



Theory of mind and empathy in patients at an early stage of relapsing remitting multiple sclerosis

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ABSTRACT

Introduction: Early after having been diagnosed with relapsing remitting multiple sclerosis (RRMS), young patients coping with the new situation require good social support and interactions. Successful social interaction is critically dependent upon the ability to understand the minds of others and their feelings. Social cognition refers to the ability to understand the mind of others. Theory of mind (ToM) defines the capability to reason about mental states of others. Empathy describes the ability to have insight into emotional states and feelings of others. Despite the knowledge of cognitive impairment, which can have profound effects on patients daily activities and quality of life in advanced stages of multiple sclerosis, little is known concerning social cognition in early stages of RRMS.

Methods: In this analysis, tests assessing executive functions (working memory, set shifting and inhibition) and instruments measuring theory of mind (the Movie for the Assessment of Social Cognition – MASC) and empathy (Baron-Cohen's Empathy Quotient) were administered to 25 young adult patients at an early stage of RRMS and to 25 healthy controls (HC). Patients and HC were carefully matched according to intellectual level, age, gender, handedness and education. An early stage of the disease was defined as being diagnosed with RRMS in the last 2 years and having an EDSS of 2 or lower.

Results: Patients had significantly more incorrect responses ("missing") ToM ($P < 0.04$). Moreover, patients showed a significantly lower level of empathy in the self-rating questionnaire ($P < 0.02$). Of the cognitive tests and depression, ToM and Empathy Quotient (EQ) scores were only significantly correlated with the interference score of the stroop test.

Conclusions: Our findings suggest that theory of mind and empathy are deficient even at early stages of RRMS. Deficits in theory of mind and empathy might negatively influence interpersonal relationships in patients with RRMS.

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1. Introduction

Multiple sclerosis (MS) is one of the most frequently diagnosed non-traumatic neurological disease in young adults [1].

Cognitive impairment, which can have profound effects on patients' daily activities and quality of life is known to be present in patients with multiple sclerosis. Cognitive decline with deficits in processing speed, visual learning and memory, attention and working memory are supposed to occur in later stages of the disease. Demyelination is thought to be the cause of working memory deficits in MS patients. Lesion load, lesion localization and brain

involution have previously been correlated with specific neuropsychological deficits [2].

Some studies have indicated cognitive disturbances are already evident in early stages of the disease [3]. Although cognitive functioning is known to be impaired in MS, literature about its impact on social cognition is sparse. Young patients confronted with the fact of having a chronic disease with unknown prognosis need stable interpersonal relationships and good communication skills to adjust to the situation [4]. Coping with the disease and learning to lead a normal life despite eminent health concerns requires good interpersonal relationships and sufficient social networks [5]. The ability to understand and interpret emotions is crucial for adequate communication, social and occupational skills. The ability to interpret intentions of others in a given situation is essential for successful social problem-solving and interpersonal communication [6–9]. Social cognition refers to the ability to understand the

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mind of others [6,10] and involves encoding, representation and interpretation of social information [7,11]. Social cognition is not a unitary skill, but involves empathy, theory of mind (ToM) [8,9], the perception of emotions from prosody [12] or faces and humor processing [6,13].

Theory of mind describes the capacity to reason about mental states of others [6]. It involves understanding and predicting other people's behavior on the basis of their mental states, their thoughts, intentions and beliefs [6]. The process by which the mind of others is represented is referred to as 'mentalizing' [6,13,14]. Theory of mind is thought to be processed in a network involving the prefrontal cortex (PFC) and temporal cortex [6,10].

While ToM refers to the knowledge of thoughts, beliefs and intentions of others, empathy describes the ability to have insight into emotional states and feelings of others [7]. The basic level of empathy is characterized by emotion recognition, e.g. to understand the other person's feelings [15]. The second level of empathy implies emotional state reasoning, which allows the empathizer to understand the other person's feelings and to predict the consequences of those feelings [10,15]. This requires more cognitive effort than the basic level of empathy [7]. The third process underlying empathy, is having the intention to respond compassionately to another person's sorrows [14,16,17]. Empathy is influenced by observations, memory, knowledge and reasoning [10,16,17]. PFC regions are also involved in empathy [10]. Moreover, empathy is associated with activation of the anterior cingulate cortex, limbic areas, somatosensory and insular cortices [7,18,19].

As mentioned, scientific knowledge about social cognition in multiple sclerosis is surprisingly sparse. After the first study about comprehension of affective prosody by the working group of Beatty et al. [20], to our knowledge only five other studies addressed this issue [15,21–24].

Henry et al. [21] studied facial affect recognition and theory of mind in 27 patients aged 47 and 30 healthy controls matched for age, sex, education and social status. In this study, cognitive impairment, depression and executive function were assessed. In this study, the MS-group was significantly impaired on the ToM tasks, and also presented with deficits in recognition of anger and fear in the facial affect recognition task [21]. These deficits were associated with deficits in executive control and processing speed. The limitation of this study was the heterogeneity of the patient cohort. Another study assessed ToM by using Faux pas-test, Baron-Cohen's Adult Eyes and faces test and empathy by using Baron-Cohen's Empathy questionnaire [15]. This study included patients with an EDSS score lower than 4.5. Most patients had RRMS, but three (3/40) had a secondary progressive disease course. In absence of marked cognitive decline ToM was more deficient in more disabled patients and patients with a longer disease course. Patients with a shorter disease course described themselves as more empathetic [15].

The Canadian working group of Ouellet and colleagues examined cognitive abilities including ToM of 43 patients with probable or definite MS [23]. They measured an MS patient cohort with an EDSS score ranging from 0 to 7.7 and subdivided them into a cognitively impaired group and cognitively intact patient group. As a control group, they also measured an age and education-matched cohort of 20 adults. MS patients with cognitive impairments were found to have more difficulties attributing mental states to others, than did cognitively intact MS patients and normal controls on the two ToM measures which were the short stories and video clip [13].

As of today, only one study assessed social cognition in MS using functional magnetic resonance imaging [22]. Results from these functional imaging and lesion mapping studies measuring emotion recognition in the patients with multiple sclerosis have suggested brain dysfunction in the VLPFC [22]. The VLPFC has previously been shown to be critically involved in affect perception [6].

Decreased emotion recognition performance was restricted to the detection of unpleasant facial expressions (angry, fearful, sad). In evaluating the functional activation maps for the unpleasant facial expressions, the working group from Greifswald [22], Germany, found decreased insular and ventrolateral prefrontal cortex (VLPFC) activation in the impaired group versus the unimpaired groups. They found a relationship between the inability of solving the task and decreased activation of the left VLPFC and the left anterior insula. Krause's data suggest that emotion recognition deficits in MS patients might be due to the interrupted processing of emotionally relevant information, which leads to a decreased activation of the VLPFC and the insula [22].

An exploratory study examined the ability to discriminate between emotional facial stimuli in 20 patients with clinically isolated syndrome, the first manifestation of suspected multiple sclerosis. Interestingly, even in this earliest stage of the disease, the patients demonstrated decreased reaction time regarding emotion recognition tests compared with healthy controls [24]. The study was controlled for the influence of depressive mood [24].

Unfortunately, except for the last [24], most of the studies about social cognition in MS dealt with heterogeneous cohorts of MS patients with different subtypes of the disease in advanced stages and a wide EDSS range. It was not surprising that patients in advanced stages of the disease suffer from deficits in social cognition. In later stages of the disease, when both gray and white matter lesions, brain atrophy and an advanced lesion load is present, executive functioning, abstract and conceptual reasoning, working memory and information processing speed might be impaired as well as social cognition.

However, it is more interesting to test theory of mind and empathy in young and non-disabled patients in early stages of the disease than in patients obviously suffering from cognitive complaints. In order to examine this question, we tested theory of mind and empathy in a homogeneous cohort of young patients with early stages of relapsing-remitting MS (RRMS). Another open issue concerns the question whether ToM and empathy impairments reflect a deficit in emotional perception per se or whether they are related to invisible impairments in cognitive domains, such as executive functions.

Moreover, in line with Ouellet and colleagues [23] we wanted to assess ToM with a modern, more naturalistic test related to everyday interactions [25–27], instead of formerly often used instruments like Faux Pas test and Baron-Cohen's the mind in the eyes and adult faces [15,28].

Advanced video based tests have been developed to increase test sensitivity and approximate the demands of everyday life social cognition [25]. We wanted to assess social cognition concepts with a new instrument never tested in multiple sclerosis: The Movie for the Assessment of Social Cognition (MASC). It was designed to be challenging so as to detect even subtle difficulties in social understanding [25–27].

The intention of the present study was to measure the connection between certain features of executive function (working memory, inhibition and set shifting) which might be predominantly relevant for deficits in ToM and empathy in a homogeneous cohort of young patients with early stages of relapsing-remitting multiple sclerosis. An early stage of the disease was defined as short time since diagnosis and a very low EDSS score [2].

Our objectives could be summarized as research questions:

(1) Do patients with relapsing remitting multiple sclerosis (RRMS) in early stage of the disease (i.e., in the absence of marked cognitive decline and disability) have deficits in interpreting social situations and performing in interpersonal contexts, in comparison with a matched healthy control group? (2) Are deficits in interpreting social situations and performing in interpersonal contexts,

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