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A 2-Year Longitudinal Neuropsychological Study in Relapsing-Remitting Multiple Sclerosis: A Selective Decline in Social Cognition?

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Abstract: Background/Objectives. Social cognition (SC), which implies the emotional and intellectual understanding of oneself and others, is an important facet of neuropsychological functioning concurrently to academic cognition (AC), which concerns non-social abilities (memory, language...). In relapsing-remitting multiple sclerosis (RRMS), it is not clear whether a cognitive decline occurs in both SC and AC nor whether a link exists between these two cognitive domains. The objective of the present longitudinal study was to conduct an extensive examination of both AC and SC in RRMS to document a 2-year evolution and to look for potential correlations between AC and SC. Methods. The neuropsychological results (AC and SC) of 48 RRMS patients obtained in clinical practice were retrospectively considered; 38 of the patients (30 females) were assessed again about 2 years later. Non-parametric tests were applied to test the intra-group cognitive evolution (Wilcoxon) and the link between AC and SC evolution (Spearman). **Results.** Whereas AC showed a stability or an improvement of performances during the retest, SC presented the reverse pattern, with a stability or a significant decline in facial emotion (recognition and discrimination) and humor perception. No significant statistical correlation was found between the significant modification of AC and SC during follow-up. **Conclusions.** The short-term deleterious evolution observed selectively for SC in the present study suggests that SC should be selected as a cognitive marker for RRMS follow-up, and that extensive examination may be preferred to investigate specific SC changes.

Keywords: emotion; humor; emotion perception; anger; social norms

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1. Introduction

Multiple sclerosis (MS) often concerns young patients, entailing the responsibility for clinicians to choose the best care for their patients (treatment, cognitive care, adjustment of working hours) according to the evolution of symptoms associated with this disease. Among them, the impairment of academic cognition (AC), including memory, language, visuo-spatial abilities, attention, and executive functions, has been well demonstrated from cross-sectional studies [1]. With regard to AC evolution in this disease, longitudinal studies have reported either a decline [2–8] or discrepant results in AC evolution [9–13]. Although considered in many studies, the radiological predictors of a potential AC decline are still debated. From morphological brain imaging, meta-analyses suggest a medium prediction for longitudinal AC based on white matter and grey matter volumes, whole brain atrophy, and lesion characteristics [14–16]. Tensor diffusion imaging also seems able to predict AC decline in MS patients [17]. Among other prognostic biomarkers, the strong myelinization of the optic nerve suggests that AC worsening may be linked in MS to the lengthening of latency for visual evoked potentials [18] and to impairment in a double-step saccadic test [19].

In comparison with AC, social cognition (SC), which concerns the emotional and social inferences about ourselves and others, has been more recently investigated in MS patients [20]. A meta-analysis conducted in 2016 [21] concluded that there was a substantial body of evidence for an SC deficit in MS, including theory of mind and facial emotion recognition (especially for fear and anger), confirmed by later studies [22–26]. In relapsing-remitting MS (RRMS), 1/3 of patients have an SC deficit at an early stage (≤5 years of the disease duration, [27]). This subtype of MS may be less impaired than progressive MS [28–30]. The damage to SC may be present precociously, as observed in clinically isolated syndrome [31]. Difficulties in SC have been associated with a poor social and psychological quality of life ([32,33] for reviews). The possibility of a primary deficit in SC for MS patients versus a deficit secondary to AC impairment has been extensively investigated in recent years, but without any definitive conclusion being reached, whatever the subtypes of MS (see the meta-analysis by [34]). While some studies did not find a statistical link between AC and SC in MS [35–37], most reported marginal correlations, with statistical links only for some AC or SC variables (i.e., pragmatic and verbal fluency, [38]; theory of mind and emotion recognition and executive functioning, [39]; affective theory of mind with AC functions but neither cognitive theory of mind nor emotion recognition, [27]). A 3-year longitudinal study conducted in RRMS patients suggested a deficit in SC at baseline, as measured by a composite score (theory of mind, emotion recognition, empathy, [40]), that remained stable during the retest [40].

Despite the need for a comprehensive cognitive evaluation for both onset and follow-up of MS disease [41], most of the above-mentioned studies used an elementary assessment for AC (SDMT or short batteries) and SC (Reading in the mind test or short batteries). The objective of the present study was to retrospectively and longitudinally assess the neuropsychological functioning of RRMS patients (2-year follow-up). An extensive outcome measure of both AC and SC was applied. AC was documented with a complete clinical examination rather than isolated tests or short batteries targeting MS. Likewise, SC was assessed using a French battery developed for neurological patients [42–44] and by evaluating numerous SC abilities (facial emotion recognition and discrimination, facial expressive intensity judgment, first- and second-order theory of mind, faux-pas detection and comprehension, judgment of moral and conventional norms, judgment of social situations, humor identification). A worsening of both AC and SC performances during the retest as compared to the first assessment was expected. In view of the discrepant results reported in the literature on the association of the impairments in these two domains in MS [27,34–39], it was not possible to predict a potential correlation between AC and SC decrease.

2. Materials and Methods

2.1. Participants

The neuropsychological data (AC and SC) collected several years ago during 1 year of RRMS patients clinically seen for their annual neurological checkup in the neurology department of the Maison-Blanche hospital (Reims) were analyzed. Only patients who had given their written consent for the possible scientific publication of their anonymous results were included in the study (n = 48 RRMS patients; 38 females). The neuropsychological results obtained 2 years later for the same patients and with the same clinical assessment were also analyzed; patients provided a new written consent for this use. Progressive MS subtypes were not included because they are less frequently addressed to neuropsychologists than RRMS for this regular annual checkup and because of a greater loss of patients linked to more frequent relapses. For the RRMS patients included in the study, a loss bias of 10 patients was observed (seven patients long-lost, two patients with recent relapses, one refusal of consent, see Table 1) with respect to the first assessment. The final cohort included 38 RRMS patients (30 females; mean education level: 11.3 years ± 2.5 (median: 10.5; range: 9–17); mean age: 39 years ± 10.4 (median: 38.5; range: 17–59); mean EDSS 3 ± 1.5 (range: 1–6.5, median: 2.7); the mean disease duration was 9 ± 7.4 years (range: 1–39; median: 8).

In addition to the above criteria, inclusion implied: (i) that patients met the diagnosis of RRMS according to the 2017 revised McDonald criteria [45] with an Expanded Disability Status Scale score (EDSS [46]) ≤ 6; (ii) no history of relapse in the previous 4 weeks nor of any other neurological or psychiatric disease; (iii) a start of the treatment more than 3 months earlier; (iv) the preservation of auditory and visual acuity; (v) to be a native French speaker. Furthermore, none of the patients had received a bolus of steroids in the previous 4 weeks.

Table 1. Results of academic cognition. Significant differences between the two assessments are in bold. The asterisks indicate the significant differences which maintain when Bonferroni correction was applied (new threshold: $p < 0.00111$). AF indicate tests with an available alternate form. GB = Grober and Buschke test. For subtests of the WAIS-III, values correspond to the standard scores of this scale.

	First Assessment (Mean ± Standard Deviation)	**Second Assessment (Mean ± Standard Deviation)**	**Wilcoxon Test**
	Efficiency (WAIS-III)		
Global IQ	91.8 ± 13.2	95.7 ± 13.6	**W = 81, *p* < 0.001 ***
Verbal IQ	90.9 ± 14.8	93.1 ± 12.8	**W = 195.5, *p* = 0.03**
Performance IQ	90.7 ± 19	98.8 ± 16.1	**W = 119, *p* < 0.001 ***
Information	7.3 ± 2.7	8.3 ± 3.3	**W = 28, *p* < 0.001 ***
Digit memory (spans)	9.2 ± 2.8	9.8 ± 2.8	**W = 155, *p* = 0.04**
Arithmetic	8.8 ± 3	9 ± 3.1	W = 192, NS
Similarities	9.8 ± 3	9.6 ± 2.3	W = 340, NS
Picture completion	9.2 ± 3.1	11.2 ± 2.5	**W = 90, *p* = 0.002**
Cubes	8.8 ± 2.4	9.4 ± 3.3	W = 170, NS
Digit symbols	8.9 ± 2.7	9.2 ± 3	W = 177.5, NS
	Memory		
Forward digit span	6.1 ± 1.2	6.3 ± 1.9	W = 132, NS
Backward digit span	5 ± 1.4±	5.3 ± 1.7	W = 146, NS
GB Encoding ^{AF} (/16)	15.8 ± 0.4	15.7 ± 0.6	W = 22, NS
GB immediate free recall 1 ^{AF} (/16)	9.3 ± 2.5	9.5 ± 2.4	W = 216.5, NS
GB immediate free recall 2 ^{AF} (/16)	11.3 ± 2.2	11.6 ± 2.1	W = 194, NS
GB immediate free recall 3 ^{AF} (/16)	12.3 ± 2	12.4 ± 2.3	W = 272.5, NS
GB immediate total recall 1 ^{AF} (/16)	15.3 ± 1.1	15.3 ± 1	W = 114, NS
GB immediate total recall 2 ^{AF} (/16)	15.8 ± 0.5	15.7 ± 0.8	W = 255, NS
GB immediate total recall 3 ^{AF} (/16)	15.7 ± 0.6	15.9 ± 0.4	W = 8, NS
GB total immediate recognition ^{AF} (/16)	15.8 ± 0.5	16 ± 0	**W = 43, *p* = 0.02**
Neutral false recognition (/16)	0.03 ± 1.6	0 ± 0	W = 0, NS
GB delayed free recall ^{AF}	11.8 ± 2.9	12.5 ± 2.2	W = 160, NS
GB total delayed recall ^{AF}	15.6 ± 1.1	15.9 ± 0.3	W = 38, NS
Rey/Taylor immediate recall ^{AF} (/36)	17.3 ± 6.3	20.9 ± 6.6	**W = 480, *p* < 0.001 ***
Rey/Taylor figure delayed recall ^{AF} (/36)	16.8 ± 5.4	20.5 ± 6.4	**W = 89, *p* < 0.001 ***
Rey/Taylor figure delayed recognition ^{AF} (/24)	21 ± 1.6	20.1 ± 1.7	**W = 233, *p* = 0.02**

Table 1. *Cont.*

	First Assessment (Mean ± Standard Deviation)	Second Assessment (Mean ± Standard Deviation)	Wilcoxon Test
Language			
Token test (/163)	161.6 ± 1.6	161.8 ± 1.8	W = 45.5, NS
R fluency in 2 min	15.6 ± 6	17.3 ± 7	**W = 378.5, *p* = 0.03**
Fruits fluency in 2 min	21.8 ± 4.6	21.2 ± 3.9	W = 448, NS
DO 80 (/80)	76.4 ± 3.4	78.6 ± 2	**W = 475.5, *p* < 0.001 ***
Visuo-spatial abilities			
Bells Test number (/35)	33.6 ± 2	34.6 ± 0.7	**W = 275, *p* = 0.01**
Bells Test time (seconds)	138.9 ± 47.5	121.1 ± 42.9	**W = 502, *p* = 0.02**
Rey/Taylor figure copy [AF] (/36)	28.4 ± 3.4	28.3 ± 3.9	W = 266, NS
Executive functioning			
PASAT	54 ± 16.6	47.2 ± 7.8	W = 110, NS
Brixton (/55)	41.1 ± 7.4	44 ± 5.1	**W = 111, *p* = 0.002**
WCST categories number (/6)	5.5 ± 1.3	5.9 ± 0.8	W = 7, NS
WCST cards number (max 128)	83.2 ± 20.7	78.11 ± 11.9	W = 353, NS
WCST perseverative errors	8.5 ± 10.4	4.7 ± 2.7	**W = 401, *p* = 0.002**
WCST perseverative responses	10.5 ± 13.7	5.3 ± 3.5	**W = 606, *p* = 0.009**
WCST % conceptual responses	75.5 ± 19.1	80.7 ± 9.1	W = 215, NS
WCST failures to maintain set	0.4 ± 1	0.3 ± 0.6	W = 41.5, NS
Bimanual sequence (/1)	0.9 ± 0.3	1 ± 0.2	W = 2.5, NS
Finger tapping (/1)	0.9 ± 0.4	0.8 ± 0.4	W = 20, NS
Conflicting instructions (/1)	0.9 ± 0.3	1 ± 0.2	W = 2, NS
Go/No-go (/1)	0.8 ± 0.4	1 ± 0.2	**W = 2, *p* = 0.01**

2.2. Neuropsychological Assessment

Tables 1 and 2 present the neuropsychological abilities assessed for AC and SC, respectively. When an alternate form of the test was available, it was applied for the retest.

Table 2. Results of social cognition. Significant differences between the two assessments are in bold. AF indicate tests with an available alternate form.

	First Assessment (Mean ± Standard Deviation)	Second Assessment (Mean ± Standard Deviation)	Wilcoxon Test
Emotion recognition			
Emotion recognition total score (/60)	53.3 ± 8.3	52.2 ± 7.1	**W = 94, *p* = 0.04**
Emotion recognition for anger items (/10)	7.9 ± 2.6	6.9 ± 2.8	**W = 172, *p* = 0.01**
Emotion recognition for disgust items (/10)	9.1 ± 1.7	9.1 ± 1.6	W = 42, NS
Emotion recognition for happiness items (/10)	9.9 ± 0.3	9.9 ± 0.2	W = 2, NS
Emotion recognition for fear items (/10)	8.2 ± 2.6	8.3 ± 2.2	W = 74, NS
Emotion recognition for sadness items (/10)	8.6 ± 2.4	8.5 ± 2.1	W = 39.5, NS
Emotion recognition for surprise items (/10)	9.6 ± 0.8	9.6 ± 1	W = 24.5, NS

Table 2. *Cont.*

	First Assessment (Mean ± Standard Deviation)	Second Assessment (Mean ± Standard Deviation)	Wilcoxon Test
Emotion discrimination			
Emotion discrimination for easy identical pairs (/12)	11.9 ± 0.5	11.9 ± 0.4	W = 2, NS
Emotion discrimination for difficult identical pairs (/12)	10.9 ± 2.3	9.7 ± 3.2	**W = 25, *p* = 0.048**
Emotion discrimination for different pairs (/30)	27.1 ± 2.5	27.6 ± 2.6	W = 108.5, NS
Intensity judgment			
Intensity judgement for anger	3.1 ± 0.7	3 ± 0.7	W = 90, NS
Intensity judgement for disgust	3.3 ± 0.7	3.1 ± 0.6	W = 93.5, NS
Intensity judgement for fear	3.5 ± 0.6	3.6 ± 0.7	W = 171, NS
Intensity judgement for happiness	3.2 ± 0.7	3.3 ± 0.6	W = 136.5, NS
Intensity judgement for sadness	2.6 ± 0.7	2.5 ± 0.4	W = 102, NS
Intensity judgement for surprise	2.9 ± 0.6	2.9 ± 0.7	W = 90.5, NS
Theory of mind			
1st order [AF] (/9)	7.9 ± 0.8	7.9 ± 0.8	W = 234.5, NS
2nd order [AF] (/9)	7.3 ± 0.7	7.1 ± 0.8	W = 90.5, NS
Faux-pas [AF] (/14)	12.9 ± 2	12.4 ± 2.1	W = 137.5, *p* = 0.03
Social situation task			
Adapted social situations [AF] (/8)	7 ± 0.9	6.9 ± 0.8	W = 33, NS
Non-adapted social situations [AF] (/8)	7.6 ± 0.5	7.3 ± 0.6	W = 38.5, NS
Moral/conventional distinction task			
Initial permissibility for moral transgressions [AF] (/5)	4.7 ± 0.06	4.7 ± 0.06	W = 2, NS
Initial permissibility for conventional transgressions [AF] (/5)	4.6 ± 0.2	4.6 ± 0.1	W = 7.5, NS
Initial permissibility for normal situations [AF] (/5)	5 ± 0.1	5 ± 0.1	W = 9, NS
Gravity for moral transgressions [AF]	4.6 ± 0.4	4.5 ± 0.6	W = 160.5, NS
Gravity for conventional transgressions [AF]	3.6 ± 0.8	3.5 ± 1	W = 223, NS
Permissibility in generalization for moral transgressions [AF] (/5)	5 ± 0.1	5 ± 0.1	W = 2, NS
Permissibility in generalization for conventional transgressions [AF] (/5)	4.9 ± 0.2	4.9 ± 0.2	W = 13, NS
Permissibility in dependency for moral transgressions [AF] (/5)	5 ± 0.1	5 ± 0.1	W = 2, NS
Permissibility in dependency for conventional transgressions [AF] (/5)	4.9 ± 0.2	4.9 ± 0.2	W = 18, NS
Humor identification			
Funny items [AF] (/8)	6.5 ± 1.4	5.6 ± 2	**W = 35.5, *p* = 0.01**
Non funny items [AF] (/8)	7 ± 0.9	6.8 ± 1.1	W = 68, NS

Material to assess AC. The assessment of AC included global efficiency with a short form [47] of the French version of the WAIS-III [48] to measure global IQ, verbal and performance IQ (VIQ and PIQ), and several subtests ("Information" for semantic knowledge, "Digit memory" for attention and working memory, "Arithmetic" for mental calculation, and "Similarities" for verbal abstraction, corresponding to VIQ; "Image completion" for visual abstraction, "Cubes" for visual construction and "Digit-symbols" for speed processing in a grapho-motor task, corresponding to PIQ). Memory was assessed with previous digit spans for verbal short-term and working memory, the original and alternate forms of the Grober and Buschke test [49] for verbal episodic memory (which consists of an explicit encoding phase, three immediate free and cued recalls, an immediate recognition, and delayed free and cued recalls) and the Rey complex figure [50] or its alternate form, the Taylor figure [51], for visual episodic memory (which consists of an implicit learning with immediate and delayed free recall). The language abilities considered were comprehension (Token test, [52]), fluencies (fruits and the R letter test, [53]), and naming with the DO80 [54]. Visuo-spatial performances were assessed with the Bells Test [55] for spatial attention and the copy of the Rey/Taylor figure [50,51] for construction, i.e., the organization of visual elements. Executive functioning was explored with the Paced Auditory Serial Addition Test with a 3.0-s interstimulus interval (PASAT-3) [56] for updating; the Brixton Spatial Anticipation Test [57] for abstraction and flexibility assessed with a global score; the Wisconsin Card Sorting Test [58] for abstraction, flexibility and maintenance with different scores for each measure; the finger-tapping test [59] for motor rapid coordination; the conflict orders test [59] for motor flexibility; and the Go/No-go test [59] for motor inhibition.

For all these scores, higher scores mostly reflect better performances (more correct responses to questions of general knowledge for "Information", more digits correctly reproduced for "Digit memory", more mentally solved problems for "Arithmetic", more common correct similarities found between two concepts for "Similarities", more correct identifications of missing visual details for "Image completion", more correct visual arrangements reproduced for "Cubes", more correct written digits corresponding to symbols for "Digit-symbols", more given words from a 16-word list for Grober and Buschke, more written units from a figure for the Rey/Taylor complex figures, more oral orders correctly produced for the Token test, more given words for fluencies, more correctly named images for DO80, more crossed targets for the Bells Test, more succeeded additions for the PASAT, more spatial anticipated movements for the Brixton, more consecutive cards according to criteria for the Wisconsin Card Sorting Test. The manual coordination between index fingers during the finger-tapping test and between hands during motor rapid coordination, during the production of conflict orders and during the inhibition of motor response for Go/No-go were scored as success/failure. Only the time for the Bells Test assumes that a lower score reflects better performance. For the error scores, that is for acceptance of neutral distractors for the Grober and Buschke, for the production of perseverative errors and perseverative responses, and for the failures to maintain a set for the Wisconsin Card Sorting Test. A higher score indicates a bad performance.

Material to assess SC. The assessment of SC was based on a French clinical battery assessing social cognition (BCS, [42]) normalized from 155 French healthy participants and including an alternate form for all tests except those which imply the perception of facial emotions (no learning effect being observed for them). The recognition of facial emotions comprised the photographed face of the same female expressing six primary emotions (anger, disgust, happiness, fear, sadness, and surprise), with 10 intensity expressive levels for each emotion, making a total of 60 items. The discrimination of emotions was a task based on the same stimuli (24 identical; 30 different) presented in pairs with two levels of difficulty for identical pairs according to previous norms in healthy participants [42]. For pairs implying the same emotion, two intensities of this expression were selected to prevent a simple identical/different judgement based on non-emotional facial information. The intensity judgement task used the same stimuli for which the participant had to decide the degree of expressive intensity on a five-point scale applied to 30 items (five expressive intensities for six primary emotions). For these three tasks of the BCS, the face appeared for a duration of 5 s at the most. The task of humor identification consisted of drawings from the comic books of Claude Serre. Sixteen were selected for the original and alternate versions, respectively, with eight funny and eight non-funny items in each. The social situations task was inspired by the material of Dewey [60] and Blair and Cipolotti [61] and assessed the identification of social transgressions. Their short verbal sketches were normalized for a French population with 16 situations to judge (eight adapted, eight non-adapted) for each version of the test (original/alternate). The moral/conventional distinction task [43] was adapted from [62] and Blair and Cipolotti [61], but we transposed the situations outside school, with adults, and added normal situations as a complement to the original conventional transgressions (according to the law and social codes) and moral transgressions (hurting others physically or morally). There were five items for each of the three categories (normal situation, conventional transgression, moral transgression) and for each version of the test (original/alternate). One or five variables were collected depending on the response to the first judgement produced. Each situation was verbally described on the screen, and the participant had to initially decide if the situation was good or bad. If the situation was judged as good, the next item was presented. If the situation was evaluated as bad, four supplementary data were gathered: estimation of the gravity of the transgression (on a five-point scale), the reasons for this transgression (verbal justifications), a second estimation of the good/bad nature of the situation in the absence of a law prohibiting the action (generalization condition), and a last estimation of the good/bad nature with a human authority (minister, Nobel Prize winner, famous scientist, etc.) recommending the action (dependency condition). Each task of the BCS was preceded by several training trials.

The RRMS patients completed the AC and SC during a 1-day clinical hospitalization for the follow-up of their disease. The second assessment took place about 2 years after the first (1.7 year in mean ± 0.7 (range: 1–3, median: 2) in the same background. The session was conducted by the same neuropsychologist assessing both AC and SC on a single day (one in the morning and the other in the afternoon).

3. Results

As most of the data did not meet the assumption of normal distribution and homogeneity of variances, longitudinal evolution was tested with non-parametric Wilcoxon tests and correlations were assessed using the Spearman Rho test. For multiple comparisons and correlations, the Bonferroni-adjusted p-value was applied. Statistical analyses were performed using the Jamovi project (2022) (Jamovi (version 2.3), Computer Software retrieved from https://www.jamovi.org), and statistical significance was set at 0.05.

No significant difference was observed for the BDI (assessment 1: mean: 6.4 ± 9.7, median: 3, range: 0–56; assessment 2: mean: 4.6 ± 4.1, median: 3.5, range: 0–18) and the fatigue scale (assessment 1: mean: 67.7 ± 34.6, median: 78, range: 0–137; assessment 2: mean: 58.9 ± 35.4, median: 64.5, range: 0–112) between the two assessments (BDI: W = 244, NS; fatigue scale: W = 327, NS).

Table 1 shows the results of RRMS patients for the AC. Most performances were better during the retest in comparison with the initial test. This improvement was statistically significant for efficiency (global IQ; verbal IQ, in particular due to progress for the subtests Information, and Digit memory; performance IQ, because of Picture completion), episodic memory (better recognition for the Grober and Buschke test and for the two recalls of the Rey/Taylor figures and their recognition), language (higher phonemic fluency by R and naming with the DO80), visuo-spatial attention (with more items crossed out in a shorter time for the Bells Test), and executive functioning (better score for the Brixton and the Go/No-go test and less perseverative errors and preservative responses for the Wisconsin test). After Bonferroni correction, only six of these comparisons remain significant.

Table 2, which presents the results of SC, indicates conversely a slight but global decline in performances which was significant for the recognition of facial emotions (global score and anger in particular), the discrimination of emotions (for difficult identical pairs), and for humor identification (for funny items). With Bonferroni correction, none of these comparisons remains significant.

No statistical correlation was found between the significant changes in the two assessments for both AC and for SC and age, disease duration, and EDSS. For educational level, only marginal correlations were observed for verbal fluency (R letter) and for the perseverative errors and responses of the Wisconsin Card Sorting Test (Table 3).

Table 3. Correlations with the cognitive scores of AC and SC that progressed significantly between the two assessments and disease characteristics.

Scores Significantly Different Between the Two Assessments	Age	Education Level	EDSS at Baseline	Disease Duration
GB total immediate recognition AF (/16)	−0.1, NS	−0.15, NS	0.19, NS	0.07, NS
Rey/Taylor immediate recall AF (/36)	−0.05, NS	0.48, NS	−0.22, NS	−0.03, NS
Rey/Taylor figure delayed recall AF (/36)	−0.08, NS	0.15, NS	−0.27, NS	−0.12, NS
Rey/Taylor figure delayed recognition AF (/24)	−0.29, NS	−0.04, NS	−0.04, NS	0.1, NS
R fluency in 2 min	−0.22, NS	**0.048, *p* = 0.002**	−0.27, NS	−0.21, NS
DO 80 (/80)	−0.14, NS	−0.15, NS	0.22, NS	−0.14, NS
Bells Test number (/35)	−0.08, NS	0.009, NS	0.03, NS	−0.04, NS
Bells Test time (seconds)	−0.09, NS	−0.09, NS	−0.02, NS	0.1, NS
Brixton (/55)	−0.16, NS	−0.03, NS	−0.25, NS	−0.27, NS
WCST perseverative errors	−0.15, NS	**0.4, *p* = 0.01**	−0.17, NS	0.21, NS
WCST perseverative responses	−0.15, NS	**0.37, *p* = 0.018**	0.21, NS	0.26, NS
Go/No-go (/1)	−0.05, NS	0.23, NS	0.006, NS	−0.12, NS
Emotion recognition total score (/60)	0.17, NS	−0.27, NS	0.15, NS	0.09, NS
Emotion discrimination for difficult identical pairs (/12)	0.23, NS	−0.24, NS	0.3, NS	−0.06, NS
Funny items AF (/8)	0.15, NS	0.15, NS	0.19, NS	0.13, NS

No statistical correlation was found between the significant changes between AC, represented by the GIQ and SC for emotion recognition (Rho = 0.03, NS), for the emotional discrimination of difficult identical items (Rho = −0.21) and for funny items (Rho = −0.16, NS). AF indicate tests with an available alternate form. Significant correlations are in bold.

4. Discussion

This study on the 2-year cognitive evolution of RRMS patients, assessed for AC and SC with an extensive examination, suggests a surprising result, with better performances in AC contrasting with a worsening of SC performances during the retest. The increased performances obtained for AC neuropsychological tests is often observed in clinical practice, largely due to the memory of the first assessment (e.g., familiarization with the neuropsychological assessment, memory of some failed items from IQ, loss of implicit learning for the Rey figure [50], and knowledge of the proceedings for the Grober and Buschke test [49]). For a standardized protocol of cognitive follow-up and to control this retest bias, good practices recommend conducting two clustered visits to create a neuropsychological baseline from the second visit [63]. Unfortunately, the present retrospective study from clinical follow-up did not enable this methodological caution to be applied. However, the negative evolution of SC seems to contradict this beneficial retest and may indicate an even larger effect for SC.

Contrary to our hypothesis and to the results of a 3-year longitudinal study [40] showing a stability of a composite score of SC, worse SC performances were observed in our sample of RRMS patients about 2 years later. This longitudinal divergence may be based on the SC composite score previously used [40] as one-third of the score concerns a subjective self-assessment of SC (empathy quotient) which may escape patients' introspection. In the present study, we only analyzed real SC abilities, with tasks focused on specific SC processes (theory of mind, emotion perception, moral and conventional norms, humor. . .). The SC decrease was demonstrated here for facial emotion recognition (more especially anger), for facial emotion discrimination (difficult identical pairs), and for humor identification (funny items). The impairment for anger recognition was consensually reported in MS [21,26,35]. Difficulties in humor identification were more rarely and more recently demonstrated in RRMS [44,64]. A link was also suggested between humor and coping in this MS subtype [65]. Furthermore, changes in functional connectivity during resting-state (fMRI) appear to be correlated with SC impairment in RRMS patients [66–68]. Ziccardi et al. [40] suggested a longitudinal stability of SC in RRMS patients with normal AC. In the present study, we did not observe a significant correlation between the evolution of global AC (global IQ) and the significant worsening in SC. This result is compatible with the meta-analysis by Deskas and colleagues [34]. Nor did we find a correlation between SC evolution and EDSS, disease duration, age, or educational level.

As for the physiological causes of the SC worsening in RRMS, normal aging seems unable to account for this pejorative evolution. A study conducted on 372 participants, ranging from 18 to 101 years, indicated a decline in emotional perception after 55 years and better empathy and social behavior [69]. Only two patients older than 55 years were concerned in our study. We did not observe an improvement in moral judgements in our RRMS group, abilities particularly related to empathy. If this SC worsening in RRMS occurs as a specific consequence of the underlying demyelination, as previously suggested [66–68], it will have to be considered in future studies.

Another important question concerns the time of occurrence of SC impairment in RRMS, its nature and, subsequently, the possible rehabilitation and therapeutic plans. In several neurodegenerative or neuropsychiatric diseases such as frontotemporal dementia, Huntington's disease, and schizophrenia [70,71], SC deficit is a core diagnostic criterion, whereas it could emerge later for other diseases (Alzheimer's and Parkinson's). In RRMS, it would be useful in future studies to examine the two questions of an SC deficit as both a potential core diagnostic criterion and as a follow-up neuropsychological criterion. The links with ecological behavior should also be addressed in RRMS with supplementary questionaries and carer views. The lower longitudinal abilities shown here in these patients for facial emotion decoding and humor may hinder their emotional comprehension of others. One consequence of this may be social rejection due to inappropriate social responses. A second major consequence that needs to be observed in medical care could be inadequate comprehension of medical messages, which may lead to an absence of follow-up in extreme cases.

This very preliminary study has several methodological weak points, namely the assessment of only one subtype and a small number of RRMS patients, the lack of a second assessment to establish a more confident baseline, and a short follow-up duration. Another important limit concerns the multiple statistical comparisons. The coherence in the opposite evolution between AC and SC gives sense to our interpretation, but larger MS groups and/or longer longitudinal delay will be needed to test if the present significant differences will maintain even with Bonferonni corrections. If the higher sensitivity of SC to cognitive decline in MS as compared to AC is confirmed in future studies, it suggests that more specific tests should be used to assess the occurrence and progress of SC dysfunctions in this disease rather than more general stimuli (such as the Reading in the mind eyes test, for example, which has sometimes been considered as assessing emotional perception and sometimes the theory of mind). Considering the current important development of disease-modifying treatments for MS, more accurate longitudinal cognitive markers are needed [72], among which SC may represent a relevant candidate. If this longitudinal option was retained, a selection of the more noticeable SC symptoms should be applied in order to choose the most appropriate SC markers for the neuropsychological follow-up, or even to create a composite test from these SC markers for MS.

5. Conclusions

An impairment of SC is likely to put MS patients at a disadvantage in understanding themselves and others and to have an impact on social integration at work and in all social interactions, impacting their quality of life [32,33], independently of mood [73]. Having at our disposal cognitive markers to better trace SC follow-up and adjust the treatment and care should be a major target of neuropsychological research applied to MS.

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Data Availability Statement: Data were obtained from patients and are available from Nathalie Ehrlé at nehrle@chu-reims.fr if patients' permission is given.

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