Social cognition in pediatric-onset multiple sclerosis (MS)

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Abstract

Background: Pediatric-onset multiple sclerosis (MS) patients represent a subpopulation who are diagnosed during the course of development. Social cognitive deficits have recently been recognized in adults with MS. It is critical to identify whether these youngest patients with the disorder are also at risk.

Objective: To determine whether pediatric-onset MS is associated with social cognitive deficits.

Methods: Consecutively-recruited participants with pediatric-onset MS were compared to a group of age- and gender-matched healthy controls on Theory of Mind (ToM) task performance. Tasks measured facial affect recognition (Reading the Mind in the Eyes Test), detecting social faux pas (Faux Pas Test), and understanding the perspective of another (False Beliefs Task).

Results: Twenty-eight (28) pediatric-onset MS participants (median age 17 years) and 32 healthy controls (median age 16 years) completed the study. The MS participants performed worse than controls on all three ToM tasks: Reading the Mind in the Eyes Test ($p = 0.008$), the Faux Pas Test ($p = 0.009$), and the False Beliefs Task ($p = 0.06$). While more MS than control participants were impaired on a measure of information processing speed (the Symbol Digit Modalities Test; 38% versus 6%), it did not account for the differences in ToM performance.

Conclusions: Social cognition may represent an area of cognitive functioning affected by MS in the pediatric-onset population. These processes are especially important to study in younger patients as they may have long range implications for social adjustment, employment, and well-being.

Introduction

Usually considered as an adult disease, multiple sclerosis (MS) also affects children and adolescents with an estimated frequency of 0.5 to 1.0 per 100,000.[1] Pediatric-onset patients represent the youngest MS subgroup.[2] Acquiring an unpredictable central nervous system (CNS) disease during development could lead to unique challenges which can have significant therapeutic implications.

Social cognition refers to the cognitive processes governing social situations.[3] Theory of Mind (ToM), a core social cognition construct, requires one to infer the mental state of another, with attributions to their knowledge, beliefs, and emotions.[4,5] ToM was first described in the characterization of autism spectrum disorders and frontal lobe injury.[4] Recently, ToM measures have been developed to identify subtle behavioral manifestations across a range of adult and pediatric neurodegenerative conditions.[7–9]

Social cognition differs meaningfully from other aspects of cognitive function. While correlated, social cognitive measures factor separately from neuropsychological measures and can link more strongly to real-world functioning.[8–12] Further, through compromise of social relationships and limit of social networks, individuals with these deficits may be at risk for cognitive decline.[7,9–13]

Differences in ToM among adults with MS relative to healthy controls include deficits in first- and second-order mental state attribution, detection of social faux pas, and in the recognition of emotion in faces and in characters.[8,13–20] Both affective and cognitive ToM deficits in MS have been

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found in otherwise cognitively intact participants[14,21] and appear to be independent from disease duration or level of neurologic impairment,[16,19] as well as symptoms such as fatigue and depressed mood.[13,16]

The purpose of this pilot study was to determine whether pediatric-onset MS is associated with impairment of social cognition. Previous studies have found that approximately one-third of pediatric MS patients have some degree of cognitive impairment.[22] However, no studies yet have addressed social cognition in this youngest MS subgroup. We compared performance in consecutively-recruited pediatric-onset MS to healthy control participants on affective and cognitive ToM tasks.

Method

Participants and procedure

The study was approved by the Stony Brook Institutional Review Board; in the case of minors, a parent provided consent, and participants signed assent forms.

MS participants were recruited through the Lourie Center for Pediatric MS and met criteria for pediatric-onset MS (i.e. disease onset prior to age 18 years).[2] MS participants were consecutively recruited between March and September 2013 during routine outpatient visits. Participants were excluded from this study if they were age 21 years or older, diagnosed with an additional neurologic disorder or other medical condition known to influence cognitive function, or if not fluent in English. At the time of testing, MS participants were required to have been steroid-free for 30 days or more and neurologically stable (i.e. at least 30 days past the last relapse).

Healthy control participants were recruited through community-based advertisements and reimbursed fifty dollars for their participation. Participants were required to be in good health without any current medical or psychiatric diagnosis, be fluent in English, have no current individualized education program (IEP), and have no history of head injury, seizures, or other neurologic illness.

Participants were administered a battery of ToM and neuropsychological tests administered by a clinical neuropsychologist or trained study psychometrician. Parents were also asked to complete demographic and study questionnaires. The set of measures for this study took approximately 45 minutes to complete.

Measures

MS participant clinical information. Diagnosis and MS subtype, Expanded Disability Status Scale (EDSS) score,[23] years of duration of illness, and total number of relapses were determined by the study neurologist (LBK) on the day of cognitive testing.

Estimated IQ. An index of general cognitive ability was provided with estimated Full Scale IQs using the Wechsler Abbreviated Scale of Intelligence (first and second editions, WASI and WASI-II).[24,25] For the MS participants, the four-subtest version was administered as part of a separate cognitive testing battery, often during a previous research visit. For the control participants, the two subtest version was administered along with the study battery measures as follows.

Theory of Mind (ToM)

Standard cognitive and affective ToM tasks were chosen to be similar to those that have been sensitive to detecting social cognition impairments in adults with MS. In all instances of narration, the participant was provided with a written copy of the story and questions to follow along and refer to in order to limit the contribution of attention, language processing, or memory functioning on task performance.

Reading the Mind in the Eyes Test – child version[26]. This ToM facial emotion recognition task requires recognition of emotional state in 28 photos of sets of eyes with a forced-choice from one of four descriptors. The initial MS participants over the age of 18 were administered a longer 36-item adult version that was prorated to a 28-item score for the purpose of analysis. When the adult version was administered, participants were provided with an accompanying sheet defining each adjective in the case that they were not familiar with any of the adjective descriptors that were listed.

Faux Pas Test – child version[5]. For this task, 10 short vignettes are read aloud to the participant featuring a character committing a social *faux pas.* The participant was asked questions addressing story comprehension, identification of the faux pas, and false beliefs (addressing the mental state of a character in the story). Correct answers for each of the three questions were tallied and averaged, with a possible total score of 10 (one for each story item). Instructions included a sample item of a control story (in which no *faux pas* is committed). As the original version was developed for use in the United Kingdom, certain words were changed to more familiar American versions (e.g. 'restroom' to replace 'loo').

First- and second-order false beliefs[27]. A narrated cartoon-illustrated vignette ("Bake Sale") was presented in which, after answering questions to confirm comprehension, the participant was asked two questions about what one character expects to find at a bake sale (first order), and one question about what one character thinks another character will find at a bake sale (second order), for a total of three possible points.

Table 1. Demographic characteristics.

Characteristic	MS (*n* = 28) mean (±sd) or %(*n*)	Control (*n* = 32) mean (±sd) or %(*n*)	*P*
Age	16.29 (±3.12)	15.69 (±2.94)	0.45
Female	68 (19)	72 (23)	0.78
Caucasian	52 (14)	81 (26)	0.11
Hispanic	50 (14)	28 (9)	0.02
Maternal education[a]	5.48 (±1.89)	7.07 (±1.24)	0.001
WASI FSIQ[b]	103.29 (±12.67)	108.06 (±13.82)	0.21

[a]*n* = 27 for MS participants vs. *n* = 27 for control participants.
[b]MS participants (*n* = 21) received 4-subtest WASI or WASI-II depending on time of testing as part of separate testing battery. Control participants (*n* = 32) received 2-subtest WASI-II with current battery.

Information processing speed

Symbol Digit Modalities Test (SDMT)[28]. The SDMT is a measure of speeded information processing sensitive to the detection of cognitive impairment in MS.[28,30,31] Using the oral condition to limit the influence of any motor slowing,[31] the participant is required to follow a key to name numbers matching abstract symbols arranged in rows as quickly as possible for 90 seconds.[28]

Empathy Systemizing Quotient (EQ-SQ) Child Version

Participants' primary caregivers were asked to complete the *Empathy Systemizing Quotient (EQ-SQ) Child Version*.[32] This questionnaire is a 55-item scale assessing the child's social behaviors and function, providing an Empathy Quotient (responding appropriately to the feelings of others) and a Systemizing Quotient (assessing an interest in the mechanical aspects of their surroundings). The questionnaire was or given to parents to complete during the visit or, when not possible at the visit, to return by mail.

Results

Demographic and clinical features

Participants were 28 individuals diagnosed with pediatric-onset relapsing–remitting MS and 32 healthy controls, with demographic features shown in Table 1. The groups did not significantly differ in age or gender. MS participants were 68% female and ranged in age from 8 to 20 years (MS) with a median age of 17 years. Control participants were 72% female and ranged in age from 8 to 19 years with a median age of 16 years.

While the groups did not significantly differ in proportion of Hispanic participants, the MS group had fewer Caucasian participants (52% Caucasian versus 81% for the controls, *p* = 0.02). The MS participants also had slightly lower maternal educational attainment corresponding to having, on average, completed two years of college vs. a

Table 2. Clinical characteristics of MS participants (*n* = 28).

Characteristic		Range
EDSS at testing	Median: 1.00	0.00–4.00
Disease duration	Mean: 33.86 (±30.11) months	1–97 months
Total relapses	2.46±2.44 relapses	0–9 relapses
Relapse rate	0.90±0.91 per year	0–3.50 per year

bachelor's degree (attainment scores of 5.48±1.89 versus 7.07±1.23, *p* = 0.007).

Twenty-one MS participants were administered the four-subtest WASI or WASI-II (depending on test date, switching to newer edition for those tested after March 2013) as part of a separate cognitive battery after their diagnosis of MS. For 17 of these participants, testing was on a separate date from the current study battery (averaging 1.71 months earlier, with a range of one to five months). However, longitudinal data from a separate sample of pediatric MS patients (*n* = 70) indicate that WASI-estimated FSIQs remain relatively stable over a period of up to four years (mean change in standard score= -0.26±7.69).[34] All control participants were administered the WASI-II two-subtest version. As also shown in Table 1, mean estimated FSIQ was within the average range for both groups (103.29±12.67 vs. 108.06±13.82, *p* = 0.21).

Clinical characteristics of the MS participants are shown in Table 2.

Theory of Mind tasks

To address the primary study hypothesis that MS participants would perform more poorly on ToM tasks than controls, a one-way between-groups multivariate analysis of variance was performed with total scores for the Eyes Test, Faux Pas Test, and False Beliefs Task as dependent variables. Of note, the False Beliefs Task included in the current analyses replaced an earlier pilot version, therefore it was not administered to the initial seven MS participants. The

Table 3. Performances on ToM tasks and SDMT.

Measure	MS n = 28 mean (±sd)	Control n = 32 mean (±sd)	P
Eyes Test	19.73 (±3.19)	21.75 (±2.49)	0.008
Faux Pas Test total	8.68 (±0.91)	9.24 (±0.69)	0.009
False Beliefs Task[a]	2.57 (±0.81)	2.88 (±0.34)	0.06
SDMT (z-scores)	−0.26 (±1.74)	0.44 (±1.19)	0.08

[a]MS n = 21; lower due to replacement of an earlier task after the study was underway.

groups significantly differed on the combined ToM variables ($F_{(3, 51)}$ = 3.94, p = 0.01; Wilks' Lambda = 0.81; partial eta square = 0.19). As shown in Table 3, the MS compared to the control group performed more poorly on the Eyes Test, $F_{(1, 51)}$ = 7.03, p = 0.001, the Faux Pas Test, $F_{(1, 51)}$ = 6.86, p = 0.01, and the False Beliefs Task, $F_{(1, 51)}$ = 3.58, p = 0.06.

Item subanalyses. Additional subanalyses compared the groups on three item subscores from the Faux Pas Test for each item addressing comprehension, faux pas identification, and false beliefs. The MS participants' lower performance was specific to the false beliefs component of their answers (p = 0.008), indicating that the groups equally understood the vignettes (comprehension p = 0.25) and identified the social missteps correctly (p=0.19). However, consistent with their lower performance on the False Beliefs Task, the MS participants were less accurate in identifying the intent and knowledge of a story character.

There were generally low number of errors in both groups on the three items of the False Beliefs Task items. The MS group made more errors for both first and second order items than the controls (29% versus 12% making at least one error), approaching significance for greater frequency of errors on the second order item (p = 0.08).

Demographic factors. Analyses comparing the MS to control participants on performance of the ToM tasks were repeated to control for age and other demographic factors with no change in the pattern of results. As noted above, the MS participants had significantly more racial diversity and lower maternal education levels. However, ToM performance in the MS participants, as measured by combined total ToM score, remained significantly lower when the group mean comparisons were repeated to control for race (Caucasian participants only, p = 0.04) and maternal education level (as a covariate) ($F_{(1, 50)}$ = 10.76, p = 0.002, partial eta squared = 0.18).

The groups did not significantly differ in age, estimated IQ, gender or ethnicity distribution. Combined ToM score remained significant when both age ($F_{(1, 53)}$ = 10.76, p = 0.002, partial eta squared = 0.18) and IQ ($F_{(1, 45)}$ = 9.66, p = 0.003, partial eta squared = 0.18) were included as a covariate. Results also did not alter when repeated to

control for gender (male only, p < 0.001, females only, p = 0.05), and ethnicity (non-Hispanic only, p = 0.002).

Clinical factors. For the MS participants, while nonsignificant, total number of relapses and longer disease duration were weakly to moderately correlated with poorer total ToM performance (r = −0.39 and r = −0.27, respectively). Relapse rate and EDSS were less predictive of ToM score (r = 0.13 and r = −0.17, respectively).

Information processing speed (SDMT)

The SDMT measured information processing speed and was scored and converted to age normative z scores for comparison.[28] The SDMT was not administered at the time of the testing for two of the MS participants. As shown in Table 3, the MS group scored lower than controls with a trend towards significance (p = 0.08). Ten (10) or 38% of the MS participants versus 2 or 6% of the control participants had scores in the impaired range (falling one standard deviation or more from the age normative mean).

SDMT performance was significantly moderately correlated with total ToM score and significant for the full sample (r = 0.35, p = 0.01). To determine whether information processing speed was a factor in ToM performance, a one-way between groups ANCOVA was conducted to compare the two groups on ToM total score using SDMT performance (SDMT age normative z score) as a covariate. After adjusting for SDMT z score, the MS participants' ToM performance remained lower than the controls, approaching significance ($F_{(1, 54)}$ = 4.04, p = 0.05, partial eta squared = 0.08).

Logistic regression was performed to assess the influence of information processing speed and ToM in predicting group membership (MS or Control), including the variables of SDMT z score and ToM scores for the Eyes Test, Faux Pas Test, and False Beliefs. The full model was significant, $X^2_{(5, N = 47)}$ = 12.05, p = 0.03, and correctly classified 83% of the cases. However, no one score had a uniquely significant contribution to the prediction model.

EQ-SQ inventory

Not all parents completed and returned the EQ-SQ inventory, resulting in scores for 18 MS participants compared to 16 controls. The groups did not significantly differ on EQ or SQ ratings, with close mean scores of 40.28±5.94 vs. 40.69±8.51 for EQ and 23.94±8.29 vs. 23.69±5.77 for SQ. Neither EQ nor SQ approached significance correlated with the ToM measures.

Discussion

In this pilot study, we found that 28 consecutively-recruited participants with pediatric-onset MS performed worse than

32 healthy controls on ToM tasks as a measure of social cognitive ability. The MS participants had lower performance on all study ToM tasks including both affective (Eyes Test) and cognitive (Faux Pas Test and False Beliefs Task) measures. Further item analyses of the Faux Pas Test indicated that the MS participants made errors on the questions addressing false beliefs. Therefore, they were able to understand the story and identify the social missteps of characters, but were not able to understand the informational perspective of another character. These are the types of errors that might be seen in a cognitively intact adolescent who is unable to understand the knowledge or intentions of another during a social interaction.

The ToM performance in the MS participants was not explained by demographic factors. As ToM continues to develop with increased age into adulthood, older age would be considered an advantage. However, age was not related to ToM performance in our sample and repeated analyses controlling for age did not change the findings. Repeated analyses also did not suggest a relation between other demographic factors including estimated IQ, race, ethnicity, gender, or maternal education. Among the MS participants, weak to moderate negative correlations were found between ToM performance and total relapses and disease duration, indicating a possible link between disease activity and reduced social cognitive ability.

ToM deficits in adult MS have been found in otherwise cognitively intact participants.[14,20] As findings in other conditions have suggested,[11,33] information processing may be an important mediator for social cognitive ability in MS. As expected, the MS participants had slower processing speed measured by the SDMT, with a 38% versus 6% of the control participants scoring in the impaired range. Nonetheless, when SDMT performance was controlled for, the group differences on the ToM measures remained, indicating that MS associated deficits in ToM ability and information processing speed may be independent processes.

The groups did not differ on the parent behavioral inventory measuring EQ or SQ. These findings suggest that parents are not observing problems with social functioning in MS relative to healthy control participants. However, this scale was developed to primarily detect the deficits that characterize autism spectrum disorders. Therefore, EQ and SQ may not be particularly sensitive to detect the more subtle differences in social functioning that may occur in MS. Future studies should include more detailed measures of real-world functioning including behavioral inventories more sensitive to the types of difficulties that may be associated with MS.

These initial findings in a pediatric-onset group extend the previous studies of social cognition in adults with MS. Of concern is that changes in social cognition can occur in an MS subgroup for whom the consequences of poor social cognition could be most problematic. Pediatric-onset MS patients resemble their adult-onset MS counterparts in that both MS groups perform more poorly on ToM tasks relative to controls. ToM deficits noted among those with adult-onset MS relative to controls include first- and second-order false beliefs, recognition of emotion in faces, and detecting social missteps depicted in film.[8,13-20] In adult samples, these findings have also been separate from disease duration and severity[26,19] as well as other measures of cognitive function.[16,21]

While statistically significant, the absolute differences between the two groups are relatively minor. Nonetheless, the MS participants' performance on the Eyes Test is comparable to that found in adolescents and young adults with other clinical disorders (i.e. adolescents with psychiatric impairment),[35] suggesting a generalized disadvantage for processing social information associated with a wide range of disorders.

The clinical meaningfulness of the poorer ToM performance requires additional study. It can be argued that even minor deficits in social cognitive ability could have major implications for functioning and continued development into adulthood. Identifying social cognitive deficits and intervening can be crucial in an adolescent's healthy development.

There are several limitations to the current study. First, this is a cross-sectional pilot study with a wide range of disease duration (one to 97 months). Second, we included only preliminary measures of ToM and follow-up studies should include more expanded assessment of these abilities. Additional measures of cognitive functioning, and executive functioning in particular,[32] could provide understanding of how these social cognitive processes relate to other areas of cognitive functioning affected by pediatric MS. Third, while the measures did not link to the parent-reported inventories, we did not include comprehensive measures of actual social functioning. These findings would be better understood in the context of an indicator of real-world social functioning (e.g. friendships, peer interactions, etc.). Finally, while age and other demographic factors did not appear to meaningfully contribute to social cognition performance in our study, future studies would benefit from more detailed matching of participants on these factors.

The finding of both cognitive and affective ToM deficits in pediatric-onset MS suggests that MS may influence social cognitive ability among adolescents even at the earliest stages of the disease. Interventions to promote socially rewarding behavior could enhance long term outcomes including the mitigation of risk-taking behaviors, optimization of career choice, and the ability to form and maintain lasting personal relationships.

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Conflict of interest

None declared.

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