Chapter 10

Social Cognition Impairments in Patients with Multiple Sclerosis and Comparison with Imaging Studies, Disease Duration and Grade of Disability

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Additional information is available at the end of the chapter

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Abstract

Cognitive impairments in multiple sclerosis (MS) are heterogeneous and their rate varies between 43% and 70%. A less studied aspect of cognition is social cognition, which is not a uniform theoretical construct. It includes emotion perception, prosody, empathy, theory of mind (ToM) and assessment of mood. In addition to progressive physical disability, social cognitive impairments are a reason for job loss in 24–80% of patients with MS, increased divorce rate, dissolution of partnerships and social communication difficulties.

Social cognitive impairments are the result of disruptions in the mentalization network at the neuroanatomical, neurochemical and/or genetic level, which can lead to malfunctions in the dopaminergic–serotoninergic system and to compromising the development of neuroanatomical targets within the network. The wide dissemination of demyelinating lesions and cortical thinning typical of patients with MS often lead to anatomic and functional disorders of the above-mentioned specific brain structures. A correlation has been established among specific cortical areas involved in emotion identification from facial expression (right and left fusiform face area, frontal eye), emotion processing (right entorhinal cortex) and socially relevant information (left temporal pole). The most active brain region involved in social cognitive processing is the medal frontal cortex (MFC), which is described as the brain's social cognitive center. During performance of various sociocognitive tasks for mental state attribution, common areas of increased activation in the medial prefrontal gyrus and the temporoparietal junctions are registered bilaterally, while the area of the medial prefrontal cortex (the paracingulate cortex) is the only region uniquely activated by the performance of ToM.

Most MRI studies of patients with MS found a correlation between the cognitive and/or affective disorders, on the one hand, and lesion localization, total lesion load, or cerebral atrophy, on the other. A significant correlation was also reported between

abnormal activities in specific cortical zones on fMRI, on the one hand, and clinical manifestation, conventional MRI findings and behavioral changes, on the other. Altered patterns of brain activity were found in all clinical phenotypes of MS, including when cognitive abilities were intact and/or restored, social cognitive dysfunction in MS actually affects all stages of the disease and all types of clinical course. The cortical plastic changes are a dynamic phenomenon that can be modulated by external factors. This phenomenon would facilitate the mapping of individual strategies for adequate treatment and rehabilitation of each patient.

Keywords: social cognition, multiple sclerosis, empathy, theory of mind, mentalization, emotional perception, faux pas, disability, social brain, imaging studies

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune degenerative disease of the central nervous system (CNS) leading to both physical and neuropsychological disability. These two types of impairment may occur simultaneously or independently [1]. Until now the focus of scientific research has predominantly been on the physical disablement in patients with MS and its impact on their quality of life. Over the last few decades, researchers have shown an increasing interest in mood disorders, behavior and cognition in this disease.

Cognitive impairments in MS are heterogeneous [2] and their rate varies between 43% and 70% [3–5]. They are in an independent form of disability and make the performance of routine daily activities difficult, sometimes impossible. Up to now studies have mostly been conducted on impairments in the main cognitive domains such as memory, attention and executive functions. A less studied aspect of cognition is social cognition, which is not a uniform theoretical construct. It includes emotion perception, prosody, empathy, theory of mind (ToM) and assessment of mood [6, 7]. Findings in MS show disturbance not only in emotion recognition from facial expressions but in the whole area of general emotion processing. The connection between cognitive decline and impaired social cognitive skills in MS remains debatable.

Social cognitive dysfunction in MS actually affects all stages of the disease and all types of clinical course. Such disturbances are reported even in clinically isolated syndrome (CIS). Relatively, little is known about the evolution of cognitive deficits in MS, especially about those manifested in the early stages of the disease [8].

The frequency of social cognition impairments and the nature of pathological changes in the brain in patients with MS are reasonable grounds for seeking a relationship between deteriorated mentalization and findings from imaging/functional brain studies. Studies looking for a correlation between cognitive decline and MRI changes (lesion volume, lesion load, cortical thinning) are still at an early stage. This also applies to studies seeking to detect functional changes in specific brain areas responsible for the performance of relevant sociocognitive tasks. Additional data from future research in this field are needed for better understanding of social cognition impairments [9].

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In addition to progressive physical disability, social cognitive impairments are a reason for job loss in 24–80% of patients with MS [10, 11], increased divorce rate, dissolution of partnerships [12] and social communication difficulties. Furthermore, these disturbances restrict the career development and social life of patients. This calls for a multidisciplinary approach in research and concurrent assessment of the physical, neuropsychological and social aspects of disability in MS.

The main objective is to evaluate the frequency and degree of social cognition impairments in patients with MS based on systematic analysis of advanced scientific research and to outline scientific trends in the field.

2. Methods

We conducted advanced search based on the following key words in different combinations: "social cognition", "multiple sclerosis", "empathy", "theory of mind (ToM)", "faux pas", "mentalization", "emotional perception", "disability", "social brain" and "imaging studies". The selection was made by two independent reviewers who retrieved relevant scientific works (original articles, book chapters, systematic reviews) published in English from electronic database (PubMed, MEDLINE). The search period was unrestricted. The following inclusion criteria were determined: (1) subjects, suffering from multiple sclerosis; (2) assessment of social cognition abilities; and (3) brain imaging findings and impaired social cognition. Case report articles were excluded. A relationship between social cognition skills, physical disability and duration of the disease was searched. We also checked up the bibliography of the related sources and included the relevant articles. We also checked up the bibliography of the related sources and included the relevant articles. We selected six books, seven book chapters, 43 scientific reviews, 86 original articles, one thesis, two conference papers and one manual regarding social cognition and/or MS. Finally, we retrieved two book chapters, 10 scientific reviews, 32 research studies, one thesis and two conference papers on the current topic "social cognition" in MS. Meta-analysis was not suitable for summarizing of the results due to methodological heterogeneity between reviewed studies. Quantitative assessment of the relevant data was conducted. Different points of views, as well as controversies within the scientific field, were presented. We highlighted key results, determined importance of social cognition impairments for quality of life in patients with MS and outlined a framework of research trends.

3. What is social cognition?

Numerous attempts to define social cognition have been made. In early 1994, Thomas M. Ostrom collected more than 100 definitions and accepted conceptual orientation in information processing in the context of cognitive psychology as the core of social cognition. According to him, the sociocognitive approach is based on the belief that constructs relevant to cognitive performance and processing are fundamental to understanding all human responses regard-

less of whether these responses are social or unsocial in nature. This basic definition has been supplemented and updated over time. Augoustinos et al. accept that social cognition is not a theory per se but an approach or perspective strongly influenced by the methods and concepts of cognitive psychology [13].

In 1980s, scientific research postulated that humans store and give meaning to complex social information by simplifying and organizing this information in understandable cognitive structures called schemata. The schemata theory implies that we use the same mental structures for the selection and processing of incoming information from the surrounding social environment. Schemata are based on the general expectations from experience (socialization) and allow the prediction and control of social interactions. This theory is applied to the following four key zones: person schemata, self-schemata, role schemata and event schemata [14]. The categorization process is borrowed from cognitive psychology. It includes the identification of stimuli, their grouping as part of a category similar to other parts in the same category and differentiating them from the components of other categories. It is fundamental to perception, thought, language and actions. In the 1990s, the concept was further developed with the assumption that categorization may present not only average abstraction but also a number of specific and concrete cases or samples found in this category. According to Mead and Vygotsky, intrapersonal processes originate and are modeled after interpersonal processes.

Social cognition is a level of mental capacity developed over the evolution process for successful adaptation to the social environment. The basic domains of social cognition are empathy and ToM.

Empathy is the natural ability to understand the emotions and feelings of others regardless of whether one is directly participating in a given situation, viewing photos, reading a book, listening to a story or just imagining. It refers to the phenomenological experience of compassion [15]. The term "empathy" comes from the German word Einfühlung translated by Titchener as "feeling into" [16, 17]. Empathy includes an intuitive feeling of having something in common with others which relies on socially shared emotional experience, cognitive mechanisms of perspective taking, the ability to maintain a self-other distinction during interpersonal interaction. The cognitive aspect of empathy is also defined as empathy accuracy [18].

ToM, also called mentalization, was described as a cognitive component of empathy by Baron-Cohen in 2003 [19, 20]. ToM is viewed as a specific capacity of the mind to understand ourselves and others in terms of mental states. It is based on "reading the thoughts and emotions" of others through analyzing their facial expressions and other behavioral signs [21, 22]. ToM provides the opportunity for establishing a connection between internal conditions manifested through expressions, gestures, signals and internal states of mind. The capacity to recognize the emotions, intentions and thoughts of others can be regarded as an important component of a broader set of skills called social competence or social intelligence.

More recent studies have explored ToM in two aspects—cognitive ToM (the ability to understand the intentions of others – 'cold') and affective ToM (the ability to infer others' emotional

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states – 'hot') [23]. The affective component of ToM requires empathy. According to Ickes, "everyday mind reading" [24] is not a skill that needs to be learned. However, one develops it in the course of life experience. In addition to personality traits, at least three types of mind-reading accuracy tests need to be examined, that is, the ability to assess someone in terms of the following: (1) mental state (both affective and nonaffective), (2) behavior, and (3) roles, identity and/or condition [25]. Emotion recognition is perhaps the most thoroughly investigated and best known of all mind-reading tasks.

The contemporary neurobiological ToM model includes both neuroanatomic and neurochemical levels of specificity. In this model, cortical and subcortical zones are functionally organized so as to ensure the expression of cognitive and affective mental states for both self and others. According to this model, the cognitive and affective aspects of ToM are based on dissociable but interacting prefrontal networks. The cognitive ToM network includes primarily the dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex (ACC) and the dorsal striatum, while the affective ToM network comprises mainly the ventromedial and orbitofrontal cortices, the ventral anterior cingulate cortex, the amygdala and the ventral striatum. The ability to distinguish the mental condition for self from that for others is based on different brain representations within the mentalizing network and is modulated by the functional interaction between the dorsal and ventral systems for attention and selection in the temporoparietal junction and the anterior cingulate cortex.

The functioning of ToM depends on the integrity of the dopaminergic and serotonergic systems, which are primarily involved in the process of comprehension of mental states. Social cognitive impairments are the result of disruptions in the mentalization network at the neuroanatomical, neurochemical and/or genetic level, which can lead to malfunctions in the dopaminergic–serotoninergic system and to compromising the development of neuroanatomical targets within the network [26]. ToM abilities are variably influenced, depending on the type of pathology in the functioning of the mentalization network.

It is presumed that there are two systems involved in belief processing in humans: implicit ToM (iToM) and explicit ToM (eToM). The iToM system builds a hypothesis empirically in the absence of awareness. It is supposedly available from birth [27]. The eToM system is associated with thinking, control and awareness of the approach in mental state recognition. It responds and develops in the first years of life. Little is known about the connection between implicit and explicit processing of social cognition [28]. It is assumed that they are largely independent.

Social cognition comprises two levels relating to all its domains. The first level includes quick, relatively routine cognitive processing which is largely automatic, implicit and can occur without awareness. At the higher level, these processes are slow, flexible and explicitly require exertion of mental effort [28].

4. Clinical assessment of social cognition in patients with MS

Research on social cognition is experimental and focuses on intra-individual mental processing. Studies on emotional and cognitive impairments in patients with MS are based on different

test batteries. Mental schemata are used for focusing attention and facilitating information encoding and retrieval.

Empathy can be regarded as a set of interrelated constructs including social competence, self-assessment, emotion and sensitivity to others [29]. Therefore, there is no universal tool objectively assessing empathy in all its aspects. In a recent review of empathy measurement tools [30], 1147 citations were used to select 50 articles describing 36 empathy tests, eight of which demonstrated satisfactory reliability, internal consistency and validity.

The empathy quotient is most often determined through self-assessment questionnaires. Interpersonal empathy is usually studied by applying the Hogan Empathy Scale (HES) [31], the Toronto Empathy Questionnaire (TEQ) and the 50 Item Interpersonal Skills Questionnaire (50 IISQ). The affective component of empathy can be assessed through the Questionnaire Measure of Emotional Empathy (QMEE), while the cognitive component is more precisely determined through HES. The Balanced Emotional Empathy Scale (BEES), developed by Mehrabian, evaluates responders' reaction to the mental state of others [32].

The instrument most often used for determining the level of self-empathy is Neff's self-compassion scale, which assesses self-kindness, common humanity and mindfulness [33]. The measurement of compassionate or altruistic love toward different targets through the Compassionate Love Scale (CLS) provides additional information about the perception of close others and all of humankind [34]. The Empathy Construct Rating Scale (ECRS) can test the ability to understand accurately the feelings of others through careful listening, thus checking whether the subject properly understands what others experience.

More complex information regarding compassion to self and others is provided by Baron-Cohen and Wheelwright in The Empathy Quotient, which measures cognitive empathy, emotional reactivity and social skills [35] and most of all in the Interpersonal Reactivity Index (IRI), which allows measuring of multidimensional individual empathy differences [36].

Recently, tests with nonverbal stimuli have also been applied to the evaluation of empathy. They are commonly used in patients with autism and aphasia but are also an important complement to self-assessment questionnaires, because they contribute to the greater objectivity of overall empathy assessment. Nonverbal tests provide additional information on the empathy quotient through analyzing what feelings and thoughts are inferred from facial expressions in pictures. Most often they are based on a series of photographs which depict people with different mental and emotional charge, thus measuring the cognitive and affective components of empathy. The most frequently used ones are the multifaceted empathy test (MET) [37], the visual recognition test, the Florida Affect Battery (FAB) and Ekman and Friesen's black and white stimulus set. The results of these tests minimize subjectivity in the patient's self-assessment [38].

ToM, as a key aspect of social cognition, requires greater cognitive effort for slower and more explicit processing. In general, ToM tests are classified into three groups: attribution of epistemic mental states, attribution of intention and attribution of affective mental states [39]. They are based on verbally or visually delivered information, and in recent years, ToM movies have been developed for increasing test sensitivity and approximating the demands of

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everyday life social cognition [40]. Verbal tests, such as "Strange Stories" and "Faux Pas Recognition", require interpretation of auditory information for grasping false belief and deception based on short stories with social context similar to real situations. Such tasks could be accompanied by pictures. Decoding complex emotions from voice is measured by "Reading the Mind in the Voice" [41] and the "Voice Emotion Identification Test" [42] and prediction of intentions and emotions—by "Reading the Mind in the Eyes" [43] and the "Facial Symbol Test", [44] which are sensitive indicators of the socioperceptual component involved in the immediate recognition of mental states [45]. Even more informative is the "Cambridge Mind-reading Face Voice Battery", [46] which combines verbal and dynamic visual stimuli.

ToM cartoons assess the ability to understand emotions and intentions by interpreting graphic design images and/or cartoon strips. Some of these use jokes involving false beliefs [47], and others combine representations of mental and physical states [48]. The following are some video tasks appropriate for ToM assessment in patients with MS: conversations and insinuations (C&I) [49], the social inference-enriched subtest of the TASIT, containing video-taped social interactions in which lies and sarcasm are presented [50], the Face Puzzle—for measuring the explicit and implicit aspects of facial emotion recognition, the social cue recognition test [51] and the videotape emotion identification test [52].

In the comprehensive evaluation of social cognitive skills in patients with MS, it is necessary to take into account the level of general cognition, personal characteristics, such as individual perspective, idiosyncrasies, purpose and attitudes [53], as well as a possible genetic modulation of individual empathic ability [54].

So far ToM research has used small groups of patients with MS and a narrow range of cognitive tasks. The fact that there is no unified neuropsychological battery for the assessment of social cognitive impairments should also be taken into account. For the reasons outlined earlier, it is difficult to generalize on their results for the entire MS population, numbering about 1.3 million worldwide, as well as to reach definitive conclusions

5. Impairment of social cognitive abilities in patients with MS

Social cognition is considered a main determinant of the functional outcome in many psychiatric and neurologic degenerative diseases, including MS. Social cognitive impairments have been registered even in the first clinical episode prior to conversion to MS.

Decreased empathy was reported in patients with MS (cohort of 34 MS subjects) compared to healthy controls of the same age and education level ($p < 0.01$) [55]. These results were obtained from a study by Benedict et al., which is the first of its kind. It matched self-reports of patients with MS on their level of empathy against external evaluation by informants. The authors found large discrepancies between the responses from the two groups—the scores obtained from patients were significantly higher ($p < 0.01$) than those of the informants. Personal abnormalities, such as elevated neuroticism, agreeableness and conscientiousness, were also registered in the patients. The authors emphasize the predictive role of executive control over the manifestation of these anomalies and suggest frontal lobe syndrome [55]. Ten years later,

Kraemer et al. also revealed a significantly lower level of empathy in patients with MS assessed by self-rating questionnaire ($p < 0.02$). A study of Banati et al. registered a higher level of empathy, attributed by ambulatory MS subjects to themselves by using self-assessment questionnaire. The patients ($n = 40$) showed 14 times better empathizing abilities to themselves compared to control individuals ($p < 0.05$) [56]. Ot self-compassion mechanisms suppress anxiety and negative thinking [57]. When self-compassion is lowered, mild symptoms of depression and anxiety could escalate into more severe ones.

A systematic review of 72 studies provides evidence of worse adjustment in MS, which is associated with emotional stress and specific emotionally focused coping strategies in these patients. The authors stress the need for further research in this direction because of insufficient evidence on the relation between adjustment outcomes and level of cognition, interaction with others, disease symptoms, social support obtained [58].

Significantly reduced self-perception in different subcategories was established in patients with MS as compared to healthy controls with similar demographic characteristics. Perception of emotional and social functioning (including global health perception) is impaired but mental characteristics are preserved [59].

Incorrect recognition of emotional information during the daily activities of patients with MS hinders the performance of social cognitive skills [60]. Alexithymia, the impaired ability to verbalize emotions due to violation of their processing, might have a significant impact on self-perception, emotion regulation, behavior control and interaction with others in these patients [61]. Alexithymia is a personal construct, characterized by subclinical inability to identify and describe the emotions in the self [62]. It is a common finding in patients with MS and further hinders social cognition [63], making them nonempathic and ineffective in emotional responding [64]. For example, in a study comparing 40 MS patients with the same number of normal volunteers, Montreuil and Petropoulo registered alexithymia in 50% of the patients and only in 9% of controls [65]. No correlation was found between alexithymia, on the one hand, and cognitive impairment, mood disorders and disease duration in MS patients, on the other. However, MRI studies established a significant connection between alexithymia and atrophy of the posterior part of corpus callosum [66]. This result supports the hypothesis of interhemispheric transfer dysfunction in patients with alexithymic MS [67].

One of the most sensitive indications of social cognition impairment, in particular in MS, is the difficulty in facial expression recognition [68, 69]. Most MS research detects a deficiency in emotional facial expression recognition. Beatty studied patients with MS and established impaired identification not only of facial affect, but also of neutral facial expressions [60]. Testing this ability in patients with MS again (cohort of 22 patients with MS and 11 healthy controls), Krause et al. detected unequivocal emotion recognition deficits in patients with MS who had shown no difficulties in face identification. In line with current findings, these impairments were most common in the recognition of unpleasant facial emotions, while deficits in the recognition of happy expression were not observed. Furthermore, the reaction times to happy facial expressions were significantly faster ($p < 0.001$) compared to that to negative emotional expressions. One reason may be that it is usually easier to recognize a happier facial expression, and consequently, these impairments can be better compensated for

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[70]. Based on specific tests for perception from facial photographs, Philips expanded and supplemented the currently available data with the conclusion that MS leads to an impaired ability for processing emotional information from both static and dynamic images [71]. However, differences in emotion recognition are discreet and subtle, and according to some researchers, correlate significantly with cognitive functioning, suggesting a global deficiency in the speed of information processing [50]. Despite some variability in findings, several contemporary studies support the thesis that ToM impairments are independent from neuropsychological functioning in adult patients with MS [49, 56]. A correlation between impaired emotional perception and the physiological and social aspects of quality of life was found in MS [71]. Some studies have shown a correlation between the inability to recognize facial emotions from presented photographs and alexithymia [72–74].

In a study of patients with MS in 2003, which was the first of its kind, Beatty revealed affective prosody comprehension deficits not due to a hearing loss, cognitive decline, aphasia or depression (47 patients, 19 demographic controls). MRI studies of these patients did not detect a connection between affective prosody violations and the size of the corpus callosum or lesion load [75].

Empathy reflects the ability to infer and share the emotional state of others, therefore it is strongly related to ToM [76]. ToM (mentalization) refers to the perception of the mental condition of ourselves and others, which may serve for understanding and predicting their behavior [77].

ToM disorders are often detected in patients with MS. Their ability to read thoughts is reduced due to their impaired decoding of nonverbal signs such as facial expressions, gestures, gaze fixation and comprehensive processing of abstract verbal information.

The first study assessing ToM abilities in patients with MS was conducted in 2009 by Henry et al. [45], who applied both a test for basic recognition of emotional facial expressions and ToM tests (27 patients with MS and 30 controls). The "Reading the Mind in the Eyes" test (belonging to ToM tests) allowed the differentiation of more complex emotional states often associated with social relationships (e.g., attraction or repulsion, friendly or hostile attitude, noticing or ignoring the tested). The authors found impaired recognition of anger and fear in patients with MS but did not establish intergroup differences between subjects and controls in the recognition of surprise, sadness, disgust and happiness. A significant correlation was registered between dealing successfully with facial emotion recognition and ToM tasks. For both groups, a statistical correlation was discovered between the level of coping and executive control.

In the same year, Ouellet arrived at the conclusion that patients with MS suffering from cognitive deficits tend not to recognize the mental state of others unlike MS patients with preserved cognition (15 cognitively intact and 26 cognitively impaired patients) [49], while Henry (64 patients with relapsing-remitting MS (RRMS), 30 controls) [78] and Pöttgen (45 patients with MS, 45 healthy controls) [21] found that ToM deficits in MS appear independently of the well-known cognitive deficits. Emotion recognition impairments were more pronounced in patients with MS than impairments in thought and intention recognition [21, 79].

More errors of interpretation and lower total scores were reported in patients with MS when using nonverbal tests [56]. Subjects performed worse than controls ($p < 0.05$) at the facial symbol test (FST) [80].

In their pilot study, Genova et al. used a dynamic sociocognitive task—The Awareness of Social Inference Test (TASIT)—and established an impaired ability in patients with MS to interpret and understand lies and sarcasm. These impairments correlated with severe cognitive disorders in information processing speed, working memory, learning and memory and with premorbid IQ [50].

Charvet et al. devoted their scientific work on social cognition in patients with MS, which has debuted in childhood. The authors reported significantly worse results of the pediatric onset MS patients ($n = 28$) compared to those of healthy peers ($n = 32$) in the following three domains of social cognition: facial affect recognition ($p = 0.008$), detection of social faux pas ($p = 0.009$), perspective taking ($p = 0.06$) [81].

5.1. Social cognition impairments in different clinical subtypes of MS

Studies exploring the relatedness of social cognition impairments to clinical subtypes of MS are still insufficient. The available data indicate significant variation in the degree of cognitive impairment among individual phenotypes of the disease.

5.1.1. Clinically isolated syndrome (CIS)

In 2010, Jehna et al. conducted a study in which they established significant slower speed of emotional facial expression processing in patients with CIS compared to healthy persons ($p < 0.01$). They suggested storage of facial emotion recognition based on the lack of significant differences in the number of correct answers. Since response time is an indicator of cognitive processing speed, the authors interpreted these results as evidence of general delay in information processing in MS [80].

5.1.2. Relapsing-remitting multiple sclerosis (RRMS)

Patients with RRMS demonstrated significantly lower levels of empathy toward others and fantasy compared to healthy subjects [82]. An earlier study by Beatty conducted in 1989 with MS patients assessed their ability to identify facial affect by viewing photographs depicting basic emotional states. Patients with RRMS fulfilled these tasks properly [60]. The findings of a new study, conducted by Kraemer et al. in 2013, with a homogeneous cohort of 25 patients with RRMS in the early stages of the disease (less than two years' duration) and with low levels of disability Expanded Disability Status Scale- <2 (EDSS <2) showed significantly worse results in affective prosody comprehension in MS subjects compared to the same number healthy controls. Patients gave less accurate solutions to "discrimination of affective prosody" and more incorrect responses in the subtest "matching of affective prosody to facial expression" for the emotion "anger". Paradoxically, regarding the emotion "fear" they showed better results than controls [6]. Gleichgerrcht et al found that MS subjects (patients $n = 38$; controls n

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= 38) had significantly higher self-oriented personal distress ($p < 0.01$) and higher levels of alexithymia compared to controls [82].

So far the only available study in patients with MS examining the cognitive and affective components of ToM separately is that of Roca et al. from 2014. Using faux pas and executive function tests in 18 RRMS patients with low grade of disability, Roca et al. found deficits in the cognitive component of ToM in the presence of a stored affective component. Such dissociation between the cognitive and affective components of ToM has also been reported in other neurological and psychiatric disorders [83].

5.1.3. Primary progressive MS (PPMS)

Patients with primary progressive MS (PPMS) have experienced considerable difficulties in identifying the emotions of others, as well as their own emotions. Patients from this subgroup gave lower results in faux pas tasks compared to RRMS patients [84].

5.1.4. Secondary progressive multiple sclerosis (SPMS)

Patients with secondary progressive MS (SPMS) are significantly more alexithymic compared to healthy controls [61]. Beatty's study in 1989 revealed that the patients with chronic progradient MS experienced difficulties in the discrimination of facial affect and neutral faces, unlike those with RRMS. Error analysis demonstrated that patients had the same difficulties in depicting each of the represented seven emotional states without serious errors in indicating their polar opposites [60]. Current studies have not shown abnormal identification of neutral faces by subjects with SPMS. In patients with this subtype, lower accuracy has been reported in performing tasks for perception of fear, surprise, anger and sadness [61], while difficulties in identifying disgust and happiness were not reported. Compared to healthy controls, patients took less time in recognizing fear and surprise, while detecting anger and sadness took them longer.

A retrospective longitudinal review with 1845 MS patients, 351 of whom with chronic progradient multiple sclerosis (CPMS), 636 — with RRMS and 858 — with mixed or nonspecific MS, compared to 265 healthy individuals registered worse results in patients with CPMS than in RRMS patients at the Benton Facial Recognition Test (BFRT) [85].

5.2. Social cognition impairments depending on MS duration

A positive correlation was detected between duration of MS and level of empathy, that is, the greater the duration of the disease, the lower the empathy quotient [55, 56, 86]. Banati et al. found profoundly increasing of the empathizing quotient (p 0.03) among patients with short-term MS ($n = 40$) compared to controls ($n = 35$). In addition, Pakenham and Cox in longitudinal study of 388 persons with MS and 232 caregivers registered positive correlation between the time since diagnosis and compassion/empathy ($p < 0.01$), mindfulness ($p < 0.01$) and personal growth ($p < 0.01$). Contrarily, other studies found a significant decrease in the empathy level in patients with MS who are still in the early stages of the disease and with a low degree of disability compared to healthy subjects. The authors explain the unrealistic self-assessment

results of most subjects with the greater impairment of ToM skills and partly with the higher emotional stress they were experiencing [22, 86].

In 2010, Banati et al. found more prominent ToM deficits in patients with longer disease duration ($p = 0.05$) [56]. In some research, the duration of the disease did not correlate with the emotional and cognitive scores from nonverbal tests [80], while Kraemer reported positive correlation between impaired social cognitive skills and executive function deficits in the early stages of the disease in fully ambulatory patients [6].

5.3. Social cognition impairments in MS depending on the grade of physical disability

Paradoxically, patients with more severe physical disorders relatively often show a higher level of empathy compared to controls and patients with mild neurological deficits. A positive correlation was found between the difficulty in emotional facial expression recognition and the degree of disability [44]. Patients with a higher grade of disability demonstrated greater difficulties in affective prosody recognition [75]. More interpretation errors and lower scores were reported for patients with MS when nonverbal tests were used [56]. With deterioration of the disability the results from ToM verbal tests also get worse [87]. In a study of Jehna, EDSS scores did not correlate significantly with scores from emotion recognition tests or with results from FST in MS subjects (sample of 20 patients: CIS $n = 12$, RRMS = 7, SPMS = 1) [80]. Results from other recent studies indicate that the severity of the disease (respectively the degree of physical disability) does not correlate with the degree of impaired emotion recognition or with the psychological and social aspects of the quality of life [71, 88]. Therefore, some researchers consider social cognition as a separate domain of cognition which could independently affect the quality of life of the individual, in particular, that of patients with MS. Based on the extensive review of the literature available, we can conclude that social cognition impairments in these patients require further in-depth research.

6. Social brain

Leslie Brothers was one of the first scientists talking about the social brain, using proof from studies in nonhuman animals [89]. Later Prinz created the common coding theory, according to which perception and actions rely on common codes [90]. The discovery of the so-called "mirror neurons" within the premotor and parietal cortices [91], activated while an action directed to the object is performed and while an action is perceived by the object [92, 93], became a basis for extensive research on the so-called social brain [91].

The discovery of social cognitive impairments in patients with MS presupposes brain damage. The difficulty in facial expression identification is among the most sensitive indicators for social cognition impairments. It is supposed that a disconnection mechanism due to white matter lesions and cortical thinning of specific brain zones causes a cognitive decline. This worsens the processing of emotions and the decoding of mental states from facial expressions. Functional MRI study, conducted by Jehna et al., provides evidence of altered functional brain processing in the posterior cingulate cortex and precuneus during emotion recognition in

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subjects with MS (sample of 15 patients and 15 healthy individuals) [88]. Abnormalities in face encoding and recognition vary in different stages of MS. Patients with CIS experience increased recruitment of the posterior visual areas. In patients with RRMS, the thalamus, parahippocampal gyrus and right anterior cingulum are more activated than in patients with CIS and SPMS. In SPMS, an increased recruitment in the frontal areas is also registered. Significant correlation has been described between the above-mentioned abnormal activations, on the one hand, and clinical symptoms, conventional MRI findings and behavioral disorders, on the other [94].

It is considered that mentalization is carried out by a large network of functionally related neurons [26]. A correlation has been established among specific cortical areas involved in emotion identification from facial expression (right and left fusiform face area, frontal eye), emotion processing (right entorhinal cortex) and socially relevant information (left temporal pole) [95]. According to a model of Ross and Mesulam, affective prosody comprehension could be related to the right-sided perisylvian region, whose structure is similar to the language areas in the left hemisphere [96]. Later studies have suggested an involvement of the basal ganglia and prefrontal cortex (PFC) [97, 98]. Alexithymia may be associated with deactivation and activation of the anterior cingulate cortex (ACC) in response to highly negative and respectively highly positive emotional stimuli [72].

The most active brain region involved in social cognitive processing is the medal frontal cortex (MFC) [99, 100], which is described as the brain's social cognitive center. This region is activated during tasks requiring self-knowledge and reflection, person perception and attribution of intentions. It is supposed that von Economo neurons [101] serve as a relay tract from the frontoinsular and anterior cingulate cortices (responsible for fast intuitive processes) to parts of the frontal and temporal cortices (associated with making slower conscious decisions), thus playing an important role in ToM [102]. It was discovered that damage to the VM frontal lobe plays a crucial role in the existence of a higher level of social cognition: social reasoning [69].

Individuals with bilateral damage of the orbitofrontal cortex show a decline in their ability to attribute higher-order mental states to other people from stories. In particular, they fail to detect faux pas during functional imaging study. Emotion recognition tasks establish priority activation of Brodman Area 47 (orbital area) compared to activation of the medial orbitofrontal region [103]. Tissue loss in BA47 correlates with the inability to recognize negative emotions [104].

It is reported that sections of the left medial prefrontal cortex also contribute significantly to understand the mental state of others [105] or to reasoning about the beliefs and intentions of others [106]. Functional MRI studies demonstrate activation of the amydgala during attribution of mental states and intentions to other people by viewing pictures of their eyes [107].

The wide dissemination of demyelinating lesions and cortical thinning typical of patients with MS often lead to anatomic and functional disorders of the above-mentioned specific brain structures. A subsequent disconnection mechanism leads to a cognitive decline [108]. Single-photon emission computed tomography (SPECT) studies in cognitively impaired patients with MS registered a deficiency of brain perfusion, mainly in the frontal and temporal lobe of the

left hemisphere [109]. Positron emission tomography (PET) in these patients registered both global and regional reduction of cerebral glucose metabolism [110, 111]. An increase in the white matter lesion load, especially in the insula, precentral gyrus, prefrontal and temporal cortices, reduces the effectiveness of large-scale brain structural networks in patients with MS, which leads to cognitive deficits [108]. Functional MRI studies point to a positive correlation between the degree of activation of certain cerebral zones during performance of specific cognitive tasks and lesion load. These findings support the notion that increased cortical activity in patients with MS occurs as a result of axonal damage related to MS activity and aims to limit the clinical impact of structural damage [112].

According to Krause et al., the orbitoinsular cluster, which includes the ventral lateral prefrontal cortex (VLPF) and parts of the anterior insula, is crucial to deficits in emotional perception in patients with MS [70], which is one of the most sensitive indications of impaired social cognition. Functional MRI studies have indicated that after initial activation of the early visual fields visual stimuli are selectively processed in a specific region of the fusiform gyrus, the fusiform face area (FFA) and the facial part of the superior temporal sulcus (fSTS) [113]. FFA is activated mostly with invariable traits, which is possibly related to person identification [70, 113], while fSTS activation is more often associated with variable aspects related to the eyes, spoken speech and expression of emotions and intentions [114–116]. The high-level visual temporal cortex projects to a small proportion of amygdala neurons whose answers are relatively selectively modulated by viewing faces compared to other visual stimuli. Functional MRI research has proved that the amygdala is critical for emotion recognition from facial expression, especially with negative emotions, such as fear [117, 118]. The amygdala is involved in the automatic focusing of attention for detecting emotional stimuli and filtering emotionally relevant information through the signs perceived [119, 120]. Thus, it participates in making more complex social decisions in humans [121]. There is evidence that bilateral amygdala damage leads to severely impaired ability for the recognition of fear through facial expression [118, 122]. A study by Jehna et al. provided proof for functional differences between patients with MS and healthy controls concerning the perception of neutral and emotional facial expressions of anger and disgust. These differences were found relatively early in the course of the disease, even in the absence of behavioral differences between subjects and controls. Since the functional changes registered in the occipital areas of patients with MS during recognition of nonemotional faces are usually associated with face processing, the authors explain the excessive activation of the posterior cingulate and precuneus during emotion processing as an additional attentive requirement [88].

As regards the ability to simulate the emotional state of others, the anterior insula, functionally connected to the ventrolateral prefrontal cortex (VLPFC), shows reduced activation in subjects experiencing problems in facial emotion recognition [123]. More difficult cognitive tasks lead to higher activation of the more lateral regions of ventrolateral prefrontal cortex (VLPFC) [70, 124].

During performance of various sociocognitive tasks for mental state attribution, common areas of increased activation in the medial prefrontal gyrus and the temporoparietal junctions are

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registered bilaterally, while the area of the medial prefrontal cortex (the paracingulate cortex) is the only region uniquely activated by the performance of ToM tasks [47].

A hypothesis has been developed for explaining social cognition via three related but distinct dimensions of anatomical and functional brain organization [124]. It states that the medial-lateral dimension connects the medial prefrontal cortex (MPFC) (emotional aspects of mental state attribution and emotions) to the lateral prefrontal cortex (LPFC), associated with visuospatial centers supporting externally generated representations (cognitive aspects of mental state attribution and emotions) [125, 126]. The midline posterior-anterior dimension links the "first-order" perceptual substratum for the flow of socioemotional processing (superior temporal sulcus), the posterior insula and the middle ACC to the anterior insula and MPFC, where it is presented again with increased complexity [99, 127] and results in awareness and explicit judgments of affective mental states. The third dimension is the projection from ventral regions of the frontal midline involved mainly in stimulus-driven processes (amygdala, striatum and OFC) to dorsal regions supporting monitoring and reflective processes (dorso-medial and lateral prefrontal cortex) [124, 126]. This means that mental state attributions are supported by various neural structures depending on the type of sociocognitive task and processing demands.

Most MRI studies of patients with MS found a correlation between the cognitive and/or affective disorders, on the one hand, and lesion localization [128], total lesion load [129] or cerebral atrophy, on the other [129, 130]. A significant correlation was also reported between abnormal activities in specific cortical zones on fMRI, on the one hand, and clinical manifestation, conventional MRI findings and behavioral changes, on the other [94]. However, a study of voxel-based lesion symptom mapping did not reveal a significant connection of the total lesion volume to the degree of emotional recognition or to the activation of specific cortical areas during task performance. A statistically significant relationship was discovered between lesions in the left temporal periventricular white matter and decreased accuracy in dealing with cognitive tests, which points to a disturbance in information transmission from the temporal visual processing areas to the frontal regulation areas [70, 131].

Altered patterns of brain activity were found in all clinical phenotypes of MS, including when cognitive abilities were intact and/or restored [112, 132, 133]. However, such research is still insufficient. A recent fMRI study of different forms and stages of MS reported results from performance of face encoding and recognition [94]. In patients with CIS an increased recruitment of the posterior visual area, where face perception and encoding is processed, was revealed. The result was interpreted as an adaptive response of cerebral reorganization for compensating sociocognitive functioning in the early stages of the demyelinating disease. In patients with RRMS, an increased activation of the thalamus, parahippocampal gyrus and right anterior cingulum was reported. In patients with SPMS, an increased recruitment of the frontal fields, associated with higher cognitive functions, was registered. The findings suggest disadaptation and inadequate coping with cognitive tasks in a social context as the disease progresses. MRI findings show that in different clinical subtypes of MS the decreased cortical recruitment often correlates with increased T2 lesion load [112, 134].

Functional MRI studies in patients with MS prove that cortical plastic changes are a dynamic phenomenon that can be modulated by external factors. Unfortunately, fMRI studies of social cognitive abilities are still scarce, especially in patients with MS. Accumulation of data from future studies will allow early registering of the specifics of morphological and functional brain changes. This would facilitate the mapping of individual strategies for adequate treatment and rehabilitation of each patient.

7. Discussion

People are profoundly social creatures, and therefore, successful social communication is crucial to their satisfactory lifestyle. The quality of this communication depends on their ability to detect emotional and cognitive processes in others and to understand their own internal state. These two features of social cognition—affective and mental—are the basis for empathy and ToM (mentalization). During social interactions, these different levels of social cognitive response are highly intertwined and each is influenced by the other.

Between 40% and 70% of patients with MS are affected by cognitive impairments [5], which are linked to a significant decline in activities of daily living. Despite the rapidly growing amount of research establishing frequent social cognitive deficits in such patients, there is still no statistics on the frequency of this type of disturbances. We set ourselves the goal of providing an overview of studies in this scientific area and contributing, through summarizing the results, to a better understanding of the specifics of social cognitive disorders and the way they determine the functional outcome and quality of life of patients with MS. We also made attempts at discussing controversies, discovering outstanding issues and outlining a framework for future research.

A wide range of literary sources report that the pathology of white matter in MS has the potential not only to disrupt the basic parameters of cognitive functions but also to hinder important social perception skills. The accumulated data suggest that the neuronal processes of ToM and empathy are performed in different brain networks which partially overlap [56]. No significant controversies exist concerning the pathophysiological significance of altered brain activation patterns in MS [112]. Rather, various studies complement the knowledge on functional processing in specific brain areas responsible for the different aspects of social cognition. Common activation areas include the medial prefrontal cortex, the temporoparietal junction and the temporal poles. ToM stimuli lead to increased activation of the lateral orbitofrontal cortex, the middle frontal gyrus, the cuneus and the superior temporal gyrus, while empathy is associated with enhanced activations of the paracingulate, the anterior and posterior cingulate and the amygdale [135]. A more pronounced global and regional cortical atrophy in the left hemisphere, which is a frequent finding in MS [136], suggests more severe ToM deterioration. However, no studies have been conducted yet of the functional relation between empathy and ToM in MS.

Pathways composed of white matter, which have a key role in coordinating the information flow between different regions of gray matter of the brain, are particularly vulnerable in MS

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[108]. Patients with lesions located in the ventromedial prefrontal cortex demonstrate selective deficits in affective ToM. Lesions in the inferior frontal gyrus are associated with extremely impaired empathy and emotion recognition [137].

ToM tests based on verbal and nonverbal stimuli not only serve for clinical evaluation of social cognitive impairments, but are also at the core of studying the functional anatomy of ToM in fMRI research [47]. The MPFC, associated with mentalizing tasks, activates whenever the person is attending to certain states of the self or others. The MPFC is equally active when the person is engaged in true beliefs, knowledge of the world based on past experience applied to the current situation, and partially in personal observations and behavioural predictions (STS) [48] There is increasing evidence of functional cortical changes in the early stages of MS, even after a single clinical episode [138, 139], when expansion and recruitment of additional cortical fields as common compensation of brain damage are registered [112].

The ability to decode specific facial emotions and ToM skills, which largely determines social communication in the real world, was first studied in MS patients in 2009 by Henry et al. For the first time, researchers presented clear evidence of increased difficulties in both aspects of emotion understanding, as well as in mental state attribution. Although the authors realized that their research was limited due to the lack of study of structural brain changes, their data were the first to establish a correlation between cognitive capacities and important aspects of emotion perception [45].

The diffuse demyelination and atrophy of both gray and white matter typical of MS lead to pronounced deficits in empathy and ToM. While white matter lesion load accounts only for some cognitive deficits in MS, this type of disorders can be better explained through pathological processes affecting gray matter, which are revealed in very early stages of the disease [140–142]. A significant positive correlation was established between neocortical volume and cognitive damage in patients with RRMS [143], as the gray matter atrophy occurring faster than white matter atrophy and, as recent research indicates, probably playing a central role in the emerging and deepening of cognitive deficits [144].

New technologies can help maximize our ability to assess cerebral integrity in MS. Regardless of the rapid development of imaging technology for detecting the earliest possible morphological abnormalities in MS, the focus of research has primarily been on the physical disability and/or general cognition. Unfortunately, the study of social cognition still remains outside the scope of such type of research. We strive to contribute to a better understanding of the neurobiological correlates of social cognitive deficits, hoping in this way to provide opportunities for future research to develop medicinal and therapeutic strategies for modifying the pathological brain processes involved in these deficits. This would increase the level of empathy and ToM skills in patients with MS and could also facilitate their successful social adaptation.

On the other hand, morphological damage in MS is highly variable both with regard to the load, location and size of demyelinating lesions and in relation to individual global and regional cortical thinning. The particular phenotype of MS introduces additional specific features of brain damage. This explains the heterogeneity of social cognition impairments in

terms of their severity and regarding the predominant disturbance of certain social cognitive domains. According to Henry, while testing empathy and ToM skills, it is also recommended to perform in parallel direct mapping of underlying MS-related neuropathology for detecting a link between structural brain pathology and social cognitive impairments. Pöttgen established a deficient ability to reason about the mental state of others (ToM) and to have insight into the emotional stages and feelings of others (empathy) in the early stages of RRMS [21, 22], even in patients who have no substantial neuropsychological deficits. Emotional prosody comprehension may also be disrupted in the early stages of RRMS [6]. It is argued that this is the earliest social cognitive impairment in patients with MS. Deteriorated emotional perception at this early stage can create a difficulty in perceiving nuances, such as sarcasm, irony and sincerity, which may lead to interpersonal problems. To confirm these observations, international research with larger groups of patients is required. Data from this study indicate that one year after diagnosing a patient with CIS and RRMS, they experience diminished power of attention and memory speed, which is related to a capacity for fewer working hours, fatigue, depression and may have a negative impact, as opposed to self-efficacy, which affects working hours positively. The level of ToM abilities and their relation to the above-mentioned consequences have not been followed up.

Information on social cognition impairments and different forms of MS is still scarce. The main controversies that we encountered in the course of reviewing the material on the topic are about how the grade of disturbance of social cognition skills relates to the state of general cognition, on the one hand, and to the grade of physical disability and/or the duration of the disease, on the other. These issues remain disputable due to the small size of patient cohorts and the lack of homogeneity within the groups of conducted studies. Moreover, the majority of studies on social cognition skills in MS assess the patients' social cognitive skills at a given point without following up on their development over time. This prevents us from making conclusions about their dynamics during the course of the disease or taking into account the effect of a therapeutic and/or rehabilitation approach. Extensive long-term follow-up studies with well-defined inclusion criteria, consistent sample characteristics and a wide range of clinical and imaging measurements could establish which domains of ToM change in the course of the disease, in what way and at to what extent.

We devoted a lot of time to reviewing studies on social cognition also in other neurodegenerative and mental diseases. We were impressed with the extensive research in skills for interpersonal problem solving, for recognizing social cues, for detecting situational characteristics and for solving situation connection tasks. Our opinion is that a similar approach towards social cognitive impairments in MS would throw additional light on the objective evaluation of the patient's dealing with real situations in a social context. Even studies on the relation between social cognition disturbances and functional outcome define this relation in general terms, without specifying which domains of social cognition should refer to which functional outcome domains. Resolving these issues in the MS field is a challenge for scientists requiring uniform strategies, long-term follow-up, creativity and interdisciplinary cooperation among researchers.

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Two longitudinal studies in schizophrenia provide evidence for the predictive role of emotional perception in the functional outcome at a later point in time [145, 146]. Their findings support the causal relationship between social cognition and functional outcome, which gives us good grounds for drawing attention to the opportunity for similar long-term studies in patients with MS. Surprisingly, despite the chronic nature of MS, which affects young people and inevitably disables them both physically and neuropsychologically, psychotherapeutic or psychoeducational programs are still widely lacking for MS, while being successfully implemented for other neuropsychiatric diseases associated with social cognition deficiency, such as alcoholism, schizophrenia, autism, Parkinson's disease and depression [22].

Irrespective of the limitations of most studies, they share the unanimous opinion that social cognition impairments in MS are a common finding in the early stages of the disease and are characterized by clinical significance. Functional MRI often objectifies deteriorations within the mentalizing network before structural brain disorders are detected. The cortical reorganization reported in these studies may serve as an objective marker for follow-up over time. Unfortunately, fMRI is not yet a routine method of examination due to the high cost, study complexity and lack of unified standards of interpretation.

8. Conclusion

Social cognitive impairments are a common finding in patients with MS and are often manifested at the initial stages of the disease. Both empathy and ToM deficits, regardless of physical disability, lead to psychosocial consequences such as failure to achieve life goals, limitations to employment and leisure activities, inadequacy in social relationships and daily activities [58, 61]. The preservation of a better quality of life in patients with MS requires special attention to the above mentioned aspects of the disease. Timely recognition of the deficit and adequate rehabilitation of social cognition would help patients enjoy a fulfilling social life for a longer time.

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