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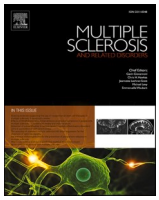

Original article

# Cognitive trajectories in relapsing-remitting multiple sclerosis: Evidence of multiple evolutionary trends

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A B S T R A C T

*Background:* Cognitive impairment (CI) frequently occurs in multiple sclerosis (MS) and is assumed to increase over time. However, recent studies have suggested that the evolution of cognitive status in patients with MS may be more heterogeneous than expected. Predicting CI remains also challenging, and longitudinal studies exploring the baseline determinants of cognitive performances are limited. No studies have explored the predictive value of patient-reported outcome measures (PROMs) regarding future CI.

*Objective:* To explore the evolutionary patterns of cognitive status in a cohort of RRMS patients initiating a new disease modifying treatment (DMT), and to determine whether PROMs may have a predictive value for future CI.

*Methods:* The present prospective study is a 12-month follow-up of a cohort of 59 RRMS patients who underwent yearly a comprehensive, multiparametric assessment combining clinical (with EDSS assessment), neuropsychological (BVMT-R, SDMT, CVLT-II), MRI-derived metrics and a set of self-reported questionnaires. Lesion and brain volumes were analyzed and processed by the automated MSmetrix® software (Icometrix®, Leuven, Belgium). Spearman's correlation coefficient was used to evaluate the association of collected variables. A longitudinal logistic regression analysis was performed to find baseline correlates of CI at 12 months (T1).

*Results:* A total of 33 patients (56%) were defined as cognitively impaired at baseline, and 20 (38%) were defined as impaired at follow-up after 12 months. The mean raw scores and Z-scores of all the cognitive tests were significantly improved at T1 ($p < 0.05$). There was a statistically significant improvement in most PROM scores at T1 ($p < 0.05$) in comparison with baseline scores. Among the variables assessed, lower education and physical disability level at baseline correlated with impaired SDMT (OR: 1.68, $p = 0.01$; OR: 3.10, $p = 0.02$, respectively) and impaired BVMT-R (OR: 4.08, $p$=<0.001; OR: 4.82, $p = 0.001$, respectively) at T1. Neither baseline PROMs nor MRI volumetric parameters were predictive of cognitive performances at T1.

*Conclusions:* These findings provide additional evidence that evolution of CI in MS may be a dynamic phenomenon and will not usually follow an inevitable, declining trajectory, and do not support the utility of PROMs in predicting CI in RRMS. The present study is still ongoing to determine whether our findings are confirmed at 2 and 3 years of follow-up.

## 1. Introduction

Cognitive impairment occurs in 40–65% of patients with MS (PwMS) (Amato et al., 2006). Cognitive decline may emerge in early stages of the disease, frequently affecting information processing speed, working memory, verbal and visual memory, and executive functions (Rao et al., 1991). CI considerably impacts the lives of patients with MS, especially employment status and health-related quality of life (HRQoL) (Langdon, 2011). Once apparent, MS-related CI is classically considered as permanent and is assumed to unequivocally result in progressive and widespread decline over time (Amato et al., 2001). However, contradictory findings have been reported by 2 recent studies showing that the cognitive performances of several MS patients defined as cognitively impaired at study entry were improved during follow-up (Skorve et al., 2020; Katsari et al., 2020). It was therefore suggested that CI in MS could be a dynamic phenomenon. Although they may improve patient-physician communication by focusing on the patients' perspective, patient-reported outcome measures (PROMS) are not yet an integral part of routine clinical care. Their usefulness as longitudinal outcome measures is not well established and there is still a lack of evidence that incorporating and focusing on more extensive measures of MS-related impairments provides prognostic information and improves prediction of disease course beyond the traditional indicators (van 't Hullenaar et al., 2021). A recent cross-sectional study showed

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[1] This manuscript is dedicated to Alice de Haan.

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correlations between processing speed and PROMs but investigations were limited to a single cognitive domain (Macaron et al., 2020). No longitudinal studies have explored the predictive value of combining a set of validated PROMs with clinical and MRI-derived measures on cognitive performances in a cohort of RRMS patients in a routine clinical setting. Based on these considerations, we aimed to evaluate the evolution of cognitive status in a cohort of RRMS patients initiating a new disease modifying treatment (DMT). In addition, the aim of this 12-month longitudinal study was to (a) investigate the relationships between PROMs, the clinical and cognitive status and quantitative MRI parameters, and (b) determine whether PROMs may have a predictive value for predicting future CI. We hypothesized that PwMS would exhibit different temporally evolving patterns regarding cognitive status, with stable, worsened or improved cognitive status at follow-up.

## 2. Patients and methods

### 2.1. Study design and study population

This 3-year prospective study (PROMS; B403201837614) was approved by the local institutional ethics review boards. All participants provided written informed consent prior to participation, following a complete description of the study. The study was performed in accordance with the Declaration of Helsinki in its currently applicable version.

The study protocol has been outlined previously (London et al., 2023). Briefly, 59 RMS patients initiating a new DMT underwent a multiparametric assessment including a full neurological examination performed by Neurostatus level-C certified examiners, with EDSS scoring, cognitive tests, a brain MRI, and PROMs, at baseline (T0) and after 12 months (T1). Inclusion criteria were as follows: (1) 18–60 years of age; (2) confirmed diagnosis of active RRMS justifying treatment; (3) relapse- and steroid-free for at least 1 month before inclusion. Exclusion criteria were: (1) presence of a medical condition besides MS or concomitant use of medications or substance abuse that might affect cognition; (2) presence of concomitant impaired visual or auditory performances limiting the ability to perform cognitive testing; (3) progressive forms of MS. Previous work on this cohort identified cross-sectional correlations between PROMs, cognitive and disability status, and structural MRI measures, at study entry (London et al., 2023). In this paper, we present follow-up data from evaluations after 12 months (T1).

### 2.2. Neuropsychological tests

As previously described (London et al., 2023), cognitive function was assessed using the three sub-tests of The Brief International Cognitive Assessment for MS (BICAMS): trial 1–3 of the revised Brief Visuospatial Memory Test (BVMT-R) for visuospatial memory and learning (Benedict, 1997); the oral version of the Symbol Digit Modalities Test (SDMT) as a measure of information processing speed (IPS), visual scanning and to a lesser extent working memory (Smith, 1982); the initial learning trials of the California Verbal Learning Test, second edition (CVLT-II) (Delis et al., 2000), for verbal learning and memory. The same versions of the SDMT and the CVLT-II tests were used for the repeated measurements. Parallel versions were used for the BVMT-R. Individual raw scores of each cognitive test were converted to standard z-scores based on normative data correcting for age-, gender-, and education (Maubeuge et al., 2021). On each cognitive variable, impairment was defined as a z-score $<$ - 1.5 standard deviation of the mean normative values. We considered patients as cognitively impaired when scoring below a z-score of -1.5 SD in one or more of the 3 cognitive tests (Dusankova et al., 2012).

### 2.3. PROMs

All of the following self-reported questionnaires were administered: the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI); the MS Impact Scale-29 (MSIS-29) version 2; the EMIF-SEP; the Dysexecutive Questionnaire (DEX-Q) of the BADS; the SEP-59 questionnaire, a French version of the Multiple Sclerosis Quality of Life questionnaire (SEP-59); the Work Role Functioning Questionnaire (WRFQ) second version; the Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23). Participants also completed the Treatment Satisfaction Questionnaire for medication (TSQM) at T1.

### 2.4. MRI acquisition protocol

The imaging data were acquired as previously described (London et al., 2023). In short, a brain MRI examination was performed in each participant as standard of care, using a standardized MS protocol on a 1.5T system (Magnetom Aera®; Siemens Healthcare®, Erlangen, Germany) at one institution, and two 3T systems (Magnetom Skyra® Siemens Healthcare®, Erlangen, Germany, and Philips Ingenia®, Philips Healthcare®, Best, The Netherlands) at the other, at both time points. The following sequences were included: 3-mm-thick axial transverse T2-weighted and diffusion-weighted views without interslice gap, 3-dimensional (3D) fluid attenuated inversion recovery (FLAIR), and 3D T1-weighted Gradient Echo (GRE) volumes. The anatomical data were processed by the MSmetrix® software (Icometrix®, Leuven, Belgium) to extract volumetric measurements for whole brain (WB), white matter (WM), (whole) gray matter (GM), cortical GM (CGM), deep gray matter (DGM), specific anatomic subsites of interest (thalamus, hippocampus, corpus callosum), and for lesion load volumes calculated on both 3D-FLAIR and T1 vol (Poullet et al., 2007). All measures were corrected for the intracranial volume and only normalized values were used for further analyzes. Quality check of the segmentation was performed by a trained neuroradiologist. In cases of unsatisfactory segmentation, values were excluded from the analyzes and constituted a blank in the database.

### 2.5. Statistical analyzes

JMP Pro 16.0.0 software was used for statistical analysis. Descriptive statistics are presented as absolute number (percentage) for discrete variables and mean $\pm$ SD for continuous variables as appropriate. The non-parametric Wilcoxon-Mann–Whitney test was used to assess group differences between cognitively impaired patients (CIP) and cognitively preserved patients (CPP) for not normally distributed demographic variables and EDSS. The bivariate correlations between the demographic characteristics, EDSS, cognitive performances, PROMs and MRI measures were explored using Spearman's correlation coefficients. *P*-values $< 0.05$ were considered statistically significant after false discovery rate-correction for multiple comparisons; corrected p values were reported. Correlations analyzes were not performed within MS patient subgroups according to level of disability, due to the small subgroup sample sizes. Preliminary univariate logistic regressions were carried out, to identify the significant predictors of impaired performance on the baseline objective cognitive measures (SDMT, BVMT-R, CVLT-II). The following independent variables were explored: sex, age (in years), education (in years), disease duration (in years), EDSS, all the PROMs and MRI metrics. The significant predictors of the univariate logistic regression ($p < 0.05$) were then tested in multivariate logistic regression analyzes adjusting on demographic data (age, sex, disease duration and education). Results are expressed as standardized beta coefficient, odds ratios and 95% confidence interval. For all analyzes, $p$ values $< 0.05$ were considered statistically significant.

## 3. Results

### 3.1. Demographic characteristics

Fifty-nine RMS patients (47 women, 12 men) were included at baseline, with mean age of 39.7 ± 9.8 years, mean disease duration 7.2 ± 7.5 years, and educational time in years 14.3 ± 2.5. Of these patients, 53 completed the multiparametric assessment at T1 (41 women, 12 men). Two patients were lost to follow-up (moved to another MS center), and 4 patients who missed the evaluation window but are still involved in the study for follow-up assessments planned at 24 and 36 months. Thirty-nine patients (66%) were employed at T0, and 37/53 (69.8%) were still employed at T1 ($p = 0.67$).

### 3.2. Clinical characteristics of the study population

Clinical data for the study population are summarized in Table 1.The median EDSS score was 2.0 (interquartile range 1.5–3.0) at inclusion and remained stable at T1 (median 2.0, interquartile range 1–5–3.0). At T1, 83% (44/53) of patients had either stable or improved EDSS scores. The patients' upper extremity functions were evaluated with the 9-HPT, and there was no statistically significant difference between the evaluations ($p = 0.6$ and $p = 0.9$ for dominant hand and non-dominant hand, respectively). Out of 53 patients with longitudinal follow-up, three patients experienced one relapse within the study period. At T0, 100% of the patients started a DMT and were still on active treatment at T1. One patient switched from dimethylfumarate to ocrelizumab because of the occurrence of a radiologically confirmed spinal cord relapse during the follow-up period, while the remaining patients had not changed their DMT.

**Table 1**
Clinical and neuropsychological characteristics at baseline and 12 months follow-up of the whole sample of relapsing MS patients.

| Characteristics | Baseline $n = 59$ | 12 months $n = 53$ |
|---|---|---|
| 9-HPT, Dom | 21.59 (9.17) | 20.63 (5.84) |
| 9-HPT, non Dom | 22.62 (6.70) | 22.67 (6.93) |
| EDSS, median (IQR) | 2.0 (1.5–3.0) | 2.0 (1.5–3.0) |
| EDSS, mean (SD) | 2.20 (1.60)- | 2.28 (1.50) |
| EDSS, change from baseline | | |
| Stable, N (%) | - | 38 (71.7) |
| Worsening, N (%) | - | 9 (17) |
| mean score Δ | - | -1.11 points |
| Improvement, N (%) | - | 6 (11.3) |
| mean score Δ | - | + 1.0 points |
| MS treatments, n (%) | | |
| Naïve at T0 | 20 (34) | 17 (32) |
| No treatment | 0 | 0 |
| Injectable immunomodulators | 3 (5.1) | 2 (3.8) |
| Teriflunomide | 2 (3.4) | 2 (3.8) |
| Dimethylfumarate | 10 (17) | 9 (17) |
| Natalizumab | 3 (5.1) | 3 (5.6) |
| Fingolimod | 3 (5.1) | 3 (5.6) |
| Ocrelizumab | 25 (42.3) | 21 (39.6) |
| Cladribine | 9 (15.2) | 9 (17) |
| Alemtuzumab | 4 (6.8) | 4 (7.5) |
| Cognitive status | | |
| Cognitively impaired | 33 (56) | 20 (38) |
| Cognitively preserved | 26 (44) | 33 (62) |
| Neuropsychological tests | | |
| Mean (SD) | | |
| SDMT | 52.18 (12.13) | 55.26 (10.65)* |
| CVLT-II | 59.44 (9.27) | 62.98 (10.31)* |
| BVMT-R | 24.32 (7.13) | 26.96 (6.08)* |
| Z-scores, mean (SD) | | |
| SDMT | -0.769 (1.09) | -0.528 (0.98)* |
| CVLT-II | -0.102 (1.15) | 0.362 (1.25)* |
| BVMT-R | -0.676 (1.25) | -0.198 (1.16)* |
| Impaired SDMT, n (%) | 18 (30.5) | 12 (22.6) |
| Impaired CVLT-II, n (%) | 9 (15.2) | 6 (11.3) |
| Impaired BVMT-R, n (%) | 18 (30.5) | 12 (22.6) |

n, number of patients; 9-HPT, Dom, 9-Hole Peg test, dominant hand; 9-HPT,non-Dom, 9-Hole Peg Test, non-dominant hand; EDSS, Expanded Disability Status Scale; SD, standard deviation; IQR, interquartile range; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test; CVLT-II, the California Verbal Learning Test, second edition.

* indicate statistically significant changes from baseline ($p < 0.05$).

### 3.3. Cognitive performance from baseline to follow-up examination

A total of 33 patients (56%) were defined as cognitively impaired at baseline on at least one test (23 showed impairment on one test, 8 on two tests and 2 on the three tests), and 20 (38%) were defined as impaired at T1 (14 showed impairment on one test, 3 on two tests and 3 on the three tests). Five of the six patients lost to follow-up had CI at baseline. When performing a case-by-case investigation, we found that 17 patients impaired at baseline showed either improvement and/or impairment in fewer domains at T1 in comparison with T0, whereas 5 patients with normal cognitive scores at baseline showed deterioration and were classified as 'cognitively impaired' at T1. From T0 to T1, there was a statistically significant improvement in SDMT, BVMT-R and CVLT-II raw scores ($p = 0.01$, $p = 0.002$, $p = 0.001$, respectively) and Z-scores ($p = 0.02$, $p = 0.005$, $p = 0.001$, respectively) (Table 1). The cognitively impaired patient (CIP) group did not differ from the cognitively preserved patient (CPP) group on baseline demographic variables but CIP patients had significantly higher EDSS than CPP at T0 and T1 (Supplementary table S1).

### 3.4. MRI-derived metrics

Supplementary table S2 shows the mean values and the standard deviations of the investigated MRI volumetric parameters, at T0 and T1. No statistically significant changes were observed during the follow-up period.

### 3.5. PROMs scores from baseline to follow-up examination

PROM data completeness was good (only one missing EMIF-SEP and two missing WRFQ and MSWDQ-23 questionnaires at T0; no missing questionnaire at T1). The mean scores of PROMs at T0 and T1 are presented in Fig. 1 and supplementary table S3. There was a statistically significant improvement in most PROM scores at T1, except for depression ($p = 0.4$), executive functions ($p = 0.08$) and the global score of WRFQ ($p = 0.7$).

When investigating evolution of PROMs between CIP and CPP at T1, CIP reported significantly worse functioning on multiple domains explored by the selected PROMs, except for depression ($p = 0.2$) and executive functions ($p = 0.08$) (Supplementary table S3). High mean treatment satisfaction scores (ranging from 66.5 to 84.4) were seen at T1 across all TSQM domains (not shown).

Table 2 shows the correlation between PROMs and EDSS and cognitive performances. At T0, there was a moderate to strong correlation between EDSS and most PROM scores. At T1, the correlation persisted but was weaker. Some moderate correlations were found between PROMs and SDMT and, in a lesser extent, BVMT-R at T1. CVLT-II scores were not associated with any of the investigated PROMs, at any time point. While some significant, but modest, correlations were found between MRI measures and the total MSWDQ-23 score at T0, no consistent correlations with the investigated PROMs were observed at T1 (not shown).

### 3.6. New initiator vs switcher groups

We performed additional statistical analyzes to evaluate whether cognitive and PROMs scores and their evolution from baseline to T1 significantly differ between DMT-naïve ('new initiators') and switch

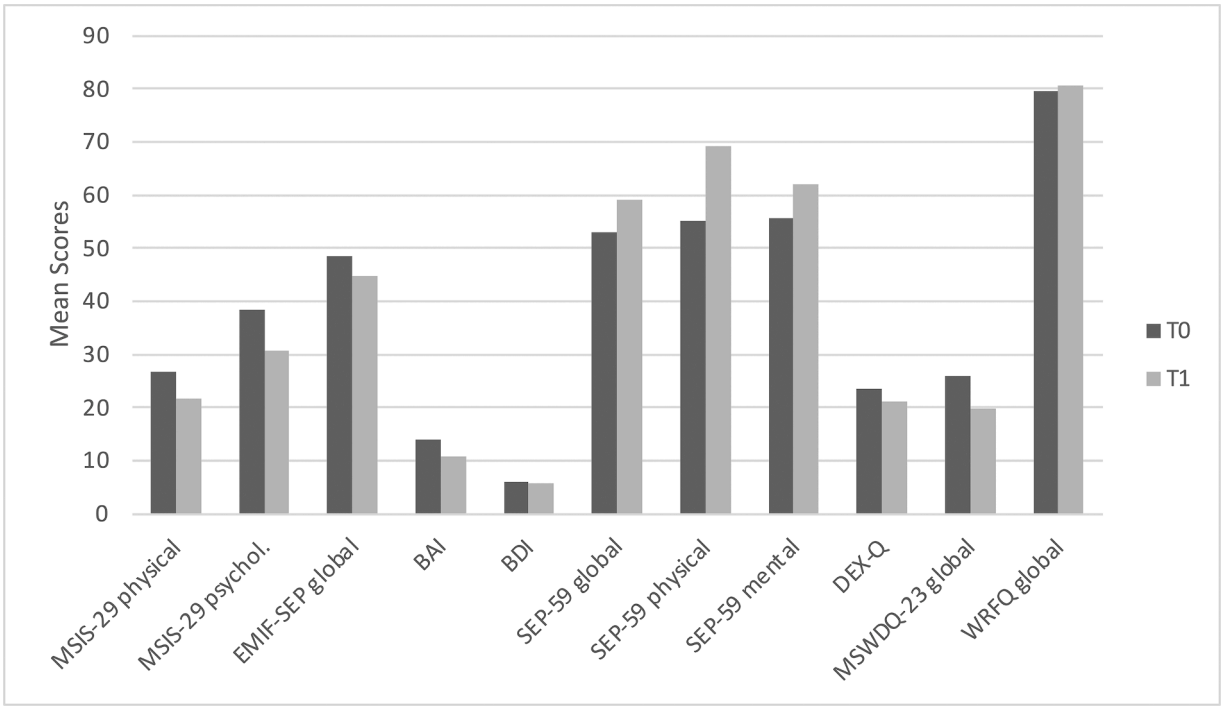


**Fig. 1.** Mean scores of patient-reported outcome measures (PROMs) in the entire cohort at baseline (T0; $n = 59$) and at 12-month follow-up (T1; $n = 53$). MSIS-29, Multiple Sclerosis Impact Scale-29; DEX-Q, Dysexecutive Questionnaire; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; MSWDQ-23, Multiple Sclerosis Work Difficulties Questionnaire; WRFQ, Work Role Functioning Questionnaire; RRMS, relapsing-remitting multiple sclerosis.

**Table 2**
Correlation analysis between patient-reported outcome measures and cognitive and physical disability ($n = 59$), using Spearman's coefficient correlation test (R).

| Test<br>R<br>p | *EDSS* | | *SDMT* | | *BVMT-R* | | *CVLT-II* | |
|---|---|---|---|---|---|---|---|---|
| | *T0* | *T1* | *T0* | *T1* | *T0* | *T1* | *T0* | *T1* |
| *BAI* | 0.37 | 0.09 | -0.19 | -0.22 | -0.07 | -0.22 | 0.03 | -0.08 |
| *BDI* | 0.23 | 0.05 | -0.11 | -0.25 | -0.11 | -0.11 | -0.002 | -0.09 |
| *EMIF-SEP Global score** | 0.43 | 0.32 | -0.24 | -0.32 | -0.04 | -0.18 | -0.13 | -0.05 |
| *SEP-59* | | | | | | | | |
| *Global* | -0.44 | -0.29 | 0.24 | 0.35 | 0.08 | 0.26 | 0.12 | 0.07 |
| *Physical* | -0.47 | -0.24 | 0.25 | 0.18 | 0.10 | 0.21 | 0.12 | -0.006 |
| *Mental* | -0.34 | -0.21 | 0.19 | 0.36 | -0.03 | 0.25 | 0.16 | 0.09 |
| *MSIS-29* | | | | | | | | |
| *PHYS* | 0.55 | 0.45 | -0.26 | -0.29 | -0.11 | -0.30 | -0.11 | -0.13 |
| *PSYCH* | 0.23 | 0.15 | -0.22 | -0.28 | -0.02 | -0.02 | -0.033 | -0.04 |
| *MSWDQ-23* | | | | | | | | |
| *total score*** | 0.44 | 0.27 | -0.43 | -0.46 | -0.14 | -0.20 | -0.20 | - 0.05 |
| *DEX-Q* | 0.23 | 0.03 | -0.37 | -0.32 | -0.046 | -0.17 | -0.16 | -0.21 |
| *WRFQ*** | -0.03 | -0.37 | 0.28 | 0.52 | -0.14 | 0.32 | -0.02 | -0.01 |

Bold values denote statistical significance at the $p < 0.05$ level.
SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test; CVLT-II, the California Verbal Learning Test, second edition; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; MSIS-29, Multiple Sclerosis Impact Scale-29; PHYS, physical; PSYCH, psychological; MSWDQ-23, Multiple Sclerosis Work Difficulties Questionnaire; DEX-Q, Dysexecutive Questionnaire; WRFQ, Work Role Functioning Questionnaire; EDSS, Expanded Disability Status Scale.
* $n = 58$ at T0 and $n = 53$ at T1 for EMIF-SEP.
** $n = 37$ at T0 and T1 for self-reported measures of MSWDQ-23 and WRFQ.

('switchers') RRMS patients. Regarding PROMs, no statistical differences were observed between the 2 groups of patients both at baseline and T1. At T1, PROMs improved in both groups in comparison with baseline evaluation, but results did not significantly differ between new initiators and switchers.

Although new initiators had higher mean raw scores than switchers on the three BICAMS subtests at both baseline and T1, there were no statistically differences between the 2 groups. When investigating the evolution of cognitive performances from baseline to the 12-month follow-up, the mean raw scores of the 3 cognitive tests improved in both groups, but these changes were however statistically not significant.

### 3.7. Multivariate regression

The longitudinal logistic regression analysis revealed baseline level of education in years and EDSS as significant predictors of CI at T1. A high EDSS score at baseline increased the odds of impaired SDMT (OR: 3.10, $p = 0.02$) and impaired BVMT-R (OR: 4.82, $p = 0.001$) at T1). A low level of education at baseline increased the odds of impaired SDMT

(OR: 1.68, $p = 0.01$) and impaired BVMT-R (OR: 4.08, $p=<0.001$) at T1. Neither of the clinical or demographic variables nor the PROMs or MRI-derived metrics were predictive of impaired CVLT-II (Table 3).

## 4. Discussion

In this real-world, longitudinal study, we investigated the evolution of cognitive status and the predictors regarding future CI in a cohort of RRMS patients initiating a new DMT. We observed that (i) RRMS patients exhibited heterogenous cognitive trajectories, with stable, worsened or improved cognitive status at follow-up, (ii) PROMs do not predict CI at 12 months in RRMS patients, (iii) most PROMs were significantly improved at 12 months, (iiii) higher physical disability, as measured by EDSS, and lower education level at baseline were the best predictors of impaired cognitive scores at T1.

### 4.1. Multiple cognitive trajectories in RRMS?

A main finding of this study is the evidence of multiple evolutionary trends regarding cognitive trajectories in the cohort. After excluding from the analysis the 6 patients who dropped out of the study, the proportion of CIP (i.e. impaired results on at least one test) was reduced from 53% at baseline to 38% after 12 months of follow-up, while mean raw scores and Z-scores improved significantly from T0 to T1 for all of the 3 neuropsychological tests. Our case-by-case investigation showed that there were patients with stable, improving, or worsening cognitive status at 12-month follow-up, suggesting that the cognitive trajectory in MS could be rather more heterogeneous than assumed. Our data replicate and confirm prior reports which have pointed out that cognitive function can not only worsen, but also improve. In a short term (2 years) longitudinal study assessing cognitive performances in a cohort of newly diagnosed MS patients, using the BICAMS battery and a similar threshold than ours to define CI (1.5 below normal of a z-score of one or more cognitive domains), the proportion of CIP decreased from 50% to below 30% after 2 years of follow-up (Skorve et al., 2020). Our study has also converging results with an earlier report, focusing on a sample of clinically isolated syndrome and RRMS patients with a longer-term follow-up (at least 10 years) (Katsari et al., 2020). These findings raised the possibility that the trajectories of cognitive changes in MS may be much more fluctuating and complex than expected, with varied patterns of evolution (Katsari et al., 2020). Although the meaningfulness of cognitive changes observed in the present study needs longitudinal confirmation, with a longer interval between assessments, our findings could contradict the concept that CI in MS is unlikely to improve and will inevitably increase over time (Amato et al., 2001; DeLuca et al., 2015). However, in the long-term study from Amato and colleagues, the study sample included patients with progressive forms of MS whereas we focused on a homogeneous RRMS population. This difference in the methodology might explain contradictory results. Beyond the impact caused by the proportion of dropouts (5 of the 6 patients who missed evaluation at T1 were cognitively impaired at baseline), several factors could have affected the results of cognitive assessment during the study. First, anxiety, which is a significant confounder of cognitive performance in MS, independently of other clinical confounding variables (Ribbons et al., 2016; Katsari et al., 2020), was significantly improved at T1, according to self-reported measures, whereas no statistical difference was found for perceived depression between evaluations. However, we cannot reliably explore the impact of these changes on cognitive performances in our cohort due to the limited sample size. Second, Wojcik et al. (2022) previously showed that positive change in work functioning was associated with SDMT improvement. Although changes were not statistically significant, subtle gains in work functioning, as reported in our cohort at T1, may therefore partly account for improvement on neuropsychological tests. Third, practice effects on neuropsychological tests cannot be excluded. However, the testing at follow-up was conducted at an interval of 12 months after baseline testing, limiting the impact of such effects. The duration of learning effects is not established, but Glanz et al. (2012) reported that the SDMT is not prone to practice effects when retested after 1 year. Some authors have shown that these learning effects are however dependent on the cognitive domain tested (Ferrer et al., 2004). Parallel versions were used for the BVMT-R to limit these practice effects. Fourth, although the concept of isolated cognitive relapses (i.e. a transient and significative decrease in objective cognitive performances with concordant gadolinium enhancement on MRI but no physical worsening) is still under debate, we cannot exclude such a phenomenon in some participants at the time of the evaluations (Katsari et al., 2020; Ruet, 2021). Fifth, a potential protective effect of DMT on cognitive function should also be considered but evidence is limited (Kappos et al., 2016; Cohan et al., 2018). Considering the short follow-up period, such effect remains therefore uncertain. Sixth, it should also be noted that cognitive abilities may fluctuate from day-to-day in people considered as 'healthy'. Indeed, previous research showed individual variability on performance-based measures of everyday cognition (Gamaldo et al., 2016). The influence of some environmental factors such as stress and sleep has been suggested to account for this variability in cognitive skills. Finally, neuropsychological assessment in the present study only includes screening measures of the cognitive domains more frequently involved in MS (information processing speed, verbal and visuospatial learning). We cannot exclude that changes in cognitive functioning occurred in domains not explored by this study (for example, executive functioning). A more extensive cognitive evaluation would have therefore provided additional information regarding the trajectories of cognitive changes. All of these considerations imply that our observations regarding the evolutionary trends of cognitive performances should be interpreted with caution. We tried to limit the influence of several factors that could impact cognitive performances, by applying several exclusion criteria in the recruitment of the participants and by using a valid, reliable and clinically implementable neuropsychological battery.

**Table 3**
Multivariate regression analyzes for prediction of cognitive impairment on SDMT, BVMT-R and CVLT-II, at T1.

| Cognitive outcome Measures | Significant Covariates at T0 | Standardized beta coefficient | OR (95% CI) | Sig. |
|---|---|---|---|---|
| SDMT | EDSS<br>Education, years | 1.13 0.52 | 3.10 (1.26–7.64)<br>1.68 (1.04–2.72) | 0.002<br>0.01 |
| BVMT-R | EDSS<br>Education, years | 1.57<br>1.41 | 4.82 (11.33–17.48)<br>4.08 (1.16–14.40) | 0.001<br><0.001 |
| CVLT-II | / | | | |

Results are demonstrated for significant variables only.
MRI data missing for 6 patients at T0 and 4 patients at T1.
SDMT, Symbol Digit Modalities Test, BVMT-R, Brief Visuospatial Memory Test; CVLT-II, the California Verbal Learning Test, second edition; EDSS, Expanded Disability Status Scale; sig.; significance level; OR, Odds Ratio; CI, confidence interval.

### 4.2. Improvement of PROMs

As expected, most RRMS patients reported at the start of the study that MS had a considerable negative impact on their well-being, affecting both physical and psychological aspects as well as HRQoL. Although objective physical disability level (as measured by EDSS) remained stable over the 12-month study period, meaningful improvements were reported by MS patients in almost all investigated PROMs. These findings might indicate that, in a real-world setting, the clinical benefits of initiating a new DMT are translated into patient-reported benefits, which is supported by the reported general treatment

satisfaction score (close to 80%). Similar beneficial effects on the well-being of PwMS have been suggested by previous studies (Stephenson et al., 2012; Chen et al., 2018). Whether the observed improvements in PROMs are a direct result of DMT is however uncertain because of the lack of a control group and given that the longitudinal comparisons are performed within the same population. No comparison between the multiple DMTs can be performed due to the small size of our cohort.

By essence being subjective, PROMs are vulnerable to several bias which can potentially influence the responsiveness and the interpretability of the data. First, the time of assessment could have biased PROMS assessment since these were collected early after initiation of a new DMT ('naïve' vs. 'switchers'), which means that the participants were not in a completely stable condition at inclusion. Second, the accuracy of self-reported measures among MS patients with cognitive decline is questionable, although a previous study concluded that PwMS with cognitive impairment can validly self-report PROMs (Baumstarck et al., 2013). In addition, emotional symptoms (such as depression and anxiety), which were frequently reported in our study, may also reduce the accuracy of self-reporting measures (Goverover et al., 2005). Consequently, we cannot rule out that the accuracy of PROMs was reduced in the cognitively impaired patients in the present study, especially since we administered a wide spectrum of PROMs in order to obtain a full understanding of patients' situation. These bias in collecting and interpreting PROMs imply that participants in this study may therefore have overestimated or underestimated the burden of disease and treatment. However, collecting multiple PROMS in a longitudinal course may help to overcome these limitations.

### 4.3. Predicting CI

In agreement with previous cross-sectional and longitudinal studies, we confirmed some of the identified early predictors of CI (physical disability level and education level at baseline) (de Medeiros Rimkus et al., 2018; Carotenuto et al., 2022). However, we failed to demonstrate a predictive role of the investigated PROMs to predict cognitive performances at 12 months of follow-up. The small size of the study population and the relatively short follow-up duration would have limited power for identifying weaker predictors. A longer follow-up period is therefore needed to confirm these results.

### 4.4. Limitations

Several limitations should be acknowledged. The current study is limited by a small sample size, which could influence the generalizability of the results, and would have limited power to identify standard clinical and neuroimaging markers that predict cognitive status. Although our cohort is relatively small, it is well-defined with little loss of follow-ups. The exclusion of progressive forms of MS also limits the generalizability of our results. A few missing data in the PROM collection should also be acknowledged though we believe this had no major impact on the results since only 3 questionnaires at T0 were involved. MRI metrics should also be interpreted with caution given that neuroimaging data were not obtained uniformly, as some scans were obtained using 1.5T MRI. However, the MSmetrix median percentage error of the brain volume measurement between a 1.5T and a 3T scanner has been reported to be 0.52% for GM volume and 0.35% for parenchymal volume; thus, effects of field strength on parenchymal volume measurements could be considered as minor (Lysandropoulos et al., 2016). Although we evaluated important MRI metrics, other measures associated with cognitive performance such as diffusion tensor imaging and magnetization transfer ratio were not used.

## 5. Conclusions

These findings provide additional evidence that evolution of CI in MS may be a dynamic phenomenon and will not result in inevitable and progressive cognitive decline with advancing age, and do not support the utility of PROMs in predicting CI in RRMS. The present study is still ongoing to determine whether our findings are confirmed at 2 and 3 years of follow-up.

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## Compliance with ethical standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

## CRediT authorship contribution statement

**Frédéric London:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Alice De Haan:** Investigation, Resources, Writing – review & editing. **Zohra Benyahia:** Investigation, Resources, Writing – review & editing. **Gaëtane Landenne:** Investigation, Resources, Writing – review & editing. **Thierry Duprez:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – review & editing. **Vincent van Pesch:** Conceptualization, Methodology, Investigation, Supervision, Formal analysis, Writing – review & editing. **Souraya El Sankari:** Conceptualization, Methodology, Investigation, Supervision, Formal analysis, Writing – review & editing.

## Declaration of Competing Interest

The authors did not report any conflict of interest in relation to the study.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104848.

## References

Amato, M.P., Zipoli, V., Portaccio, E., 2006. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. J. Neuro Sci. 245, 41–46.

Amato, M.P., Ponziani, G., Siracusa, G., Sorbi, S., 2001. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch. Neurol. 58 (10), 1602–1606.

Baumstarck, K., Boyer, L., Boucekine, M., Michel, P., Pelletier, J., Auquier, P., 2013. Measuring the quality of life in patients with multiple sclerosis in clinical practice: a necessary challenge. Mult. Scler. Int., 524894

Benedict, R.H.B., 1997. Brief visuospatial memory test-revised: professional manual. Psychol. Assess. Resour. Inc. Odessa.

Carotenuto, A., Costabile, T., Pontillo, G., Moccia, M., Falco, F., Petracca, M., et al., 2022. Cognitive trajectories in multiple sclerosis: a long-term follow-up study. Neuro Sci. 43 (2), 1215–1222.

Chen, J., Taylor, B.V., Blizzard, L., Simpson, S., Palmer, A.J., van der Mei, I.A.F., 2018. Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data. J. Neurol. Neurosurg. Psychiatry 89 (11), 1200–1207.

Cohan, S.B.R., De Seze, J., Hauser, S., et al., 2018. Time to cognitive worsening in patients with relapsing multiple sclerosis in Ocrelizumab phase III trials. Am. Acad. Neurol. 90, S44.

Delis D.C., Kramer J.H., Kaplan E., and Ober B.A. (2000). California Verbal Learning Test-Second Edition. Adult Version. Manual. The Psychological Corporation: San Antonio, TX.

DeLuca, G., Yates, R.L., Beale, H., Morrow, S.A., 2015. Cognitive impairment in Multiple Sclerosis: clinical, radiologic and pathologic insights. Brain Pathol. 25 (1), 79–98.

de Medeiros Rimkus, C., Bello Avolio, I.M., Correa Miotto, E., Apostolos Pereira, S., Mendes, M.F., Callegaro, D., da Costa Leite, C., 2018. The protective effects of high-education levels on cognition in different stages of multiple sclerosis. Mult. Scler. Relat. Disord. 22, 41–48.

Dusankova, J.B., Kalincik, T., Havrdova, E., Benedict, R.H., 2012. Cross cultural validation of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) and the brief international cognitive assessment for multiple sclerosis (BICAMS). Clin. Neuropsychol. 26, 1186–1200, 2012.

Ferrer, E., Salthouse, T.A., Stewart, W.F., Schwartz, B.S., 2004. Modeling age and retest processes in longitudinal studies of cognitive abilities. Psychol. Aging 19 (2), 243–259.

Gamaldo, A.A., Allaire, J.C., 2016. Daily fluctuations in everyday cognition: is it meaningful? J. Aging Health 28 (5), 834–849.

Glanz, B.I., Healy, B.C., Hviid, L.E., Chitnis, T., Weiner, H.L., 2012. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. J. Neurol. Neurosurg. Psychiatry 83, 38–43. https://doi.org/10.1136/jnnp.2010.237834.

Goverover, Y., Chiaravalloti, N., DeLuca, J., 2005. The relationship between self-awareness of neurobehavioral symptoms, cognitive functioning, and emotional symptoms in multiple sclerosis. Mult. Scler. 11, 30. https://doi.org/10.1191/1352458505ms1153oa, 203–212.

Kappos, L., Edan, G., Freedman, M.S., et al., 2016. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology 87 (10), 978–987.

Katsari, M., Kasselimis, D., Giogkaraki, E., Breza, M., Evangelopoulos, M.E., Anagnostouli, M., et al., 2020. A longitudinal study of cognitive function in multiple sclerosis: is decline inevitable? J. Neurol. 267 (5), 1464–1475.

Landgon, D.W., 2011. Cognition in multiple sclerosis. Curr. Opin. Neurol. 24, 244–249.

London, F., El Sankari, S., De Haan, A., et al., 2023. Patient reported-outcome measurements in a selective cohort of relapsing-remitting multiple sclerosis patients: relationships with physical disability, cognitive impairment, and MRI-derived metrics. Acta Neurol. Belg. https://doi.org/10.1007/s13760-023-02225-x.

Lysandropoulos, A.P., Absil, J., Metens, T., Mavroudakis, N., Guisset, F., Van Vlieberghe, E., Smeets, D., David, P., Maertens, A., Van Hecke, W., 2016. Quantifying brain volumes for multiple sclerosis patients follow-up win clinical practice – comparison of 1.5 and 3 tesla magnetic resonance imaging. Brain Behav. 6, e00422. https://doi.org/10.1002/brb3.422.

Macaron, G., Baldassari, L.E., Nakamura, K., Rao, S.M., McGingley, M.P., Boss, B.P., Li, H., Miller, D.M., Jones, S.E., Bermel, R.A., Cohen, J.A., D'Ontaneda, D., Conway, D.S, 2020. Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment and magnetic resonance metrics. Eur. J. Neurol. 27, 1238–1249. https://doi.org/10.1111/ene.14239.

Maubeuge, N., Deloire, M.S.A., Brochet, B., Erhlé, N., Charré-Morin, J., Saubusse, A., Ruet, A., 2021. BICAFMS study investigators. Rev. Neurol. 177 (1–2), 73–79 (Paris).

Poullet, J.B., Sima, D.M., Simonetti, A.W., De Neuter, B., Vanhamme, L., Lemmerling, P., Van Huffel, S., 2007. An automated quantitation of short echo time MRS spectra in an open source software environment: AQSES. NMR Biomed. 20 (5), 493–504. https://doi.org/10.1002/nbm.1112, 27.

Ribbons, K., Lea, R., Schofeld, P.W., et al., 2016. Anxiety levels are independently associated with cognitive performance in an Australian multiple sclerosis patient cohort. J. Neuropsychiatry Clin. Neurosci. 29 (2), 128–134.

Skorve, E., Lundervold, A., Torkildsen, Ø., Myhr, K.M., 2020. A two-year longitudinal follow-up of cognitive performance assessed by BICAMS in newly diagnosed patients with MS. Mult. Scler. Relat. Disord. 46, 102577.

Smith A., 1982. Symbol Digit Modalities Test: Manual. Western Psychological Services, Los Angeles.

Stephenson, J., Kern, D.M., Agarwal, S.S., Zeidman, R., Rajagopalan, K., Kamat, S.A., Foley, J., 2012. Impact of natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study. Health Qual. Life Outcomes 10, 155.

Rao, S.M., Leo, G.J., Unverzagt, F., 1991. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41, 685–691.

Ruet, A., 2021. Do isolated cognitive relapses exist? Commentary. Mult. Scler. 27 (10), 1489–1490.

van 't Hullenaar, C.A.A., Coerver, E., Kalkers, N.F., van Kempen, Z., Koch, M., Uitdehaag, B.M.J., Killestein, J., Strijbis, E.M.M., 2021. The use of multi-domain patient reported outcome measures for detecting clinical disease progression in multiple sclerosis. Mult. Scler. Relat. Disord. 55, 103165.

Wojcik, C., Jaworski, M., Dwyer, M.G., Youngs, M., Unverdi, M., Weinstocj-Guttman, B., Benedict, R.H.B., 2022. Benchmarks of meaningful improvement on neurocognitive tests in multiple sclerosis. Mult. Scler. 28 (3), 487–491.