2015).

CONCLUSION

Taken together, these data provide convergent evidence on the occurrence of social cognitive deficits even at early stages of MS. Deficits in recognizing negative emotions seem to be more pronounced that those of positive ones among MS patients.

Here, two questions might arise: (i) how individuals with MS could preserve their social cognitive performance early in the disease process despite the continuous accumulation of brain lesions and then, at a certain point in their life, start experiencing deficits; and (ii) why an inhomogeneity in social cognitive performance was observed across MS studies. The hypothesis of "functional brain reorganization" could answer the first question. In fact, in front of the neural damage encountered in MS, compensatory neuroplasticity mechanisms and functional reorganization would take place in an attempt to limit subsequent behavioral deficits that might arise from MS-related pathologies. Later on, the increase in disease burden may exhaust the adaptive mechanisms and functional reserves (Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2006; Pantano et al., 2005) leading to poor social cognitive performance.

The second question could be addressed in light of "cognitive reserve hypothesis." Cognitive reserve is thought to be a moderator between the amount of brain damage and the extent of clinical outcome (Stern, 2012). This could apply to MS patients in a way that those with higher cognitive reserve might experience less social cognitive deficits than others with similar extent of brain lesions (Sumowski et al., 2009; Sumowski & Leavitt, 2013).

Other important issues remain unresolved and need a careful assessment in future studies. First, the prevalence of social cognitive deficits in MS is still undetermined. In fact, a large number of reported trials dealt with heterogeneous MS cohorts with different disease subtypes, wide ranges of physical disability and advanced stages, which make them more prone to social and non-social cognitive deficits.

Second, whether the social cognitive deficits constitute a primary impairment, or they result from cognitive deficits, or other MS-related symptoms is still a matter of debate. Henceforth, future in-depth assessment of social cognition should focus on confounding factors and the onset of these deficits.

Third, neural components of social cognition need further deciphering. Thus, coupling non-conventional neuroimaging and neurophysiological modalities with more detailed neuropsychological testing could be of particular help.

Fourth, the evaluation of social cognition might benefit from combining static, and dynamic assessment tools since videotaped tasks seem to have better accuracy than classical static tests in evaluating social cognition (Dziobek et al., 2006).

In summary, these considerations would shed the light on the social cognitive deficits in MS and may open a venue for an optimal multidisciplinary approach in MS patient care. By doing so, affected patients will be able to overcome their interpersonal difficulties and improve their QoL.

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REFERENCES

Abdel-Hamid, M., Lehmkämper, C., Sonntag, C., Juckel, G., Daum, I., & Brüne, M. (2009). Theory of mind in schizophrenia: The role of clinical symptomatology and neurocognition in understanding other people's thoughts and intentions. *Psychiatry Research*, *165*(1-2), 19–26. doi: 10.1016/j.psychres.2007.10.021

Ackerer, A.W. (2003). *Emotional intelligence, academic intelligence and speed of mind: The case of emotion perception*. Munich: GRIN Verlag.

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology*, *12*(2), 169–177.

Adolphs, R. (2006). How do we know the minds of others? Domain-specificity, simulation, and enactive social cognition. *Brain Research*, *1079*(1), 25–35.

Adolphs, R., Baron-Cohen, S., & Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *Journal of Cognitive Neuroscience*, *14*(8), 1264–1274.

Allison, T., Puce, A., & McCarthy, G. (2000). Social perception from visual cues: Role of the STS region. *Trends in Cognitive Sciences*, *4*(7), 267–278.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.) Washington, DC: American Psychiatric Association.

Asthana, H.S., Mandal, M.K., Khurana, H., & Haque-Nizamie, S. (1998). Visuospatial and affect recognition deficit in depression. *Journal of Affective Disorders*, *48*(1), 57–62.

Auyeung, B., Wheelwright, S., Allison, C., Atkinson, M., Samarawickrema, N., & Baron-Cohen, S. (2009). The children's empathy quotient and systemizing quotient: Sex differences in typical development and in autism spectrum conditions. *Journal of Autism and Developmental Disorders*, *39*(11), 1509–1521. doi: 10.1007/s10803-009-0772-x

Ayache, S.S., Palm, U., Chalah, M.A., Nguyen, R., Farhat, W.H., Créange, A., & Lefaucheur, J.P. (2015). Orienting network dysfunction in progressive multiple sclerosis. *Journal of the Neurological Sciences*, *351*(1-2), 206–207. doi: 10.1016/j.jns.2015.02.044

Baas, D., Aleman, A., & Kahn, R.S. (2004). Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. *Brain Research. Brain Research Reviews*, *45*(2), 96–103.

Bagby, R.M., Parker, J.D., & Taylor, G.J. (1994). The twenty-item Toronto alexithymia scale-I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research*, *38*, 23–32.

Banati, M., Sandor, J., Mike, A., Illes, E., Bors, L., Feldmann, A., … Illes, Z. (2010). Social cognition and theory of mind in patients with relapsing-remitting multiple sclerosis. *European Journal of Neurology*, *17*(3), 426–433. doi: 10.1111/j.1468-1331.2009.02836.x

Baron-Cohen, S. (2000). Theory of mind and autism: A review. *International Review of Research in Mental Retardation*, *23*, 169–184.

Baron-Cohen, S., Leslie, A.M., & Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition*, *21*(1), 37–46.

Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., & Plaisted, K. (1999). Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. *Journal of Autism and Developmental Disorders*, *29*(5), 407–418.

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: An investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders*, *34*(2), 163–175.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry*, *42*(2), 241–251.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). A further advanced test of theory of mind: Evidence from very high functioning adults with autism or Asperger syndrome. *Journal of Child Psychology and Psychiatry*, *38*(7), 813–822.

Beattie, L., Kyle, S.D., Espie, C.A., & Biello, S.M. (2015). Social interactions, emotion and sleep: A systematic review and research agenda. *Sleep Medicine Reviews*, *24*, 83–100. doi: 10.1016/j.smrv.2014.12.005

Beatty, W.W., Goodkin, D.E., Weir, W.S., Staton, R.D., Monson, N., & Beatty, P.A. (1989). Affective judgments by patients with Parkinson's disease or chronic progressive multiple sclerosis. *Bulletin of the Psychonomic Society*, *27*(4), 361–364.

Beatty, W.W., Orbelo, D.M., Sorocco, K.H., & Ross, E.D. (2003). Comprehension of affective prosody in multiple sclerosis. *Multiple Sclerosis*, *9*(2), 148–153.

Benedict, R.H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*(4), 549–558.

Benedict, R.H., Priore, R.L., Miller, C., Munschauer, F., & Jacobs, L. (2001). Personality disorder in multiple sclerosis correlates with cognitive impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(1), 70–76.

Benton, A.L., Sivan, A.B., Hamsher, K., Varney, N.R., & Spreen, O. (1994). *Contributions to neuropsychological assessment*. New York: Oxford University Press.

Berneiser, J., Wendt, J., Grothe, M., Kessler, C., Hamm, A.O., & Dressel, A. (2014). Impaired recognition of emotional facial expressions in patients with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *3*(4), 482–488. doi: 10.1016/j.msard.2014.02.001

Bird, G., Silani, G., Brindley, R., White, S., Frith, U., & Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain*, *133*(Pt 5), 1515–1525. doi: 10.1093/brain/awq060

Bisecco, A., Caiazzo, G., d'Ambrosio, A., Sacco, R., Bonavita, S., Docimo, R., & Gallo, A. (2016). Fatigue in multiple sclerosis: The contribution of occult white matter damage. *Multiple Sclerosis*, *22*, 1676–1684.

Bodini, B., Mandarelli, G., Tomassini, V., Tarsitani, L., Pestalozza, I., Gasperini, C., … Pozzilli, C. (2008). Alexithymia in multiple sclerosis: Relationship with fatigue and depression. *Acta Neurologica Scandinavica*, *118*(1), 18–23.

Bowers, D., Blonder, L.X., & Heilman, K.M. (1991). *The Florida affect battery*. Gainesville, FL: Center for Neuropsychological Studies, University of Florida.

Bowers, D., Blonder, L.X., & Heilman, K.M. (2001). *The Florida affect battery, manual (revised)*. Gainesville, FL: Center for Neuropsychological Studies, University of Florida.

Bradley, M.M., & Lang, P.J. (2007). *The International Affective Digitized Sounds (IADS-2): Affective ratings of sounds and instruction manual*. Technical report B-3, (2nd ed.). Gainesville, FL: University of Florida.

Brothers, L. (1990). The social brain: A project for integrating primate behavior and neurophysiology in a new domain. *Concepts in Neuroscience*, *1*, 27–51.

Buhse, M. (2008). Assessment of caregiver burden in families of persons with multiple sclerosis. *Journal of Neuroscience Nursing*, *40*(1), 25–31.

Cader, S., Cifelli, A., Abu-Omar, Y., Palace, J., & Matthews, P.M. (2006). Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. *Brain*, *129*(Pt 2), 527–537.

Calder, A.J., & Young, A.W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews Neuroscience*, *6*(8), 641–651.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(9), 5497–5502.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., & Reinoso-Suarez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex*, *10*(3), 220–242.

Cavanna, A.E., & Trimble, M.R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*, *129*(Pt 3), 564–583.

Cecchetto, C., Aiello, M., D'Amico, D., Cutuli, D., Cargnelutti, D., Eleopra, R., & Rumiati, R.I. (2014). Facial and bodily emotion recognition in multiple sclerosis: The role of alexithymia and other characteristics of the disease. *Journal of the International Neuropsychological Society*, *20*(10), 1004–1014. doi: 10.1017/S1355617714000939

Chahraoui, K., Duchene, C., Rollot, F., Bonin, B., & Moreau, T. (2014). Longitudinal study of alexithymia and multiple sclerosis. *Brain and Behavior*, *4*(1), 75–82. doi: 10.1002/brb3.194

Chahraoui, K., Pinoit, J.M., Viegas, N., Adnet, J., Bonin, B., & Moreau, T. (2008). Alexithymie et liens avec la dépression et l'anxiété dans la sclérose en plaques. *Revue Neurologique*, *164*(3), 242–245. doi: 10.1016/j.neurol.2007.09.006

Chalah, M.A., Riachi, N., Ahdab, R., Créange, A., Lefaucheur, J.P., & Ayache, S.S. (2015). Fatigue in multiple sclerosis: Neural correlates and the role of non-invasive brain stimulation. *Frontiers in Cellular Neuroscience*, *9*, 460. doi: 10.3389/fncel.2015.00460

Chartrand, T.L., & Bargh, J.A. (1999). The chameleon effect: The perception-behavior link and social interaction. *Journal of Personality and Social Psychology*, *76*(6), 893–910.

Charvet, L.E., Cleary, R.E., Vazquez, K., Belman, A.L., & Krupp, L.B., US Network for Pediatric M.S.. (2014). Social cognition in pediatric-onset multiple sclerosis (MS). *Multiple Sclerosis*, *20*(11), 1478–1484. doi: 10.1177/1352458514526942

Citri, A., & Malenka, R.C. (2008). Synaptic plasticity: Multiple forms, functions, and mechanisms. *Neuropsychopharmacology*, *33*(1), 18–41.

Compston, A., & Coles, A. (2008). Multiple sclerosis. *Lancet*, *372*(9648), 1502–1517. doi: 10.1016/S0140-6736(08)61620-7

Costa, P.T., & McCrae, R.R. (1992). *Professional Manual for the Revised NEO Personality Inventory and NEO Five-Factor Inventory*. Odessa, FL: Psychological Assessment Resources.

Critchley, H.D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*, *493*(1), 154–166.

Davis, M.H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, *44*, 113–126.

Decety, J., & Jackson, P.L. (2004). The functional architecture of human empathy. *Behavioural and Cognitive Neuroscience Reviews*, *3*(2), 71–100.

Di Bitonto, L., Longato, N., Jung, B., Fleury, M., Marcel, C., Collongues, N., … Blanc, F. (2011). [Reduced emotional reactivity to negative stimuli in multiple sclerosis, preliminary results]. *Revue Neurologique*, *167*(11), 820–826. doi: 10.1016/j.neurol.2011.01.024

Dziobek, I., Fleck, S., Kalbe, E., Rogers, K., Hassenstab, J., Brand, M., … Convit, A. (2006). Introducing MASC: A movie for the assessment of social cognition. *Journal of Autism and Developmental Disorder*, *36*(5), 623–636.

Ekman, P., & Friesen, W.V. (1976). *Pictures of facial affect*. Palo Alto, CA: Consulting Psychologists Press.

Ethofer, T., Anders, S., Erb, M., Herbert, C., Wiethoff, S., Kissler, J., … Wildgruber, D. (2006). Cerebral pathways in processing of affective prosody: A dynamic causal modeling study. *Neuroimage*, *30*(2), 580–587. doi: 10.1016/j.neuroimage.2005.09.059

Fan, Y., Duncan, N.W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*(3), 903–911. doi: 10.1016/j.neubiorev.2010.10.009

Feinstein, A. (2011). Multiple sclerosis and depression. *Multiple Sclerosis*, *17*(11), 1276–1281. doi: 10.1177/1352458511417835

Franz, M., Popp, K., Schaefer, R., Sitte, W., Schneider, C., Hardt, J., … Braehler, E. (2008). Alexithymia in the German general population. *Social Psychiatry and Psychiatric Epidemiology*, *43*, 54–62.

Frith, C.D. (2004). Schizophrenia and theory of mind. *Psychological Medicine*, *34*(3), 385–389.

Frith, C.D., & Frith, U. (2006). The neural basis of mentalizing. *Neuron*, *50*(4), 531–534.

Gajofatto, A., & Benedetti, M.D. (2015). Treatment strategies for multiple sclerosis: When to start, when to change, when to stop? *World Journal of Clinical Cases*, *3*(7), 545–555.

Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences*, *8*(9), 396–403.

Gay, M.C., Vrignaud, P., Garitte, C., & Meunier, C. (2010). Predictors of depression in multiple sclerosis patients. *Acta Neurologica Scandinavica*, *121*(3), 161–170. doi: 10.1111/j.1600-0404.2009.01232.x

Genova, H.M., Cagna, C.J., Chiaravalloti, N.D., DeLuca, J., & Lengenfelder, J. (2016). Dynamic assessment of social cognition in individuals with multiple sclerosis: A pilot study. *Journal of the International Neuropsychological Society*, *22*(1), 83–88. doi: 10.1017/S1355617715001137

Ghashghaei, H.T., Hilgetag, C.C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage*, *34*(3), 905–923.

Gleichgerrcht, E., Tomashitis, B., & Sinay, V. (2015). The relationship between alexithymia, empathy and moral judgment in patients with multiple sclerosis. *European Journal of Neurology*, *22*(9), 1295–1303. doi: 10.1111/ene.12745

Gobbi, C., Rocca, M.A., Pagani, E., Riccitelli, G.C., Pravatà, E., Radaelli, M., … Filippi, M. (2014). Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis. *Multiple Sclerosis*, *20*(12), 1633–1640. doi: 10.1177/1352458514530022

Gobbi, C., Rocca, M.A., Riccitelli, G., Pagani, E., Messina, R., Preziosa, P., … Filippi, M. (2014). Influence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis. *Multiple Sclerosis*, *20*, 192–201. doi: 10.1177/1352458513493684

Greene, J., Nystrom, L.E., Engell, A.D., Darley, J.M., & Cohen, J.D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, *44*(22), 389–400.

Greene, J., Sommerville, R.B., Nystrom, L.E., Darley, J.M., & Cohen, J.D. (2001). An fMRI investigation of emotional engagement in moral judgment. *Science*, *293*(5537), 2105–2108.

Grynberg, D., Chang, B., Corneille, O., Maurage, P., Vermeulen, N., Berthoz, S., & Luminet, O. (2012). Alexithymia and the processing of emotional facial expressions (EFEs): Systematic review, unanswered questions and further perspectives. *PLoS One*, *7*(8), e42429. doi: 10.1371/journal.pone.0042429

Habel, U., Klein, M., Kellermann, T., Shah, N.J., & Schneider, F. (2005). Same or different? Neural correlates of happy and sad mood in healthy males. *Neuroimage*, *26*(1), 206–214.

Happé, F.G.E., Winner, E., & Brownell, H. (1998). The getting of wisdom: Theory of mind in old age. *Developmental Psychology*, *34*(2), 358–362.

Haxby, J.V., Hoffman, E.A., & Gobbini, M.I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*(6), 223–233.

Haxby, J.V., Hoffman, E.A., & Gobbini, M.I. (2002). Human neural systems for face recognition and social communication. *Biological Psychiatry*, *51*(1), 59–67.

Heikkinen, J., Jansson-Verkasalo, E., Toivanen, J., Suominen, K., Vayrynen, E., Moilanen, I., & Seppanen, T. (2010). Perception of basic emotions from speech prosody in adolescents with Asperger's syndrome. *Logopedics, Phoniatrics, Vocology*, *35* (3), 113–120. doi: 10.3109/14015430903311184

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. doi: 10.1017/S1355617709090195

Henry, A., Tourbah, A., Chaunu, M.-P., Rumbach, L., Montreuil, M., & Bakchine, S. (2011). Social cognition impairments in relapsing remitting multiple sclerosis. *Journal of the International Neuropsychological Society*, *17*(6), 1122–1131. doi: 10.1017/S1355617711001147

Henry, J.D., von Hippel, W., Molenberghs, P., Lee, T., & Sachdev, P.S. (2016). Clinical assessment of social cognitive function in neurological disorders. *Nature Reviews Neurology*, *12*(1), 28–39. doi: 10.1038/nrneurol.2015.229

Herold, R., Feldmann, A., Simon, M., Tényi, T., Kövér, F., Nagy, F., … Fekete, S. (2009). Regional gray matter reduction and theory of mind deficit in the early phase of schizophrenia: A voxel-based morphometric study. *Acta Psychiatrica Scandinavica*, *119*(3), 199–208.

Hogan, R. (1969). Development of an empathy scale. *Journal of Consulting and Clinical Psychology*, *33*(3), 307–316.

Ihme, K., Dannlowski, U., Lichev, V., Stuhrmann, A., Grotegerd, D., Rosenberg, N., … Suslow, T. (2013). Alexithymia is related to differences in gray matter volume: A voxelbased morphometry study. *Brain Research*, *1491*, 60–67. doi: 10.1016/j.brainres.2012.10.044

Jehna, M., Langkammer, C., Wallner-Blazek, M., Neuper, C., Loitfelder, M., Ropele, S., … Enzinger, C. (2011). Cognitively preserved MS patients demonstrate functional differences in processing neutral and emotional faces. *Brain Imaging and Behavior*, *5*(4), 241–251. doi: 10.1007/s11682-011-9128-1

Jehna, M., Neuper, C., Ischebeck, A., Loitfelder, M., Ropele, S., Langkammer, C., … Enzinger, C. (2011). The functional correlates of face perception and recognition of emotional facial expressions as evidenced by fMRI. *Brain Research*, *1393*, 73–83. doi: 10.1016/j.brainres.2011.04.007

Jehna, M., Neuper, C., Petrovic, K., Wallner-Blazek, M., Schmidt, R., Fuchs, S., … Enzinger, C. (2010). An exploratory study on emotion recognition in patients with a clinically isolated syndrome and multiple sclerosis. *Clinical Neurology and Neurosurgery*, *112*(6), 482–484. doi: 10.1016/j.clineuro.2010.03.020

Julian, L.J., Vella, L., Vollmer, T., Hadjimichael, O., & Mohr, D.C. (2008). Employment in multiple sclerosis. Exiting and reentering the work force. *Journal of Neurology*, *255*(9), 1354–1360. doi: 10.1007/s00415-008-0910-y

Kano, M., Fukudo, S., Gyoba, J., Kamachi, M., Tagawa, M., Mochizuki, H., … Yanai, K. (2003). Specific brain processing of facial expressions in people with alexithymia: An H2 15O-PET study. *Brain*, *126*(Pt 6), 1474–1484.

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *361*(1476), 2109–2128.

Kesselring, J., & Klement, U. (2001). Cognitive and affective disturbances in multiple sclerosis. *Journal of Neurology*, *248*(3), 180–183.

Kessler, H., Bayerl, P., Deighton, R., & Traue, H. (2002). Facially Expressed Emotion Labeling (FEEL): PC-gestützer Test zur Emotionserkennung. *Verhaltenstherapie und Verhaltensmedizin*, *23*, 297–306.

Knight, M., & Mather, M. (2013). Look out-it's your off-peak time of day! Time of day matters more for alerting than for orienting or executive attention. *Experimental Aging Research*, *39*(3), 305–321. doi: 10.1080/0361073X.2013.779197

Koelkebeck, K., Abdel-Hamid, M., Ohrmann, P., & Brune, M. (2008). Theory of mind in schizophrenia: Clinical aspects and empirical research. *Fortschritte der Neurologie Psychiatrie*, *76* (10), 573–582. doi: 10.1055/s-2008-1038250

Kraemer, M., Herold, M., Uekermann, J., Kis, B., Daum, I., Wiltfang, J., … . . .Abdel-Hamid, M. (2013). Perception of affective prosody in patients at an early stage of relapsing-remitting multiple sclerosis. *Journal of Neuropsychology*, *7*(1), 91–106. doi: 10.1111/j.1748-6653.2012.02037.x

Kraemer, M., Herold, M., Uekermann, J., Kis, B., Wiltfang, J., Daum, I., … Abdel-Hamid, M. (2013). Theory of mind and empathy in patients at an early stage of relapsing remitting multiple sclerosis. *Clinical Neurology and Neurosurgery*, *115*(7), 1016–1022. doi: 10.1016/j.clineuro.2012.10.027

Krause, M., Wendt, J., Dressel, A., Berneiser, J., Kessler, C., Hamm, A.O., & Lotze, M. (2009). Prefrontal function associated with impaired emotion recognition in patients with multiple sclerosis. *Behavioural Brain Research*, *205*(1), 280–285. doi: 10.1016/j.bbr.2009.08.009

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., … Fischl, B. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry*, *60*(9), 878–888.

Kurtzke, J.F. (1983). Rating neurological impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–1452.

Kuzmanovic, B., Bente, G., von Cramon, D.Y., Schilbach, L., Tittgemeyer, M., & Vogeley, K. (2012). Imaging first impressions: Distinct neural processing of verbal and nonverbal social information. *Neuroimage*, *60*(1), 179–188. doi: 10.1016/j.neuroimage.2011.12.046

LaBar, K.S., Crupain, M.J., Voyvodic, J.T., & McCarthy, G. (2003). Dynamic perception of facial affect and identity in the human brain. *Cerebral Cortex*, *13*(10), 1023–1033.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (2005). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual*. Technical report A-6. Gainesville, FL: University of Florida.

Langdon, D.W. (2011). Cognition in multiple sclerosis. emotion. *Current Opinion in Neurology*, *24*(3), 244–249. doi: 10.1097/WCO.0b013e328346a43b

Leppanen, J.M. (2006). Emotional information processing in mood disorders: A review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*(1), 34–39.

Leslie, K.R., Johnson-Frey, S.H., & Grafton, S.T. (2004). Functional imaging of face and hand imitation: Towards a motor theory of empathy. *Neuroimage*, *21*(2), 601–607.

Maddock, R.J., Garrett, A.S., & Buonocore, M.H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Human Brain Mapping*, *18*(1), 30–41.

Mainero, C., Caramia, F., Pozzilli, C., Pisani, A., Pestalozza, I., Borriello, G., … Pantano, P. (2004). fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *Neuroimage*, *21*(3), 858–867.

Mainero, C., Pantano, P., Caramia, F., & Pozzilli, C. (2006). Brain reorganization during attention and memory tasks in multiple sclerosis: Insights from functional MRI studies. *Journal of the Neurological Sciences*, *245*(1–2), 93–98.

McDonald, S., Bornhofen, C., Shum, D., Long, E., Saunders, C., & Neulinger, K. (2006). Reliability and validity of The Awareness of Social Inference Test (TASIT): A clinical test of social perception. *Disability and Rehabilitation*, *28*(24), 1529–1542.

McDonald, S., Flanagan, S., Rollins, J., & Kinch, J. (2003). TASIT: A new clinical tool for assessing social perception after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *18*(3), 219–238.

Mike, A., Strammer, E., Aradi, M., Orsi, G., Perlaki, G., Hajnal, A., … Illes, Z. (2013). Disconnection mechanism and regional cortical atrophy contribute to impaired processing of facial expressions and theory of mind in multiple sclerosis: A structural MRI study. *PLoS One*, *8*(12), e82422. doi: 10.1371/journal.pone.0082422

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & Group PRISMA. (2009). Preferred reporting items for systematic reviews and metaanalyses: The PRISMA statement. *BMJ*, *339*, b2535.

Mohr, D.C., & Cox, D. (2001). Multiple sclerosis: Empirical literature for the clinical health psychologist. *Journal of Clinical Psychology*, *57*(4), 479–499.

Montel, S.R., & Bungener, C. (2007). Coping and quality of life in one hundred and thirty-five subjects with multiple sclerosis. *Multiple Sclerosis*, *13*(3), 393–401. doi: 10.1177/1352458506071170

Morgen, K., Kadom, N., Sawaki, L., Tessitore, A., Ohayon, J., McFarland, H., … Cohen, L.G. (2004). Training-dependent plasticity in patients with multiple sclerosis. *Brain*, *127*(Pt 11), 2506–2517.

Ouellet, J., Scherzer, P.B., Rouleau, I., Metras, P., Bertrand-Gauvin, C., Djerroud, N., … Duquette, P. (2010). Assessment of social cognition in patients with multiple sclerosis. *Journal of the International Neuropsychological Society*, *16*(2), 287–296. doi: 10.1017/S1355617709991329

Pakenham, K.I., & Cox, S. (2009). The dimensional structure of benefit finding in multiple sclerosis and relations with positive and negative adjustment: A longitudinal study. *Psychology and Health*, *24*(4), 373–393. doi: 10.1080/08870440701832592

Palermo, R., & Rhodes, G. (2007). Are you always on my mind? A review of how face perception and attention interact. *Neuropsychologia*, *45*(1), 75–92.

Pantano, P., Iannetti, G.D., Caramia, F., Mainero, C., Di Legge, S., Bozzao, L., … Lenzi, G.L. (2002). Cortical motor reorganization after a single clinical attack of multiple sclerosis. *Brain*, *125*(Pt 7), 1607–1615.

Pantano, P., Mainero, C., Lenzi, D., Caramia, F., Iannetti, G.D., Piattella, M.C., … Pozzilli, C. (2005). A longitudinal fMRI study on motor activity in patients with multiple sclerosis. *Brain*, *128*(Pt 9), 2146–2153.

Parada-Fernández, P., Oliva-Macias, M., Amayra, I., Lopez-Paz, J.F., Lazaro, E., Martinez, O., … Perez, M. (2015). Accuracy and reaction time in recognition of facial emotions in people with multiple sclerosis. *Revue Neurologique*, *61*(10), 433–440.

Park, H.J., Kim, J.J., Lee, S.K., Seok, J.H., Chun, J., Kim, D.I., & Lee, J.D. (2008). Corpus callosal connection mapping using cortical gray matter parcellation and DT-MRI. *Human Brain Mapping*, *29*(5), 503–516.

Passamonti, L., Cerasa, A., Liguori, M., Gioia, M., Valentino, P., Nisticò, R., … Fera, F. (2009). Neurobiological mechanisms underlying emotional processing in relapsing-remitting multiple sclerosis. *Brain*, *132*(Pt 12), 3380–3391. doi: 10.1093/brain/awp095

Persad, S.M., & Polivy, J. (1993). Differences between depressed and nondepressed individuals in the recognition of and response to facial emotional cues. *Journal of Abnormal Psychology*, *102*(3), 358–368.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, *9*(2), 148–58.

Pfleger, C.C., Flachs, E.M., & Koch-Henriksen, N. (2010). Social consequences of multiple sclerosis. Part 2. Divorce and separation: A historical prospective cohort study. *Multiple Sclerosis*, *16*(7), 878–882. doi: 10.1177/1352458510370978

Phillips, L., Henry, J., Scott, C., Summers, F., Whyte, M., & Cook, M. (2011). Specific impairments of emotion perception in multiple sclerosis. *Neuropsychology*, *25*(1), 131–136. doi: 10.1037/a0020752

Phillips, L.H., Saldias, A., McCarrey, A., Henry, J.D., Scott, C., Summers, F., & Whyte, M. (2009). Attentional lapses, emotional regulation and quality of life in multiple sclerosis. *British Journal of Clinical Psychology*, *48*(Pt 1), 101–106. doi: 10.1348/014466508X379566

Pinto, C., Gomes, F., Moreira, I., Rosa, B., Santos, E., Silva, A.M., & Cavaco, S. (2012). Emotion recognition in multiple sclerosis. *Journal of Eye Tracking, Visual Cognition and Emotion*, *2*(1), 76–81.

Poder, K., Ghatavi, K., Fisk, J.D., Campbell, T.L., Kisely, S., Sarty, I., … Bhan, V. (2009). Social anxiety in a multiple sclerosis clinic population. *Multiple Sclerosis*, *15*(3), 393–398. doi: 10.1177/1352458508099143

Pöttgen, J., Dziobek, I., Reh, S., Heesen, C., & Gold, S.M. (2013). Impaired social cognition in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(5), 523–528. doi: 10.1136/jnnp-2012-304157

Prochnow, D., Donell, J., Schäfer, R., Jörgens, S., Hartung, H., Franz, M., … Seitz, R. (2011). Alexithymia and impaired facial affect recognition in multiple sclerosis. *Journal of Neurology*, *258*(9), 1683–1688. doi: 10.1007/s00415-011-6002-4

Rao, S.M., Leo, G.J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, *41*(5), 685–691.

Rao, S.M., Leo, G.J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. II. *Impact on employment and social functioning. Neurology*, *41*(5), 692–696.

Roca, M., Manes, F., Gleichgerrcht, E., Ibáñez, A., González de Toledo, M.E., Marenco, V., … Sinay, V. (2014). Cognitive but not affective theory of mind deficits in mild relapsing-remitting multiple sclerosis. *Cognitive and Behavioral Neurology*, *27*(1), 25–30. doi: 10.1097/WNN.0000000000000017

Rocca, M.A., Absinta, M., Ghezzi, A., Moiola, L., Comi, G., & Filippi, M. (2009). Is a preserved functional reserve a mechanism

limiting clinical impairment in pediatric MS patients? *Human Brain Mapping*, *30*(9), 2844–2851. doi: 10.1002/hbm.20712

Ross, E.D., Thompson, R.D., & Yenkosky, J. (1997). Lateralization of affective prosody in brain and the callosal integration of hemispheric language functions. *Brain and Language*, *56*(1), 27–54. doi: 10.1006/brln.1997.1731

Rovaris, M., Comi, G., & Filippi, M. (2001). The role of non-conventional MR techniques to study multiple sclerosis patients. *Journal of the Neurological Sciences*, *186*(Suppl. 1), S3–S9.

Rowe, A.D., Bullock, P.R., Polkey, C.E., & Morris, R.G. (2001). Theory of mind impairments and their relationship to executive functioning following frontal lobe excisions. *Brain*, *124*(Pt 3), 600–616.

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience*, *16*(6), 988–999.

Samson, D., Apperly, I.A., Chiavarino, C., & Humphreys, G.W. (2004). Left temporoparietal junction is necessary for representing someone else's belief. *Nature Neuroscience*, *7*(5), 499–500.

Sanfilipo, M.P., Benedict, R.H., Weinstock-Guttman, B., & Bakshi, R. (2006). Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology*, *66*(5), 685–692. doi: 10.1212/01.wnl.0000201238.93586.d9

Schulte-Rüther, M., Greimel, E., Markowitsch, H.J., Kamp-Becker, I., Remschmidt, H., Fink, G.R., … Piefke, M. (2011). Dysfunctions in brain networks supporting empathy: An fMRI study in adults with autism spectrum disorders. *Social Neuroscience*, *6*(1), 1–21. doi: 10.1080/17470911003708032

Sebastian, C.L., Fontaine, N.M., Bird, G., Blakemore, S.J., De Brito, S.A., McCrory, E.J., & Viding, E. (2012). Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Social Cognitive and Affective Neuroscience*, *7*(1), 53–63. doi: 10.1093/scan/nsr023

Segal, B.M., & Stüve, O. (2016). Primary progressive multiple sclerosis–why we are failing. *Lancet*, *387*(10023), 1032–1034.

Seitz, R.J., Nickel, J., & Azari, N.P. (2006). Functional modularity of the medial prefrontal cortex: Involvement in human empathy. *Neuropsychology*, *20*(6), 743–751.

Shamay-Tsoory, S.G., & Aharon-Peretz, J. (2007). Dissociable prefrontal networks for cognitive and affective theory of mind: A lesion study. *Neuropsychologia*, *45*(13), 3054–3067.

Skevington, S.M., Lotfy, M., & O'Connell, K.A. (2004). The World Health Organisation's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of Life Research*, *13*(2), 299–310.

Skowronski, J.J., & Carlston, D.E. (1989). Negativity and extremity biases in impression formation: A review of explanations. *Psychological Bulletin*, *105*, 131–142.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., & Ladurner, G. (2002). Cognitive function and fMRI in patients with multiple sclerosis: Evidence for compensatory cortical activation during an attention task. *Brain*, *125*(Pt 6), 1275–1282.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006–1012.

Stone, V.E., Baron-Cohen, S., & Knight, R.T. (1998). Frontal lobe contribution to theory of mind. *Journal of Cognitive Neuroscience*, *10*(5), 640–656.

Sullivan, S., & Ruffman, T. (2004). Social understanding: How does it fare with advancing years? *British Journal of Psychology*, *95*(Pt 1), 1–18.

Sumowski, J.F., Wylie, G.R., Deluca, J., & Chiaravalloti, N. (2009). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: Functional magnetic resonance imaging evidence for cognitive reserve. *Brain*, *133*(Pt 2), 362–374. doi: 10.1093/brain/awp307

Sumowski, J.F., & Leavitt, V.M. (2013). Cognitive reserve in multiple sclerosis. *Multiple Sclerosis*, *19*(9), 1122–1127.

Suslow, T., Dannlowski, U., Lalee-Mentzel, J., Donges, U.S., Arolt, V., & Kersting, A. (2004). Spatial processing of facial emotion in patients with unipolar depression: A longitudinal study. *Journal of Affective Disorders*, *83*(1), 59–63.

Sweet, L.H., Rao, S.M., Primeau, M., Durgerian, S., & Cohen, R.A. (2006). Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human Brain Mapping*, *27*(1), 28–36.

Tamietto, M., & de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nature Reviews Neuroscience*, *11*(10), 697–709.

Tangney, J.P., Stuewig, J., & Mashek, D.J. (2007). Moral emotions and moral behavior. *Annual Review of Psychology*, *58*, 345–372.

Tottenham, N., Tanaka, J., Leon, A., McCarry, T., Nurse, M., Hare, T., … Nelson, C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249. doi: 10.1016/j.psychres.2008.05.006

Uekermann, J., Abdel-Hamid, M., Lehmkamper, C., Vollmoeller, W., & Daum, I. (2008). Perception of affective prosody in major depression: A link to executive functions? *Journal of the International Neuropsychological Society*, *14*(4), 552–561. doi: 10.1017/S1355617708080740

Uekermann, J., Channon, S., Lehmkamper, C., Abdel-Hamid, M., Vollmoeller, W., & Daum, I. (2008). Executive function, mentalizing and humor in major depression. *Journal of the International Neuropsychological Society*, *14*(1), 55–62. doi: 10.1017/S1355617708080016

Uekermann, J., Channon, S., Winkel, K., Schlebusch, P., & Daum, I. (2007). Theory of Mind, humour processing and executive functioning in alcoholism. *Addiction*, *102*(2), 232–240. doi: 10.1111/j.1360-0443.2006.01656.x

Uekermann, J., & Daum, I. (2008). Social cognition in alcoholism: A link to prefrontal cortex dysfunction? *Addiction*, *103*(5), 726–735. doi: 10.1111/j.1360-0443.2008.02157.x

Uekermann, J., Kraemer, M., Abdel-Hamid, M., Schimmelmann, B. G., Hebebrand, J., Daum, I., … Kis, B. (2010). Social cognition in attention-deficit hyperactivity disorder (ADHD). *Neuroscience and Biobehavioral Reviews*, *34*(5), 734–743. doi: 10.1016/j.neubiorev.2009.10.009

Van Kleef, G.A. (2009). How emotions regulate social life. The Emotions as Social Information (EASI) model. *Current Directions in Psychological Sciences*, *18*, 184–188.

Vázquez-Marrufo, M., Galvao-Carmona, A., González-Rosa, J.J., Hidalgo-Muñoz, A.R., Borges, M., Ruiz-Peña, J.L., … Izquierdo, G. (2014). Neural correlates of alerting and orienting impairment in multiple sclerosis patients. *PLoS One*, *12*(9), e97226. doi: 10.1371/journal.pone.0097226

Vistoli, D., Brunet-Gouet, E., Baup-Bobin, E., Hardy-Bayle, M.C., & Passerieux, C. (2011). Anatomical and temporal architecture of Theory of Mind: A MEG insight into the early stages. *Neuroimage*, *54*(2), 1406–1414. doi: 10.1016/j.neuroimage.2010.09.015

Vollm, B.A., Taylor, A.N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., … Elliott, R. (2006). Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage*, *29*(1), 90–98.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, *45*(1), 174–194.

Wegner, C., Filippi, M., Korteweg, T., Beckmann, C., Ciccarelli, O., De Stefano, N., … Matthews, P.M. (2008). Relating functional changes during hand movement to clinical parameters in patients with multiple sclerosis in a multi-centre fMRI study. *European Journal of Neurology*, *15*(2), 113–122. doi: 10.1111/j.1468-1331.2007.02027.x

Wheaton, K.J., Thompson, J.C., Syngeniotis, A., Abbott, D.F., & Puce, A. (2004). Viewing the motion of human body parts activates different regions of premotor, temporal, and parietal cortex. *Neuroimage*, *22*(1), 277–288.

Williams, J.H. (2008). Self-other relations in social development and autism: Multiple roles for mirror neurons and other brain bases. *Autism Research*, *1*(2), 73–90. doi: 10.1002/aur.15

Wildgruber, D., Ackermann, H., Kreifelts, B., & Ethofer, T. (2006). Cerebral processing of linguistic and emotional prosody: fMRI studies. *Progress in Brain Research*, *156*, 249–268. doi: 10.1016/S0079-6123(06)56013-3

Wolkenstein, L., Schonenberg, M., Schirm, E., & Hautzinger, M. (2011). I can see what you feel, but I can't deal with it: Impaired Theory of Mind in depression. *Journal of Affective Disorders*, *132*(1-2), 104–111. doi: 10.1016/j.jad.2011.02.010

Young, L., Camprodon, J.A., Hauser, M., Pascual-Leone, A., & Saxe, R. (2010). Disruption of the right temporoparietal junction with transcranial magnetic stimulation reduces the role of beliefs in moral judgments. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(15), 6753–6758. doi: 10.1073/pnas.0914826107

Young, A., Perrett, D., Calder, A., Sprengelmeyer, R., & Ekman, P. (2002). *Facial expressions of emotion - Stimuli and tests* (Software Manual v2.1 Ed.), Bury St Edmunds, England: Thames Valley Test Company.

Zaki, J., Hennigan, K., Weber, J., & Ochsner, K.N. (2010). Social cognitive conflict resolution: Contributions of domain-general and domain-specific neural systems. *Journal of Neuroscience*, *30*(25), 8481–8488. doi: 10.1523/JNEUROSCI.0382-10.2010