Research article

Theory of mind in multiple sclerosis: A neuropsychological and MRI study

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ABSTRACT

Objectives: Social cognition stands among the most frequently affected yet the least studied cognitive domains in multiple sclerosis (MS). Theory of mind (ToM) is a social cognitive facet that implies the one's ability to predict others' mental states. The objective of this study was to assess the relationship between ToM and neuropsychological and neuroimaging data.
Methods: Thirty-eight consecutive MS patients completed the Reading the Mind in the Eyes test (RMET). They underwent a neuropsychological evaluation and a 3 T T1-weighted brain MRI. A fully automated volume-based morphometry algorithm (MorphoBox) was applied to calculate regional brain volumes. Correlation analysis was performed using Spearman's test.
Results: Among the sociodemographic and clinical data, significant correlations were found between RMET scores and each of years of education (r = 0.54; p < 0.01) and the duration of the disease progressive phase (r = −0.46; p < 0.01). Regarding neuropsychological measures, RMET scores were directly correlated with information processing speed (r = 0.58; p < 0.01) and empathy (r = 0.46; p < 0.01) scores. As for brain volumes, RMET scores were directly correlated with parietal (left: r = 0.39; right: r = 0.46; p < 0.05) and temporal (left: r = 0.36; right: r = 0.40; p < 0.05) white matter volumes, as well as with cingulate (left: r = 0.32; right: r = 0.44; p < 0.05) gray matter volumes.
Conclusion: These results highlight the relationship between ToM and some of the disease characteristics and cognitive domains. Importantly, ToM performance in MS is associated with brain volumes of key areas in social cognitive networks. Further works are needed to enhance the current knowledge on the underlying mechanisms of ToM deficits in this population.

1. Introduction

Multiple sclerosis (MS) is a neurodegenerative and inflammatory disease of the central nervous system (CNS) and constitutes one of the leading causes of disability in young adults. Through its course, the location and extent of CNS lesions would dictate the appearance of various sensory, motor and cerebellar symptoms, but also emotional, cognitive and behavioral ones. For instance, fatigue and psychiatric comorbidities, could concern up to 90% and 95% of MS patients, respectively [1,2]. Also, recent evidence supports the frequent occurrence of alexithymia – a personality trait characterized by difficulties in

identifying and describing one's own emotions – in this disease [3]. Of great importance, cognitive deficits could occur among MS patients and affects between 40 and 70% of this population [4–7]. In this context, the great majority of studies have focused on assessing attention, working memory, information processing speed (IPS), learning and executive functions [4–7]. However, only few reports have addressed social cognition (For reviews see [2,8,9]).

Social cognition refers to the mental operations that underlie social interactions [8,9]. Such abilities may impact employment as well as relationships with friends, family members and caregivers. Therefore, they are potentially of particular importance to MS patients whose peer

support represents one of the major determinants of quality of life (QoL) [8,9]. That is to say, social cognitive deficits may be overlooked in MS but seem to constitute an important aspect of cognitive decline in this population [2,8,9]. A key aspect of social cognition is the theory of mind (ToM), also known as mentalizing, which implies the individual's ability to understand and predict others' mental states based on their emotions, feelings, thoughts and beliefs [2,8,9]. An adequate ToM performance is critical for establishing proper social interaction and coping with chronic and stressful conditions like MS. In particular, one study has reported an association between social cognitive deficits and poor psychological and social QoL in MS patients, a finding that remained significant after accounting for patients' demographic, clinical and neuropsychological variables [10].

Therefore, it is of importance to understand the underlying mechanisms of ToM performance in MS. Only few MS studies have assessed ToM and its relationship with the neuropsychological data (For reviews see [2,8,9]) and even fewer works have included MRI measures in their evaluation [11–13]. The main objective of the present study was to examine the neural underpinnings of ToM performance in patients with MS. The secondary objective was to assess the relationship between ToM and clinical, sociodemographic and neuropsychological variables in this context.

2. Experimental procedures

2.1. Subjects

Thirty-eight consecutive patients were enrolled from the neurology department of Henri Mondor Hospital, Créteil, France. Patients were included if they (i) were between 18 and 75 years of age, (ii) had a confirmed MS diagnosis according to 2010 revised McDonald's criteria [14], and (iii) had not experienced any relapse or treatment modification in the last three months prior to inclusion. Patients were excluded if they had (i) severe visual or motor impairments that might interfere with testing, (ii) intellectual impairment as per mini mental status exam score < 24 [15], (iii) other neuropsychiatric diseases, or (iv) contraindications to MRI. All patients underwent a full neurological exam by experienced neurologists (SSA and AC), and the Expanded Disability Status Scale (EDSS) scores were calculated [16]. Sociodemographic and clinical data were collected including age, gender, education level, relationship status, medications, MS subtypes, duration of the disease, and duration of the progressive phase of illness. The latter is defined as an objectively documented neurological dysfunction/disability which has been steadily increasing without unequivocal recovery over a certain period of time (e.g. 1 year) [17]. To note, the progressive phase duration was calculated for all patients and corresponds to a value of 0 in patients with relapsing remitting (RR) MS.

2.2. Ethics statement

The local ethical committee has approved the study protocol which was performed in conformity with the declaration of Helsinki. All patients voluntarily gave their written informed consent prior to inclusion.

2.3. Neuropsychological and cognitive measures

2.3.1. Theory of mind
ToM was evaluated using the French version of 'Reading the Mind in the Eyes test' (RMET) [18]. The test contains 36 photos depicting only the eyes regions of Caucasian actors (19 actors and 17 actresses). Patients were asked to observe each photograph and select among four descriptors the best that describes the feeling or thought of the actor/actress. Scores can range from 0 to 36 (lowest to highest mentalizing abilities). A control task consisted of guessing the gender of actors featured in the photos to check for possible impairments in facial perception which might interfere with facial emotion recognition.

2.3.2. Empathy
The ability to understand others' mental state -ToM- may influence the individual's ability to empathize with others and have a compassionate response [2,8]. For this reason, empathy was considered in the evaluation and was assessed using the French version of the 60-item Empathy Quotient (EQ) [19]. It consists of 40 scored empathy items and 20 filler items that do not enter the scoring. One can score 2, 1, or 0 on each item. The total EQ score can range from 0 denoting lack of empathy to 80 designating the highest empathic ability.

2.3.3. Visuospatial attention and information processing speed
Patients were evaluated using the oral version of the Symbol Digit Modalities Test (SDMT) which assesses the visuospatial attention and IPS [20]. The test consists of a simple substitution task, where patients refer to a reference key to match a sequence of geometric figures with their corresponding numbers, as fast as possible. The test is usually performed during 90 s and the total score represents the number of correct answers (each correct answer gives one point).

2.3.4. Alexithymia
Considering the relationship between the individual's ability to understand his/her own emotions and the ability to understand others' mental states [2], alexithymia was evaluated by means of the French version of the 20-item Toronto Alexithymia Scale (TAS) [21]. TAS items are rated using a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scores can range from 20 to 100. Higher scores design worse abilities.

2.3.5. Anxiety and depression
Anxiety and depression were assessed by means of the French version of the 14-item Hospital Anxiety and Depression Scale (HADS) [22]. It contains two subscales each consisting of 7 items that evaluates anxiety ($HADS_{anxiety}$) and depression ($HADS_{depression}$). The score can range between 0 (normal mood) and 21 (severe anxiety or depressive symptoms) on each subscale.

2.3.6. Fatigue
Fatigue was assessed using the French version of the Modified Fatigue Impact Scale (MFIS) [23], which includes 21 items and assesses the physical, cognitive and psychosocial dimensions of fatigue. The score of each item can range from 0 to 4, with a total MFIS score ranging from 0 (absence of fatigue) to 84 (maximal fatigue).

2.3.7. Excessive daytime sleepiness
Excessive daytime sleepiness was evaluated by means of the French version of the 8-item Epworth Sleepiness Scale (ESS) [24]. Each item represents a situation in which the individual might have recently dozed and is graded from 0 (would never doze) to 3 (high chance of dozing). Scores can range from 0 to 24, the latter indicates excessive daytime sleepiness.

2.4. MRI protocol

2.4.1. Sequence acquisition
A T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE) MRI sequence was obtained for each patient using a 3 T scanner 64-channel head coil (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). The MPRAGE protocol introduced by a Swiss team was adapted (the Alzheimer's Disease Neuroimaging Initiative; www.adni-info.org), with a 2-fold acceleration, yielding $256 \times 240 \times 176$ voxels with slightly anisotropic size ($1 \times 1 \times 1.2$ mm^3) [25].