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SOCIAL COGNITIVE OUTCOMES IN PEDIATRIC-ONSET VERSUS ADULT-ONSET MULTIPLE SCLEROSIS

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ABBREVIATIONS

AOMS: Adult-Onset Multiple Sclerosis

AOAMS: Adult-Onset Age-matched Multiple Sclerosis

AODMS: Adult-Onset Disease Duration-matched Multiple Sclerosis

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

BVMT-R: Brief Visuo-spatial Memory Test Revised

CVLT-II: California Verbal Learning Test-II

DMT: Disease-Modifying Therapy

EDSS: Expanded Disability Status Scale

FSIQ: Full Scale Intelligence Quotient

HC: Healthy Controls

MS: Multiple Sclerosis

PIQ: Performance Intelligence Quotient

POMS: Pediatric-Onset Multiple Sclerosis

RMET: Reading the Mind in the Eyes Test

RRMS: Relapsing-Remitting Multiple Sclerosis

SDMT: Symbol Digit Modalities Test

SPMS: Secondary Progressive Multiple Sclerosis

TeLPI: Irregular Word Reading Test

ToM: Theory of Mind

VIQ: Verbal Intelligence Quotient

ABSTRACT

Introduction: Cognitive impairment in classic and social domains has been consistently reported in patients with Multiple Sclerosis (MS). However, little is known about the cognitive outcomes, particularly on social cognition, in adults with pediatric-onset MS (POMS). The primary objective of this study is to compare the cognitive performance of adults with POMS and adult-onset MS (AOMS), with particular interest on social cognition.

Methods: A group of 30 patients with POMS (age of MS onset <18 years) was compared with age-matched (AOAMS, n=30) and disease duration-matched (AODMS, n=30) patients who developed MS after the age of 18 years. Cognitive performance was assessed using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and Theory of Mind (ToM) tests.

Results: Cognitive impairment was more prevalent in POMS patients (40% vs. 16.7%, p=0.045), independent of age or disease duration, affecting more severely information-processing speed and visual memory domains. No statistically significant differences were found in ToM performance between patients with POMS and AOMS. When analyzing ToM performance according to age of disease onset (≤15 years; 15-20 years; ≥20 years), patients with disease onset ≤15 years old had significantly lower scores on ToM tests when compared to the other groups.

Discussion: The interference of POMS with critical neurodevelopmental periods, specific for each cognitive domain, may explain the differing outcomes at adulthood on social and classic cognition.

Conclusion: Patients with POMS are more prone to develop impairment on classic cognitive domains than on ToM abilities, when compared with AOMS patients.

KEY WORDS

Multiple Sclerosis; Pediatric-Onset; Adult-Onset; Social Cognition; Theory of Mind

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating disease that affects the central nervous system, with its peak incidence during young adulthood. However, it is estimated that in 3% to 10% of the whole MS population the disease onset occurs before the age of 18 years, classified as Pediatric-onset Multiple Sclerosis (POMS).[1]

There are several reported differences between POMS and adult-onset multiple sclerosis (AOMS), particularly regarding clinical manifestations and inflammatory activity.[2–4] Those in which MS has manifested for the first time before reaching adulthood appear to be more vulnerable to inflammation and axonal loss.[5] Conversely, some studies argue that in younger ages there are enhanced compensatory abilities and a higher capacity to recover from damage, that act as protective factors.[6]

Research has consistently found that approximately 30% of pediatric patients with MS have cognitive impairment,[7–9] which is somewhat less than what is typically reported in AOMS.[10] However, when analyzing the long-term outcomes, it was found that patients with POMS were more likely to experience cognitive impairment in adulthood than patients with AOMS.[11] In POMS, the cognitive domains affected are similar to AOMS, including information-processing speed, working memory, and visuo-spatial processing; nonetheless, there have been additional findings of impact on language, which is not typical in AOMS.[7]

More recently, there has been accumulating evidence suggesting that social cognition is also prominently affected in MS.[12] One essential aspect of social cognition is Theory of Mind (ToM), which is the ability to infer about others' mental states and understand their intentions, beliefs and desires.[13] While ToM has already been reported as an ability that is significantly impaired in children and adolescents with MS,[14] to the best of our knowledge, the outcomes on social cognition of patients with POMS who have entered adulthood remain undetermined.

During a period in which brain maturation should be occurring in order to acquire certain cognitive skills and reach pivotal neurodevelopmental milestones, patients with POMS are going through inflammatory and neurodegenerative aggressions that may compromise neural pathways involved in the functioning of social cognition. Thus, it is crucial to understand the magnitude of MS's impact during critical neurodevelopmental stages and how it translates into social cognitive performance in adulthood. Moreover, these processes are especially important to study in POMS as they may have far-reaching implications for social adjustment, employment, and well-being.

Therefore, the primary objective of the present study is to compare the long-term outcomes regarding both classic and social cognition in POMS and AOMS, with particular interest on establishing the impact of MS's onset during childhood and adolescence to longstanding social cognitive impairment in adulthood.

METHODS

Study population

In this cross-sectional study, a group of patients with POMS (n=30) was compared with two cohorts of AOMS patients: one matched for age (AOAMS, n=30) and the other for disease duration (AODMS, n=30).

The POMS group consisted of adults with current age between 18 and 55 years, who had the onset of MS before the age of 18 years, with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) disease course, and regularly followed in the Neurology department of Centro Hospitalar e Universitário de Coimbra. For the AOMS groups (AOAMS and AODMS), we enrolled patients with the onset of MS after the age of 18 years, current age inferior to 55 years, and RRMS or SPMS disease course. The AOAMS group was matched with the POMS cohort on age, sex and educational level, whereas the AODMS group consisted of patients who were matched with the POMS cohort on disease duration, sex, and educational level.

Additionally, two groups of healthy individuals were recruited from the community and served as healthy controls (HC): one group was matched on age, sex and educational level with POMS patients and AOAMS patients (HC-A, n=30) and the other was matched on the previously mentioned characteristics with the AODMS group (HC-B, n=30).

Exclusion criteria for all participants were history of neurological (other than MS in POMS and AOMS groups) or systemic disease; history of head injury resulting in loss of consciousness; history of psychiatric illness, with the exception of stable mild to moderate depressive symptoms; a significant visual, auditory, or language impairment that would incapacitate their ability to satisfactorily understand test instructions and complete the tasks; current or prior use of antipsychotic medication; alcohol, drug, or substance abuse; starting or stopping antidepressants in the previous 2 months; and, for MS patients, a relapse or corticosteroid treatment in the 8 weeks prior to evaluation.

All participants provided written informed consent before entering the study, which was approved by the ethics committee of Centro Hospitalar e Universitário de Coimbra.

Clinical Assessment

A full medical history and detailed neurologic examination were obtained from all patients. The following data were collected: age, sex, handedness, educational level, age of MS onset, age of MS diagnosis, disease duration, clinical subtype of MS, first disease-modifying therapy (DMT) and current DMT. Neurological disability was evaluated using the Expanded Disability Status Scale (EDSS). For HC, medical history was obtained by an interview preceding cognitive assessment.

Neuropsychological evaluation

Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

The Brief international Cognitive Assessment for Multiple Sclerosis (BICAMS) is a short neuropsychological battery recommended as a validated and standardized international screening test for cognitive impairment in MS.[15,16] BICAMS comprises 3 instruments - the learning trials from California Verbal Learning Test-II (CVLT-II)[17] and Brief Visuo-spatial Memory Test Revised (BVMT-R);[18] and the Symbol Digit Modalities Test (SDMT),[19] oral version.

The raw scores of CVLT-II, BVMT-R and SDMT were converted into T scores, using available normative values, with corrections for age, sex and education.[16]

Performance in each test was considered impaired when the T score was equal or below the 5th percentile and cognitive impairment was defined by one or more abnormal tests.[16]

Theory of Mind Testing

1. Reading the Mind in the Eyes Test (RMET)

The revised version of Reading the Mind in the Eyes Test (RMET) has been greatly used across studies as a tool to evaluate the performance in ToM. This test consists of 36 black-and-white pictures of the eye region, surrounded by 4 words describing complex mental states.[20] For each image, only one of the four words correctly characterizes it. In this task, participants were asked to verbally select one of the words, based on their perception of what mental state was represented in each picture.

Correct answers were rated 1, incorrect answers were rated 0. The total raw score ranges from 0 to 36, with higher scores indicating better performance.

2. ToM Videos Test

This component of ToM testing was designed to mirror typical situations that may be encountered in everyday-life's social interactions. It is an adaptation from Sullivan and Ruffman[21] consisting of 26 silent colored videos with characters interacting. Each video is played for a few seconds and, along with it, 2 words describing thoughts or feelings are shown on the screen. Participants were asked to verbally select the word that best applied to a person in the video.

Correct answers were rated 1, incorrect answers were rated 0. The total raw score ranges from 0 to 26, with higher scores indicating better performance.

Irregular Word Reading Test (TeLPI)

The premorbid intelligence of each participant was assessed through the use of the Irregular Word Reading Test.[22] TeLPI consists of 46 infrequent and irregular Portuguese words, which the participants were asked to read aloud. The number of words pronounced incorrectly was then applied to regression formulas that incorporate sociodemographic variables (years of education), allowing for the determination of three parameters- Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ).

Statistical analysis

The independent samples t-test was used for two-group comparisons to assess the differences in means of continuous demographic variables such as age, years of education, FSIQ, age of onset, age of diagnosis and disease duration; and in means of scores on cognitive tests. For qualitative variables, such as female to male ratio, frequency of clinical subtypes and frequency of cognitive impairment, the Chi Square test was used. The Mann–Whitney test was used to compare the EDSS median between the study groups.

Finally, to further investigate the relationship of age of MS onset with neuropsychological performance at adulthood, the samples of MS population were divided into three subgroups according to age of disease onset (≤15 years; 15-20 years; ≥20 years) and the scores on

cognitive tests were compared using the one-way analysis of variance (ANOVA). Then, these groups were also compared controlling for age and disease duration using the analysis of covariance (ANCOVA).

All tests were performed two-tailed and statistical threshold was set at $p<0.05$. Statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Sample characteristics

The demographic and clinical differences of the study groups are summarized in **Table 1**. POMS and AODMS patients were matched on disease duration, sex and educational level but patients with POMS were younger at onset, at diagnosis and at the timepoint of evaluation ($p<0.001$). In contrast, POMS and AOAMS did not have significant differences on the current age, sex and educational level but the POMS group had a longer disease duration and was younger at onset and at diagnosis ($p<0.001$). Statistically significant disparities between POMS and AOMS groups concerning other variables were not identified.

Table 1. Demographic and Clinical Characteristics of the Study Groups

	POMS (n=30)	**AOAMS (n=30)**	**AODMS (n=30)**	**HC-A (n=30)**	**HC-B (n=30)**
Age in years, mean (SD)	30.4 (8.8)	33.9 (4.9)	39.0 (7.8)	30.8 (7.1)	36.4 (8.0)
Female, n (%)	21 (70%)	20 (66.7%)	20 (66.7%)	21 (70%)	21 (70%)
Educational level in years, mean (SD)	13.3 (2.8)	13.9 (3.5)	14.4 (3.9)	14.0 (4.2)	14.6 (4.1)
FSIQ, mean (SD)	114.0 (11.8)	114.6 (9.8)	116.8 (11.0)	115.8 (9.5)	117.9 (8.4)
Age of onset in years, mean (SD, min-max)	14.9 (3.0, 8-17)	26.1 (4.5, 19-34)	26.8 (5.5, 19-40)	-	-
Age of diagnosis in years, mean (SD)	18.1 (4.3)	28.2 (4.8)	29.5 (6.7)	-	-
Disease duration in years, mean (SD)	15.5 (9.1)	7.9 (4.6)	12.1 (6.1)		
EDSS, median (IR)	1.5 (1.1)	2.0 (1.0)	2.0 (1.1)	-	-
Clinical subtype, n (%)					
RR	27 (90%)	30 (100%)	27 (90%)	-	-
SP	3 (10%)	0 (0%)	3 (10%)	-	-

AOAMS: Adult-Onset Age-matched Multiple Sclerosis; AODMS: Adult-Onset Disease Duration-matched Multiple Sclerosis; POMS: Pediatric-Onset Multiple Sclerosis; HC: Healthy Controls; SD: Standard Deviation; FSIQ: Full Scale Intelligence Quotient; EDSS: Expanded Disability Status Scale; IR: Interquartile Range; RR: Relapsing-Remitting; SP: Secondary Progressive. HC-A serves as a control group for the POMS and AOAMS cohorts; HC-B serves as a control group for the AODMS cohort.

All patients were under treatment with disease-modifying drugs at the time of examination and there were no differences between the study groups regarding type of treatment.

MS groups (POMS and AOMS) and corresponding HC cohorts did not vary significantly on age, sex, years of education or FSIQ (**Table 1**).

Comparison of MS groups with Healthy Controls (HC)

As expected, cognitive performance was worse on the MS population (POMS and AOMS) compared to HC, on both social and classic cognitive domains (**Table 2**). Statistical significance was obtained overall ($p<0.05$), except for AOAMS versus HC-A in BVMT-R ($p=0.141$) and SDMT performance ($p=0.067$).

Table 2. Cognitive Performance of Study Groups

	POMS	AOAMS	AODMS	HC-A	HC-B
RMET raw score, mean (SD)	22.2 (6.9)	21.8 (4.3)	22.4 (4.4)	30.3 (4.2)	29.2 (3.6)
ToM Videos Test raw score, mean (SD)	19.3 (3.4)	20.0 (2.0)	20.5 (1.8)	23.6 (1.8)	23.0 (1.8)
CVLT-II T score, mean (SD)	46.8 (13.2)	48.6 (9.9)	49.5 (10.1)	54.1 (6.4)	55.8 (8.2)
BVMT-R T score, mean (SD)	41.5 (13.7)	50.8 (11.9)	52.4 (11.0)	54.6 (6.9)	58.4 (5.6)
SDMT T score, mean (SD)	41.9 (12.6)	46.4 (8.7)	47.9 (8.3)	51.0 (10.2)	54.4 (8.6)

AOAMS: Adult-Onset Age-matched Multiple Sclerosis; AODMS: Adult-Onset Disease Duration-matched Multiple Sclerosis; POMS: Pediatric-Onset Multiple Sclerosis; HC: Healthy Controls; SD: Standard Deviation; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test. HC-A serves as a control group for the POMS and AOAMS cohorts; HC-B serves as a control group for the AODMS cohort.

Cognitive performance of POMS versus AOMS matched by disease duration (AODMS)

The POMS cohort performed inferiorly to the AODMS group in all cognitive tests of the BICAMS battery, with statistically significant differences in BVMT-R and SDMT ($p<0.001$ and

p=0.032, respectively) (**Table 2, Figure 1**). Regarding ToM tests, performance was not significantly different between the two groups.

Prevalence of cognitive impairment defined by BICAMS was also analyzed in each cohort. The prevalence of cognitive impairment in POMS patients was 40% (n=12), whereas in the AODMS cohort it was 16,7% (n=5) (p=0.045).

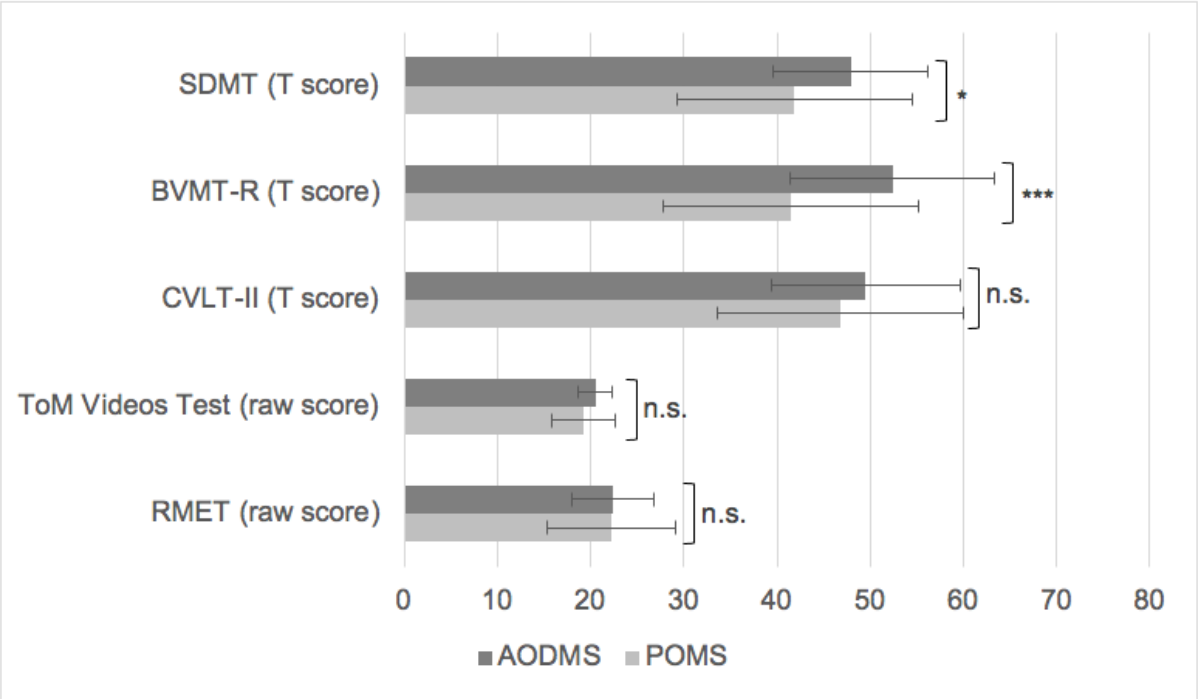

Figure 1. Cognitive Performance in POMS versus AODMS. AODMS: Adult-Onset Disease Duration-matched Multiple Sclerosis; POMS: Pediatric-Onset Multiple Sclerosis; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test. Statistical significance: ***p<0.001; **p<0.01; *p<0.05; n.s.: non-significant.

Cognitive performance of POMS versus AOMS matched by age (AOAMS)

The POMS group scored lower than the AOAMS cohort in the three components of the BICAMS battery, with significant differences found in BVMT-R (p=0.007) (**Table 2, Figure 2**). Regarding ToM tests, performance was not significantly different between the two groups.

The prevalence of classic cognitive impairment in the AOAMS cohort was 16.7% (n=5), significantly less frequent than in POMS patients (40%, n=12, p=0.045).

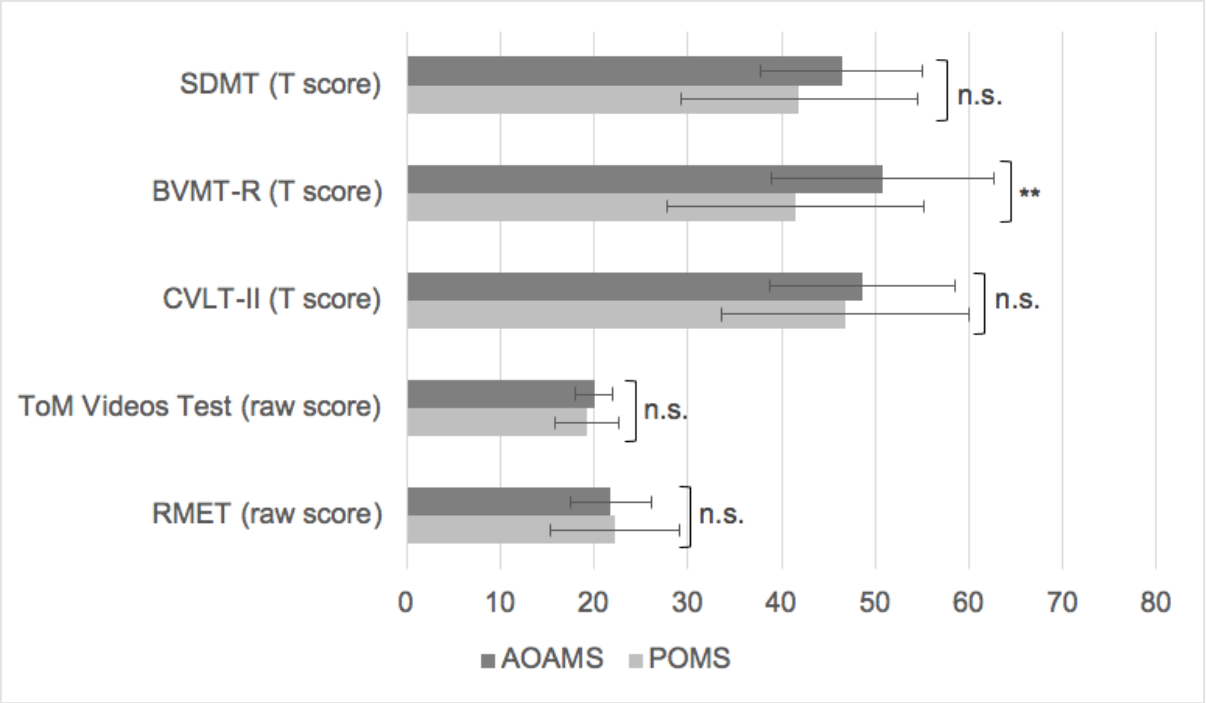

Figure 2. Cognitive Performance in POMS versus AOAMS. AOAMS: Adult-Onset Age-matched Multiple Sclerosis; POMS: Pediatric-Onset Multiple Sclerosis; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test. Statistical significance: ***p<0.001; **p<0.01; *p<0.05; n.s.: non-significant.

Effect of age of MS onset on cognitive performance at adulthood: exploratory analysis

An exploratory analysis was also performed to assess the variation of performance in cognitive tests with age of onset of MS (**Table 3, Figure 3**). For that purpose, the cohorts of POMS and AODMS were combined (n=60) and divided according to the age of disease onset in three groups: ≤15 years of age (n=10); 15-20 years of age (n=22); and ≥20 years of age (n=28).

Performance in RMET and ToM Videos Test for the group with disease onset ≤15 years old was considerably poorer when compared to the other two groups. Statistical significance was met for RMET performance when comparing the group with disease onset ≤15 years old and the cohort with disease onset between 15 and 20 years old (p=0.041); and for ToM Videos Test with the group with disease onset ≤15 years old compared to the cohort with disease onset between 15 and 20 years old (p=0.016) and to the cohort with disease onset ≥20 years old (p=0.004).

After adjusting for age, these results remained significant and patients with disease onset ≤15 years old had significantly lower scores on RMET (F=4.96; p=0.01) and ToM Videos Test (F=6.21; p=0.004) when compared to the other groups. After adjusting for disease duration, only the differences on ToM Videos Test performance remained significant, with patients with disease onset ≤15 years old having lower scores (F=3.44; p=0.039).

Regarding BICAMS, the group with MS onset ≥20 years old had the highest T scores in all three components (CVLT-II, BVMT-R and SDMT). Statistically significant differences were attained for BVMT-R when comparing the groups with disease onset ≥20 years old and disease onset between 15 and 20 years old (p=0.003).

After adjusting for age and disease duration, these results remained significant (respectively: F=6.8, p=0.002; F=4.59, p=0.014).

Similar results were found when analyzing the cohorts of POMS and AOAMS combined (**Annex I**).

Table 3. Cognitive performance according to age of MS onset

	Age of MS onset		
	≤ 15 years (n=10)	**15-20 years** (n=22)	**≥ 20 years** (n=28)
RMET raw score, mean (SD)	19.5 (6.9)	23.9 (6.5)	22.0 (4.2)
ToM Videos Test raw score, mean (SD)	17.6 (3.3)	20.1 (3.1)	20.5 (1.8)
CVLT-II T score, mean (SD)	48.3 (14.5)	46.9 (12.6)	49.1 (10.3)
BVMT-R T score, mean (SD)	44.9 (18.1)	41.1 (11.6)	52.3 (11.2)
SDMT T score, mean (SD)	43.1(12.9)	42.5 (13.2)	47.4 (7.8)

MS: Multiple Sclerosis; SD: Standard Deviation; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test.

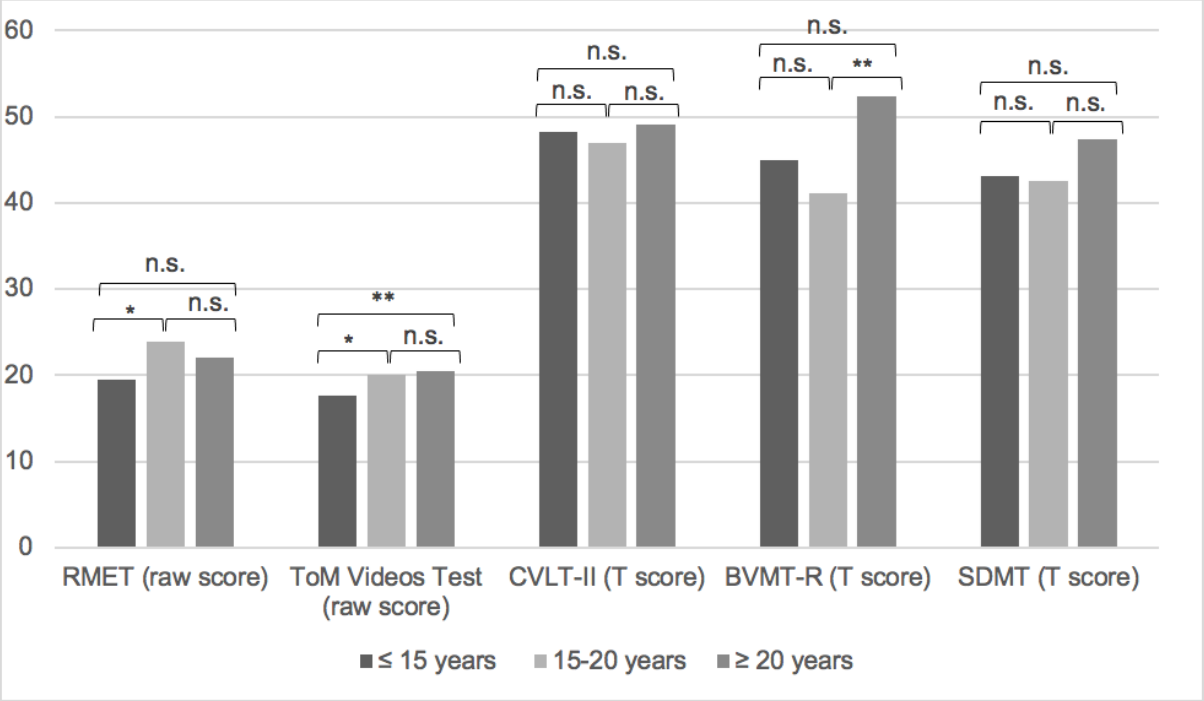

Figure 3. Cognitive performance according to age of MS onset. RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test. Statistical significance: ***p<0.001; **p<0.01; *p<0.05; n.s.: non-significant.

DISCUSSION

The results obtained in the present study confirm that, in adulthood, patients with POMS were more likely to have cognitive impairment than patients with AOMS, independently of age or disease duration. Moreover, patients with MS (both POMS and AOMS) revealed worse performance on ToM tests compared to HC, reinforcing the growing evidence that social cognition is impaired in MS. However, there were no significant differences in ToM performance between patients with POMS and patients with AOMS.

Conjecturally, we were expecting that social cognitive impairment would behave along the lines of other cognitive domains and that patients with MS-onset before 18 years of age would have poorer performance in adulthood than those who developed MS as adults. Nevertheless, our results revealed otherwise and support the emerging understanding that impairment on classic and social cognitive domains may be dissociated.[23,24]

Although not entirely independent from other cognitive domains, social cognition appears to represent a separate entity of cognitive functioning.[25] The acquisition of social cognitive competences is seemingly different from the one of other cognitive skills, translating into a different pattern of neurodevelopmental stages and milestones.

Research conducted in the field of social cognition has highlighted that ToM is established early in life, by the age of 3 to 5 independently of culture, and comprises distinguishable but overlapping affective and cognitive components.[26] The ToM tests used in this study mostly, however not exclusively, are associated with the affective component and allow to assess the first stage of attribution of ToM, based on facial expressions and eye gaze: the attribution of the type of mental state (i.e. disgust).[20] Evidence for this level of processing appears to be already present in the earliest years of life.[27] Nevertheless, there are other stages of ToM attribution, such as inferring the content of a mental state (i.e. disgust for his colleague's attitude), that involve more complex socio-emotional levels and appear to continue developing subsequently, during late childhood and adolescence.[28]

Some general predictions made about the construction of the social brain network state that it will emerge as a whole during infancy and early childhood, whereas specialization within this network will occur in later stages of neurodevelopment.[29] However, this fine tuning of the social brain can only be accurately grasped through the use of other ToM tasks rather than RMET and ToM Videos Test as these two tasks mostly rely on the first stage of attribution of ToM. Taking this into consideration, the tests used in this study to evaluate social cognitive deficits target competences that have already emerged before the pathologic aggression posed by

MS comes into play. As a matter of fact, disease onset in our POMS cohort was mostly during adolescence (mean age 14.9 years; minimum 8 years), making this a possible explanation for the merely subtle differences between POMS and AOMS groups' performances in RMET and ToM Videos Test. On the other hand, when analyzing ToM performance according to age of disease onset, we found that patients with MS onset before or at the age of 15 years have poorer performance than those with disease onset during late adolescence and young adulthood. Thus, we could hypothesize that patients with very early POMS may have significant impairment on the first stage of attribution of ToM, while those with POMS during later adolescence may have deficits on more complex stages of ToM attribution which are not revealed by RMET and ToM Videos Test. Such an interpretation is, of course, speculative and would require further studies with new ToM tests that better capture the stepwise acquisition of different social cognitive competences.

Regarding classic cognition, we found that POMS appears to render patients particularly susceptible to cognitive impairment at adulthood, particularly on information-processing speed and visual memory domains. These results are in line with the few cross-sectional studies which have directly compared cognitive outcomes of patients with POMS who have entered adulthood with AOMS patients.[11,30,31] The mechanisms by which MS onset at childhood and adolescence influences cognitive outcomes are not fully understood. It has been proposed that inflammation of the brain during critical neurodevelopmental periods, including myelinogenesis in adolescence, may irreparably damage neural networks involved in classic cognitive domains.[32] In fact, the reduced brain and deep gray matter volumes that have been reported in POMS patients in adulthood may be attributed to this mechanism.[2]

Another possible hypothesis for the higher susceptibility to cognitive impairment in POMS is the interference with the mechanisms of neuroplasticity. A growing body of literature[6,33,34] has integrated the concept of neuroplasticity into understanding the brain's ability, or lack of such, to compensate for damage induced by MS. Adolescence has been pointed out as a period during which the brain has enhanced compensatory abilities that act as a protective factor against aggressions, particularly in what concerns cognition.[35] Thus, MS onset during this critical period may halt the full development of these compensatory mechanisms and therefore patients with POMS may become subject to the effects of MS-induced damage and brain aging at an accelerated rate. Conversely, the role of neuroplasticity in limiting social cognitive impairment in patients with MS is yet to be clarified.

There are a few limitations that can be attributed to this study. First, the tests used to assess ToM performance rely exclusively on visual stimuli, static (such as in RMET) or dynamic (such

as in ToM Videos Test), which in real-life circumstances are complemented by other social cues, namely voice intonation. Second, the investigator that conducted the cognitive tests was not blinded to the disease group status. Third, this is a cross-sectional study and therefore definite correlations cannot be established. Finally, the modest sample size restricted the robustness of the study.

In conclusion, this study reinforces the construct that social cognition develops independently from classic cognitive domains such as memory and information-processing speed and therefore differing outcomes at adulthood may arise in patients with POMS. When compared with AOMS, patients with POMS seem to be more prone to develop impairment on classic cognitive domains at adulthood than on ToM abilities. Our findings call for studies that clarify the difference in the development of classic and social cognition, as well as the manner in which MS interferes with 'critical periods' for each domain. Likewise, the role of neural compensatory mechanisms in patients with POMS deserves further investigation with longitudinal studies, in an attempt to comprehend the distinct pattern in which cognitive impairment on classic and social cognitive domains progresses in this population.

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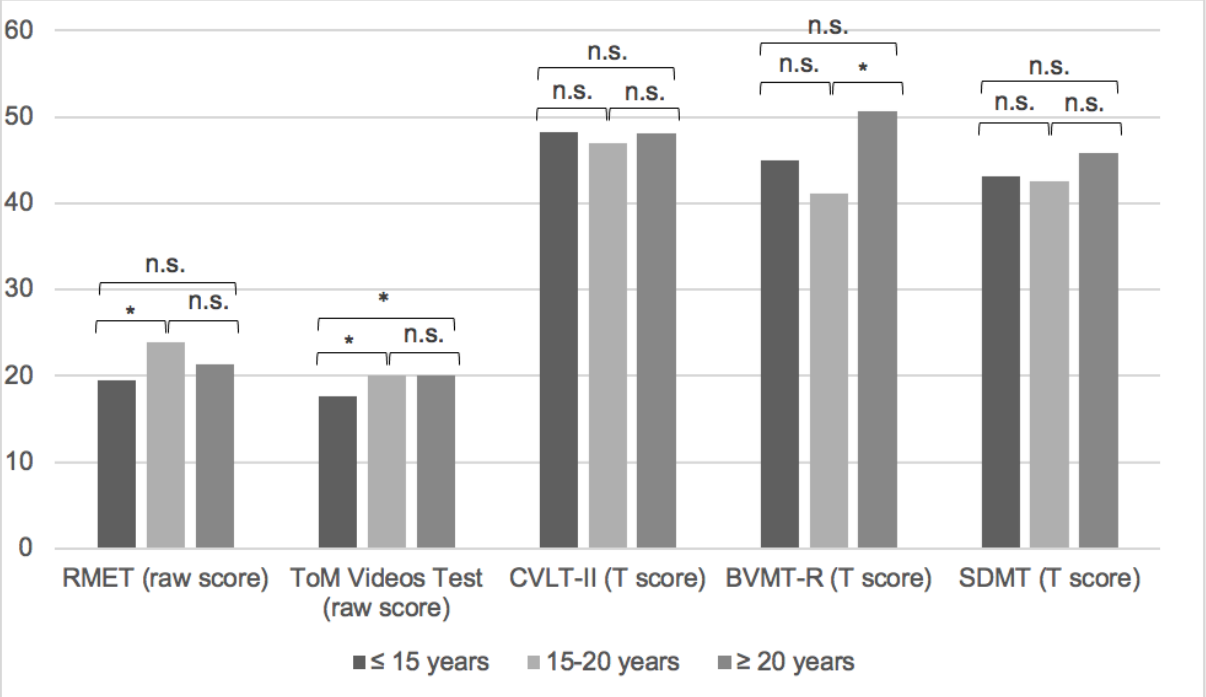
ANNEX I. Cognitive performance according to age of MS onset, POMS and AOAMS cohorts combined

Annex I, Table 1. Cognitive performance according to age of MS onset

	Age of MS onset		
	≤ 15 years (n=10)	**15-20 years** (n=22)	**≥ 20 years** (n=28)
RMET raw score, mean (SD)	19.5 (6.9)	23.9 (6.5)	21.3 (4.0)
ToM Videos Test raw score, mean (SD)	17.6 (3.3)	20.1 (3.1)	20.1 (2.0)
CVLT-II T score, mean (SD)	48.3 (14.5)	46.9 (12.6)	48.1 (10.0)
BVMT-R T score, mean (SD)	44.9 (18.1)	41.1 (11.6)	50.6 (12.2)
SDMT T score, mean (SD)	43.1(12.9)	42.5 (13.2)	45.8 (8.1)

MS: Multiple Sclerosis; SD: Standard Deviation; RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test.



Annex I, Figure 1. Cognitive performance according to age of MS onset. RMET: Reading the Mind in the Eyes Test; ToM: Theory of Mind; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuo-spatial Memory Test Revised; SDMT: Symbol Digit Modalities Test. Statistical significance: ***p<0.001; **p<0.01; *p<0.05; n.s.: non-significant.