Cognitive but Not Affective Theory of Mind Deficits in Mild Relapsing-Remitting Multiple Sclerosis

María Roca, PhD,†‡ Facundo Manes, MD,*† Ezequiel Gleichgerrcht, MD,*†*
Agustín Ibáñez, PhD,‡§ María E. González de Toledo, MD,*† Victoria Marenco, PsyD,**
Diana Bruno, PsyD, Teresa Torralva, PsyD,*† and Vladimiro Sinay, MD*†*

Objective: We studied theory of mind (ToM) in patients with mild relapsing-remitting multiple sclerosis (MS), seeking possible dissociations between its 2 components: cognitive ToM (the ability to infer others' intentions) and affective ToM (the ability to infer others' emotional states). We analyzed the relationship of ToM to executive function, depression, and fatigue.

Background: Dissociations between cognitive and affective ToM have been found in several neurologic and neuropsychiatric diseases. Most ToM studies in patients with MS have shown general ToM deficits but have not analyzed the cognitive and affective aspects individually.

Methods: We used the Faux Pas test of ToM and tests of executive function to assess 18 patients with mild relapsing-remitting MS and 16 control participants.

Results: Our patients showed deficits in cognitive ToM, but their affective ToM seemed to be spared. Their cognitive ToM deficits were not related to executive dysfunction, depression, or fatigue.

Conclusions: Our study is the first differential analysis showing cognitive but not affective ToM deficits in mild relapsing-remitting MS. Further research is needed to determine the exact nature and the real impact of these deficits, and to establish their relationship with the neuropathology and progression of MS.

Key Words: multiple sclerosis, theory of mind, executive function, cognition, frontal lobe

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Reader Benefit: Patients suffering from mild relapsing-remitting multiple sclerosis show deficits in their ability to interpret others' thoughts, a fundamental element of social interaction.

FAB = Frontal Assessment Battery. **MS** = multiple sclerosis. **PASAT** = Paced Auditory Serial Addition Test. **RRMS** = relapsing-remitting MS. **ToM** = theory of mind.

Only a few decades ago, cognitive deficits were considered uncommon among patients with multiple sclerosis (MS), but cognitive dysfunction is now well recognized as a frequent feature of the disease (Achiron and Barak, 2006; Amato et al, 2006; Potagas et al, 2008; Rao et al, 1993). The many cognitive deficits described in patients with MS have been attributed mainly to disruption of white matter tracts, predominantly affecting frontal-subcortical networks (Arnett et al, 1994; Filley, 2005; Foong et al, 1997; Roca et al, 2008; Stuss et al, 1992; Swirsky-Sacchetti et al, 1992).

An individual's "theory of mind" (ToM) can be defined as his or her capacity to infer other people's mental states, both their intentions and their feelings. ToM has been related to the prefrontal cortex (Gallagher and Frith, 2003; Stuss et al, 2001). As its definition suggests, ToM can be divided into cognitive and affective components, with "cognitive ToM" meaning the ability to infer others' thoughts, beliefs, and intentions, and "affective ToM" meaning the capacity to understand others' emotional states (Choi-Kain and Gunderson, 2008; Shamay-Tsoory and Aharon-Peretz, 2007; Shamay-Tsoory et al, 2002, 2005; Shur et al, 2008; Stone et al, 1998).

Studies have linked several brain structures to ToM: the superior temporal sulcus, the temporal poles, the amygdala, and the temporal parietal-junction (Abu-Akel, 2003; Apperly et al, 2004; Baron-Cohen et al, 2006; Frith and Frith, 2005; Gallagher and Frith, 2003; Rowe et al, 2001; Saxe and Kanwisher, 2003; Stone et al, 1998, 2003; Wicker et al, 2003). Moreover, different circuits within the prefrontal cortex have been associated with either the cognitive or the affective component of ToM. For example, while the ventromedial prefrontal cortex has been linked to affective ToM, the dorsolateral prefrontal cortex has been linked to cognitive ToM (Abu-Akel, 2003; Choi-Kain and Gunderson, 2008; Eslinger, 1998; Kalbe et al, 2010; Shamay-Tsoory and Aharon-Peretz, 2007).

Although dissociations between cognitive and affective ToM have been found in such neurologic and

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From the *Institute of Cognitive Neurology, Buenos Aires, Argentina; †Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina; ‡UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University, Santiago, Chile; and §National Scientific and Technical Research Council, Buenos Aires, Argentina.
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The authors declare no conflicts of interest.
Reprints: María Roca, PhD, Institute of Cognitive Neurology, Pacheco de Melo 1854 (C1126AAB), Buenos Aires, Argentina (e-mail: mroca@ineco.org.ar).

neuropsychiatric diseases as Parkinson disease, schizophrenia, and Asperger syndrome (Blair and Cipolotti, 2000; Choi-Kain and Gunderson, 2008; Shamay-Tsoory et al, 2005; Shur et al, 2008), most ToM studies in patients with MS have shown general ToM deficits but have not analyzed the cognitive and affective components individually (Banati et al, 2010; Henry et al, 2009, 2011; Kraemer et al, 2013; Ouellet et al, 2010). Indeed, while some investigations have used tasks that assess only 1 of the 2 dimensions, other experiments have used tasks that require both affective and cognitive ToM, but without examining the 2 dimensions separately.

For instance, Henry and colleagues (2009) were the first to investigate ToM in MS. Their study reported deficits in a facial affect recognition task and in the Mind in the Eyes Test (Baron-Cohen et al, 1997), suggesting that the patients had impaired affective ToM. Unfortunately, the patients had such heterogeneous clinical characteristics that they do not allow conclusions to be drawn from the study about affective ToM specifically in mild relapsing-remitting MS (RRMS).

Other studies have used tests that reflect primarily cognitive ToM abilities, such as the false-belief task (Baron-Cohen and Wheelwright, 2004). In particular, Henry et al (2011) showed that patients with MS had a significantly lower global score than a control group on both first-order and second-order false-belief tasks, thus suggesting deficits in cognitive ToM. Again, the patients were clinically heterogeneous, and no actual differences between cognitive and affective ToM abilities were demonstrated.

As mentioned, other studies (Banati et al, 2010; Henry et al, 2011; Kraemer et al, 2013; Ouellet et al, 2010) have used tasks that test both cognitive and affective ToM capacities. Some investigations used tasks potentially able to assess cognitive and affective ToM differentially (Henry et al, 2011; Kraemer et al, 2013), such as the Faux Pas test (Stone et al, 1998) and the Movie for the Assessment of Social Cognition (Dziobek et al, 2006); however, none of the researchers specifically analyzed the ToM components.

Two other studies (Banati et al, 2010; Kraemer et al, 2013) used a self-reported empathy questionnaire (Baron-Cohen and Wheelwright, 2004), which tapped both cognitive and affective ToM abilities. The results were contradictory. While Banati et al (2010) found higher levels of empathy in a heterogeneous group of patients with MS than a control group, Kraemer et al (2013) found lower levels of empathy in patients with early MS than controls.

Our study aimed at expanding understanding of ToM in patients with mild RRMS by analyzing the cognitive and affective components separately. We evaluated 18 patients with mild RRMS and 16 healthy controls with the Faux Pas task, which was designed to assess separately the cognitive and affective aspects of ToM.

METHODS

Participants

We recruited the 18 patients from the Multiple Sclerosis Clinic at the Institute of Neuroscience of the Favaloro Foundation in Buenos Aires, Argentina. Author V.S., a neurologist specializing in MS, evaluated the patients' disease history and drug therapy. Of the 18 patients, 13 were employed outside the home, 2 were housewives, 1 was on leave from a job, 1 was unemployed, and 1 was retired. All the patients met the McDonald criteria for definite RRMS (McDonald et al, 2001). Every patient had a magnetic resonance imaging scan compatible with the diagnosis of MS (the scans were of high enough quality or resolution for clinical purposes, but not detailed enough for research). The patients' score on the Expanded Disability Status Scale (Kurtzke, 1983) was between 0 and 3, indicating mild MS. All the patients were taking disease-modifying therapies at the time of assessment.

We excluded patients from the study if they scored <24 on the Mini-Mental State Examination (Folstein et al, 1975) or had a psychiatric or neurologic diagnosis other than MS. We also excluded patients who were having a relapse in their MS.

We recruited 16 healthy volunteers to serve as controls. We found the controls through word of mouth and included them if they reported no history of neurologic or psychiatric disorders, including traumatic brain injury and substance abuse. We matched the controls with the patients for age and education level.

Table 1 shows demographic data for both the patients and the controls, as well as clinical data for the patients.

We obtained permission to perform the study from the local research ethics committee. All participants signed an informed consent form before participating.

Neuropsychological Testing

We assessed all participants with a complete battery of executive function tests in validated Spanish-language versions: the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977), the Frontal Assessment Battery (FAB) (Dubois et al, 2000), the digit span forward and backward tests (Wechsler, 1987), the verbal fluency test (Benton and Hamsher, 1976; Butman et al, 2000), the Wisconsin Card Sorting Test (Nelson, 1976), and the Trail Making Test Part B (Partington and Leiter, 1949). To control for mood symptoms and fatigue in the patients with MS, we gave them the Beck Depression Inventory (Beck et al, 1996) and the Modified Fatigue Impact Scale (Kos et al, 2005).

Faux Pas Test of Cognitive and Affective ToM

We gave all participants the Faux Pas test to assess their cognitive and affective ToM (Stone et al, 1998). As with the neuropsychological tests, we gave this test in a validated Spanish-language version. In the Faux Pas test, the examiner reads 20 brief stories aloud to each participant. To reduce our participants' working memory load, we also placed a written version of each story in front of them. In 10 of the stories, a person commits a social faux pas, unintentionally saying something hurtful or insulting to another person. In the other 10 stories, no faux pas is

TABLE 1. Clinical, Demographic, and Neuropsychological Variables in Patients with Mild Relapsing-Remitting Multiple Sclerosis Versus Controls

	Mean (Standard Deviation)		Statistical Comparisons	*P*
	Patients	Controls		
Age (years)	40.67 (9.53)	40.88 (9.95)	$t = -0.62$	0.95
Education (years)	14.81 (3.58)	16.50 (1.63)	$t = -1.73$	0.09
Expanded Disability Status Scale score	0.58 (0.99)	—	—	—
Years since diagnosis	5.05 (3.75)	—	—	—
Age at symptom onset (years)	29.39 (8.99)	—	—	—
Executive functions				
Paced Auditory Serial Addition Test	36.86 (19.55)	40.66 (16.43)	$t = -0.48$	0.63
Frontal Assessment Battery total score	16.39 (2.06)	17.50 (0.63)	$t = -2.17$	0.04
Digit span forward	5.11 (1.02)	6.44 (1.03)	$t = -3.76$	< 0.01
Digit span backward	3.89 (1.27)	4.50 (0.89)	$t = -1.56$	0.12
Verbal fluency	15.61 (6.33)	15.81 (4.15)	$t = -0.11$	0.91
Wisconsin Card Sorting Test	4.72 (1.48)	5.88 (0.50)	$U = 66$	< 0.01
Trail Making Test Part B	133.67 (92.95)	67.13 (27.20)	$t = 2.90$	< 0.01
Faux Pas Test of Theory of Mind				
Total score (maximum = 20)	16.83 (2.97)	18.88 (1.08)	$U = 89$	0.59
Hits (maximum = 10)	7.24 (2.92)	8.94 (0.99)	$U = 96.5$	0.15
Rejects (maximum = 10)	9.67 (0.59)	9.94 (0.25)	$U = 112.5$	0.28
Intentionality (maximum = 10)	4.75 (3.06)	7.79 (0.97)	$U = 48.50$	< 0.01
Emotion attribution (maximum = 10)	6.24 (2.61)	7.20 (1.93)	$U = 99$	0.29

committed. Performance is scored in part by the accurate identification of the stories containing a faux pas ("hits") and of the stories not containing a faux pas ("rejects").

When participants correctly identify a faux pas, the examiner asks them 2 more questions, the first to measure *intentionality*—the ability to recognize that the person committing the faux pas was unaware that he or she had said something inappropriate (maximum score = 10)—and the other to measure *emotional attribution*—the ability to recognize that the person hearing the faux pas might have felt hurt or insulted (maximum score = 10).

Statistical Analysis

To compare the patient and control groups' scores for the executive function and Faux Pas tests, we performed either the Student *t* test for independent samples or nonparametric analysis with the Mann-Whitney *U* test for group-to-group contrasts, as appropriate. We also calculated the Spearman correlation coefficient for correlations between variables. We used SPSS Statistics 15.0 (International Business Machines, Armonk, NY) for all analyses.

RESULTS

As shown in Table 1, the patients and controls did not differ significantly by age or years of education. Comparison of the groups' performances on the executive function tests showed significant differences in the FAB total score, digit span forward test, Wisconsin Card Sorting Test, and Trail Making Test Part B. We did not find significant differences on the PASAT, digit span backward, or verbal fluency test.

When we compared the patients' and controls' performances on the Faux Pas test, we found no significant differences in the total score, hits or rejects scores, or emotional attribution score. However, we found a significant difference on the intentionality score: The patients' performance was almost 40% lower than the controls'.

Within the patient group, we did not find correlations between the Faux Pas test and the Beck Depression Inventory or fatigue scores, even though the depression and fatigue scores did correlate with one another (Spearman correlation coefficient [*r*] = 0.54; $P = 0.02$) (Table 2).

When we analyzed correlations between the Faux Pas test and the executive tasks, we found that the Faux Pas total score had significant correlations with the FAB ($r = 0.50$, $P = 0.03$) and with the Trail Making Test Part B ($r = -0.54$, $P = 0.02$). Although the Faux Pas hits score correlated with the same executive variables (FAB: $r = 0.53$, $P = 0.03$; Trail Making Test Part B: $r = -0.63$, $P < 0.01$), we did not find significant correlations between the intentionality score and any of the executive tasks (PASAT: $r = 0.32$, $P = 0.43$; FAB: $r = 0.42$, $P = 0.13$; digit span forward: $r = -0.15$, $P = 0.60$; digit span backward: $r = 0.60$, $P = 0.83$; verbal fluency: $r = 0.41$, $P = 0.11$; Wisconsin Card Sorting Test: $r = 0.22$, $P = 0.42$; and Trail Making Test Part B: $r = -0.06$, $P = 0.83$).

DISCUSSION

In our 18 patients with mild RRMS and our 16 control volunteers, we analyzed cognitive and affective ToM abilities separately to look for possible dissociations between them. Consistent with previous studies (Banati et al, 2010; Henry et al, 2009, 2011; Kraemer et al, 2013; Ouellet et al, 2010), we found ToM deficits in our patients. They were significantly less able than the controls to infer the intentions of others, thus revealing cognitive ToM deficits. However, their capacity to infer

TABLE 2. Correlations between Patients' Scores on the Theory of Mind Test Components and the Depression and Fatigue Questionnaires

	Faux Pas Test				
	Total Score	**Hits**	**Rejects**	**Intentionality**	**Emotion Attribution**
Beck Depression Inventory	$r = 0.25$ $P = 0.31$	$r = 0.38$ $P = 0.13$	$r = -0.43$ $P = 0.07$	$r = 0.23$ $P = 0.39$	$r = 0.13$ $P = 0.61$
Modified Fatigue Impact Scale	$r = -0.38$ $P = 0.12$	$r = -0.35$ $P = 0.17$	$r = -0.21$ $P = 0.39$	$r = -0.19$ $P = 0.47$	$r = -0.47$ $P = 0.06$

r = Spearman correlation coefficient.

others' emotions (ie, their affective ToM) was intact. Their executive deficits correlated with their total score on the ToM task and with their ability to detect a social faux pas, but we found no particular association between their executive function and cognitive ToM or between their cognitive ToM and their depression or fatigue scores.

We used several tests of executive function to compare our participants' executive function with their performance on the ToM test. Consistent with earlier studies, we found that our patients had executive deficits particularly on measures of attention, processing speed, and cognitive flexibility. Contrary to our expectations, we found no deficits in the patients' phonological verbal fluency or working memory, as measured by either the PASAT or the digit span backward. Although some executive tests correlated with the patients' ability to detect a social faux pas, none correlated specifically with their ability to infer other people's intentions. These results suggest that even if some aspects of ToM might be related to executive dysfunction and general cognitive performance, this relationship cannot account for every aspect of ToM.

Although most of the relatively few reports of ToM in MS have examined heterogeneous groups of MS patients, all studies have concluded that patients' ToM is indeed affected. While a specific cognitive ToM deficit has been suspected in MS, our study is the first to document this differential impairment.

In this regard, Banati et al (2010) were the first to investigate the components of ToM in mild and moderate MS. They showed that patients with a shorter disease duration scored higher on an empathy questionnaire designed to assess both affective ToM and emotional reactivity. Even though these results suggested that patients who have had MS for less time have higher affective ToM, the study did not directly compare the patients' ability to infer others' intentions and emotions.

Henry et al (2011) also proposed that the components of ToM could be differentially affected in RRMS. To explain why patients with RRMS were able to detect a faux pas but unable to perform a simpler false-belief task, these authors suggested that the patients might have a specific deficit in their ability to infer intentionality, while their ability to infer affective states was spared. Thus, the authors claimed, patients tended to fail in the false-belief task because it required only the inference of intentionality, while they could correctly detect a faux pas based on their ability to infer affective states. This is an elegant possible explanation of their results, but they did not report the analysis that would provide a direct test. Our study, by contrast, provides just such an analysis.

Interpreting our results in the context of previous findings, we can conclude that only cognitive ToM seems to be affected in patients with mild RRMS, but as the disease progresses, the affective aspects of ToM may also deteriorate (Banati et al, 2010; Henry et al, 2009, 2011; Ouellet et al, 2010).

Our findings also call attention to the fact that patients may have impaired ToM, particularly cognitive deficits, without showing deficits on widely used executive function tests like the Wisconsin Card Sorting Test and the PASAT. Clinicians who are assessing neuropsychological performance should know that their patients in the mild stages of MS may have specific impairments of social cognition before they show deficits on certain executive tasks. Patients in this situation may be able to compensate in their everyday executive functions but may suffer the social consequences of impoverished social cognition. This is, of course, worthy of further research.

Our study had several possible limitations. One is that, because our patients had mild RRMS, we cannot generalize our results to all patients with MS. However, studying populations with diverse clinical and disease-severity profiles can lead to overlooking individual patients' potentially different ToM impairments. A 2013 study by Kraemer et al was the first to investigate ToM in patients with early MS. The researchers evaluated patients with mild disability, within the first 2 years after diagnosis. The authors found deficits in a ToM movie interpretation task (Movie for the Assessment of Social Cognition; Dziobek et al, 2006) and an empathy questionnaire (Empathy Quotient; Baron-Cohen and Wheelwright, 2004), which together assessed both cognitive and affective ToM.

Another limitation of our study was its relatively small sample size. Future research using the same measures should build on our findings in studying more patients.

A further shortcoming was the lack of measures of quality of life and measures to detect the real impact that ToM deficits have on patients' everyday life. This is

particularly true because depression, which was our study's only proxy variable for quality of life, did not correlate with our patients' ToM impairment. Future studies should include quality of life, daily living, and other measures aimed at investigating relatives' and caregivers' perceptions of how patients' quality of life has changed.

Finally, even though the Faux Pas test has been used in several studies to assess cognitive and affective ToM separately, analyzing each ToM component is never simple. To corroborate our hypothesis further, future studies must investigate the components of ToM in groups of patients with different degrees of MS severity, using tasks that assess the cognitive and affective dimensions independently.

In summary, earlier studies suggested a possible differential compromise of cognitive and affective ToM in MS (Henry et al, 2011), but none actually showed a cognitive ToM deficit. Our results are the first to show that ToM deficits in patients with mild RRMS are in the cognitive aspect, while the affective aspect seems to be spared. Further research is needed to determine the exact nature and the real impact of these deficits, and to establish their relationship with the neuropathology and progression of MS.

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