Association Between Disease-Modifying Therapy and Information Processing Speed in Multiple Sclerosis

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ABSTRACT

BACKGROUND: Cognitive impairment (CI) is common in multiple sclerosis (MS). Processing speed (PS) is often affected, making it an ideal target for monitoring CI. This study aims to evaluate the association between disease-modifying therapy (DMT) use and intensity and longitudinal changes in Processing Speed Test (PST) scores for individuals with MS.

METHODS: A retrospective analysis of individual PST scores at a single MS center was conducted. Individuals with 2 or more PST assessments were included. Scores on the PST were compared longitudinally between those who had been on a DMT for 2 or more years and those who had been off a DMT for 2 or more years and between those on high-efficacy DMTs and those on low-/moderate-efficacy DMTs. A linear regression model was approximated to evaluate the rate of cognitive change over time. A propensity score adjustment was conducted using a multivariable logistic regression.

RESULTS: The cohort was 642 individuals, 539 on DMT and 103 off DMT. Median age and disease duration was 49.7 (IQR 42.4-57.9) and 16.6 years (IQR 9.3-23.0) in the DMT group, and 58.9 (IQR 52.2-65.3) and 20.0 years (IQR 14.1-31.4) in the non-DMT group. Both cohorts were predominantly female (75% DMT, 79.6% non-DMT), with a mean of 4 assessments (IQR 3-5), and an average monitoring duration of 1.9 years (1.2-2.4) in the DMT group, and 1.8 years (1.4-2.4) in the non-DMT group. After adjusting for multiple factors, DMT status and intensity were not found to be significant predictors of longitudinal PST change.

CONCLUSIONS: Neither DMT status nor intensity was a significant predictor of cognitive processing speed over a period of approximately 2 years. Future prospective studies are needed to further support these findings.

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Multiple sclerosis (MS) is among the most common disabling neurologic diseases in young adults.[1] Global disease prevalence continues to rise, with estimates from 2020 approximating 35.9 per 100,000 people.[2] Approximately 40% to 70% of individuals with MS demonstrate varying degrees of cognitive impairment (CI).[3] Importantly, all forms of MS have been associated with CI, including cognitive deficits in individuals with clinically isolated syndrome (CIS) and radiologically isolated syndrome.[4-6] CI can be disabling even in the early stages of the disease and arises independent of physical disability.[7,8]

Because it affects social functioning and future employment and often results in increased social isolation, CI predicts quality of life in MS.[9,10] Individuals with mild disease and early cognitive deficits have an increased likelihood of worsening disability within 5 years, as well as evolution from benign MS at 12 years.[11,12]

The most common cognitive domains affected by MS include information processing speed (IPS), verbal and visual memory, visuospatial processing, and attention.[13] Less commonly, executive functioning, language, and long-term memory are implicated.[13] IPS is the ability to manipulate information over a short period of time.[14] It is a useful cognitive marker in MS, as it is affected early in the disease course and is associated with worse vocational outcomes independent of age and self-reported physical disability.[15] IPS can be reliably measured with simple tests such as the Symbol Digit Modalities Test (SDMT),[16,17] a concise test with excellent psychometric properties that is used in most cognitive batteries,[18] or the Processing Speed Test (PST), an electronic adaptation of the SDMT.[19] The PST was found to have excellent retest reliability as compared with the SDMT and has been integrated into routine care at our center[11,19,20] and several other centers in Europe and North America.[21]

With broadened therapeutic options for MS treatment in the past decade, whether an association exists between disease-modifying therapy (DMT) and the progression of

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TABLE 1. Patient Clinical Characteristics at First Testing

	DMT (n = 539)	Non-DMT (n = 103)	*P* value
Age (y)	**49.7 (42.4-57.9)**	**58.9 (52.2-65.3)**	**< .001**
Male, n (%)	135 (25.0)	21 (20.4)	.313
Age of MS diagnosis (y)	**34.9 (27.6-43.9)**	**37.8 (31.8-46.4)**	**.015**
Disease duration (y)	**16.6 (9.3-23.0)**	**20.0 (14.1-31.4)**	**<.001**
zPST	−0.76 (−1.68 to 0.12)	−0.76 (−1.50 to −0.15)	.749
PDDS	**2 (0-4)**	**3 (1-4)**	**.011**
Education (y)	**14 (13-16)**	**13 (12-16)**	**.006**
PHQ-9 score	5 (2-9)	5 (2-9)	.345
Relapsing disease, n (%)	**375 (69.6)**	**55 (53.4)**	**.001**
Duration monitored (y)	1.9 (1.2-2.4)	1.8 (1.4-2.4)	.647
Number of PST assessments	4 (3-5)	4 (3-4)	.877
High-efficacy DMT, n (%)	102 (18.9)	N/A	N/A
MRI measures			
T2LV	11.8 (4.8-25.7)	9.9 (3.1-11.6)	.133
WBF	0.81 (0.79-0.82)	0.80 (0.78-0.81)	.111
GMF	**0.46 (0.45-0.47)**	**0.45 (0.44-0.46)**	**.007**
ThalF	0.0096 (0.0089-0.0103)	0.0097 (0.0087-0.0103)	.701

DMT, disease-modifying treatment; GMF, gray matter fraction; MS, multiple sclerosis; PDDS, Patient Determined Disease Steps; PHQ9, Patient Health Questionnaire-9; PST, Processing Speed Test; T2LV, T2 lesion volume; ThalF, thalamic fraction; WBF, whole brain fraction; zPST, z-score of Processing Speed Test.
Note: Median values (IQR) represented unless stated otherwise. *P* values for Mann-Whitney *U* test or x^2 are represented when applicable. Statistically significant results are highlighted in bold.

CI has become an increasingly pertinent question. A recent meta-analysis evaluating 44 studies with 55 distinct relapsing MS populations revealed a modest protective effect of DMT on longitudinal cognitive function in the form of processing speed,[22] but escalation DMTs did not provide a greater benefit in cognitive performance than platform therapies.[22] Furthermore, many highly effective therapies (eg, ocrelizumab, cladribine, alemtuzumab) were either poorly represented or not included in the study.[22]

The aims of the current study are to determine whether an association exists between DMT and cognitive processing speed within a large-scale clinical cohort, to evaluate whether significant differences in PST scores exist among individuals on high versus low potency therapies, and to investigate associations between DMT status and MRI correlates of MS-related CI.

METHODS

Study Design

This study was approved by the Cleveland Clinic institutional review board. We conducted a single-center observational study using a clinical practice database incorporating the Multiple Sclerosis Performance Test (MSPT)—a digital battery of tests routinely performed at each visit by patients at Cleveland Clinic—from December 2015 through April 2020.

All encounters with individuals with a diagnosis of MS, aged 18 years or older and with 2 or more PST evaluations, were included in this study. Exclusion criteria included unavailable PST scores, missing basic demographic data (ie, age, sex, level of education, disease type, and disease duration), and any switch from high-efficacy DMT to low-/moderate-efficacy DMT. Patients were divided into 2 cohorts: the DMT cohort with individuals who had spent at least 2 years on any DMT, and the non-DMT cohort with individuals who had been off of a DMT for at least 2 years and did not start one during the follow-up period. All PSTs performed outside of this 2-year DMT window (on or off) were included in our analysis. The DMT cohort was further subdivided into 2 cohorts: those on high-efficacy DMT, and those on low-/moderate-efficacy DMT. Individuals who switched from high-efficacy DMT to low-/moderate-efficacy DMT or vice versa during the follow-up period were excluded. High-efficacy treatments included ocrelizumab, alemtuzumab, natalizumab, and rituximab. Low-/moderate-efficacy treatments included dimethyl fumarate, fingolimod, teriflunomide, interferon beta-1a, interferon beta-1b, and glatiramer acetate. Efficacy was classified based on the consensus definition from an ongoing randomized clinical trial (DELIVER-MS; NCT03535298).[23]

Study Variables and Outcomes

Study variables were collected from individuals with MS via the MSPT iPad application during Cleveland Clinic Enterprise clinical visits. Data obtained from the MSPT included clinical MS history, patient reported outcomes, and MSPT performance measures. These data were supplemented by data from the electronic medical record (EMR),

TABLE 2. Summary of Clinical Predictors on Overall PST Slope

All patients (DMT + non-DMT)			DMT cohort (high + low efficacy)		
Variable	**Coefficient[a]**	***P* value**	**Variable**	**Coefficient[a]**	***P* value**
DMT status	0.0708	.573	High-efficacy DMT	−0.0931	.428
Initial zPST	**−0.1564**	**.010**	Initial zPST	−0.2494	.108
RRMS	0.2375	.066	RRMS	0.5090	.076
Age	−0.0019	.431	Age	−0.0044	.601
Male sex	−0.1030	.109	Male sex	−0.1558	.292
Disease duration	−0.0008	.800	Disease duration	−0.0022	.683
Education	0.0074	.724	**Education**	**0.0884**	**.026**
PDDS	0.0038	.840	PDDS	0.0619	.169

DMT, disease-modifying treatment; PDDS, Patient Determined Disease Steps; RRMS, relapsing-remitting multiple sclerosis; zPST, z-score Processing Speed Test.
[a]Cognitive slope is defined as change in PST over time.
Note: Statistically significant results are highlighted in bold.

as well as standardized imaging sequences and analysis conducted within our institution. All MS types were included in our study. Relevant demographics assessed included patient age, sex, education level, initial age at MS diagnosis, and MS disease duration (defined as time from initial MS diagnosis to PST performance). The Patient Determined Disease Steps (PDDS) scale was used as a measure of self-reported physical disability. The Patient Health Questionnaire-9 (PHQ-9) was used as a measure of depression severity.

Z-scores were calculated using the raw PST (zPST) scores of the individuals with MS compared with controls as a function of age, sex, and education level. The duration of time evaluated from initial PST score to last follow-up, and the number of overall PST scores were included. Several metrics thought to be associated with cognitive function in MS were derived from a subset of the study cohort (as previously described[24]) via MRI volumetric analysis, including whole brain fraction (WBF; defined as the total brain volume including gray and white matter, normalized to the outer contour volume), T2 lesion volume (T2LV; defined as native white matter lesions visualized on T2-weighted fluid attenuated inversion recovery [FLAIR]), gray matter fraction (GMF; total volume of gray matter) and thalamic fraction (ThalF; total thalamic volume in relation to outer contour volume).

Statistical Analysis

Baseline demographics among study groups (DMT vs non-DMT, and high- vs low-/moderate-efficacy treatments) were tested using the Mann-Whitney *U* test, the 2-tailed Student *t* test, and the x^2 test. For each study participant, a linear regression model was fitted with z-PST as the dependent variable and age of assessment as the independent variable. The coefficient of this model, the cognitive slope, was used to approximate the rate of change in cognitive function over time. The mean of all available quantitative MRI metrics during the time range used in the analysis above were also calculated for each participant. Disease course was dichotomized into relapsing-remitting MS (RRMS) vs progressive MS. *P* values less than or equal to .05 were used for statistical significance testing. Statistical analysis was conducted using R. Slopes of cognitive dysfunction among the different groups were tested within the linear model.

The association between DMT use and PST score was determined using propensity score (PS) adjustment and PS was calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of receiving DMT, while the covariates included baseline age, sex, level of education, disease duration, disease subtype, and baseline z-PST score. Matching using the full method with a caliper width of 0.25 SD was conducted using MatchIt library in R. Standardized mean biases were evaluated to ensure balance after propensity score matching between the DMT and non-DMT cohorts. A multivariable linear regression model was then fitted with the cognitive slope as the dependent variable, and the binary DMT status as the independent variable. Covariates included baseline age, sex, education level, disease duration, disease subtype, and baseline z-PST score. A similar process was done for the high-efficacy and low-/moderate-efficacy DMT cohorts.

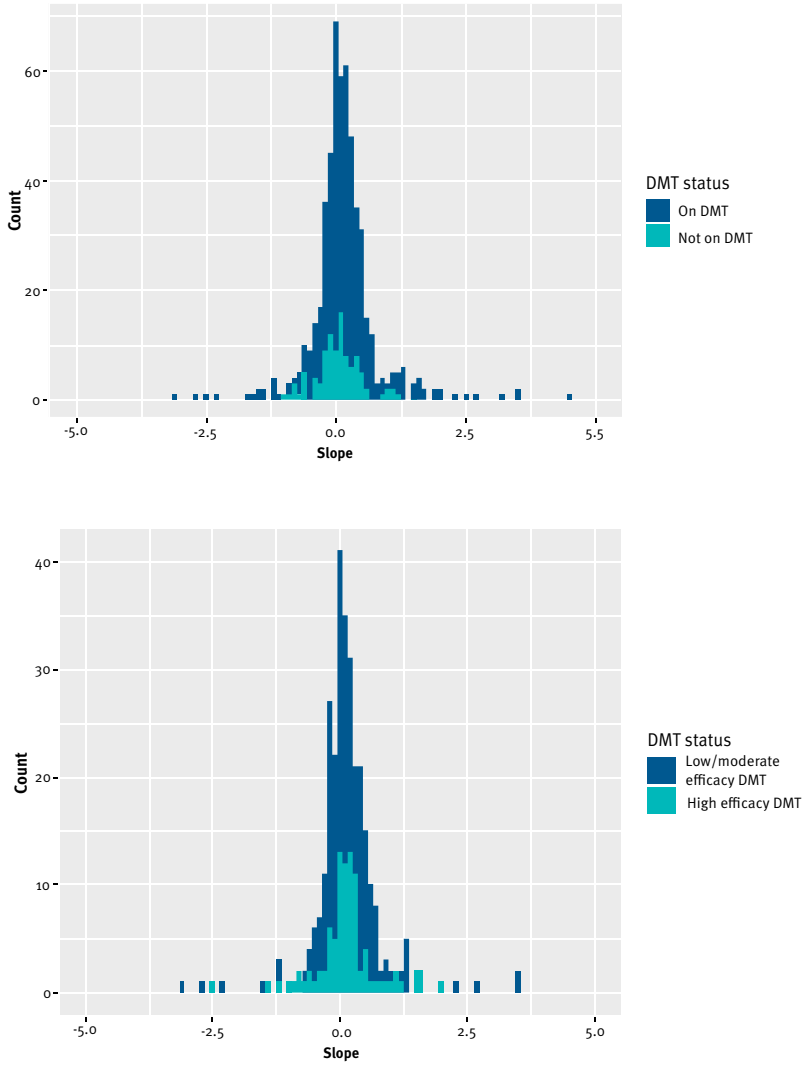
RESULTS

A total of 749 individuals were identified, of which 710 had at least 2 PST scores. After exclusion criteria were applied, 642 were included in the analysis (**FIGURE S1**). The average follow-up was 1.9 years (SD: 1.2-2.4) in the DMT group and 1.8 years (SD: 1.4-2.4) in the non-DMT group. The average number of PST scores was 4.0 (SD: 3-5).

Cognitive Slope Comparison Between DMT vs Non-DMT Groups

Of the 642 study participants, 539 were on DMT (DMT group) and 103 were not on a DMT (non-DMT group). The cohort's clinical characteristics are summarized in **TABLE 1**. On average, the DMT group was significantly younger ($P < .001$), with a younger age at diagnosis ($P \leq .015$), shorter overall disease duration

FIGURE 1. Distribution of Cognitive Slopes



DMT, disease-modifying therapy
Panel A: Distribution in DMT vs non-DMT cohorts Panel B: Distribution in high-efficacy DMT vs low-/moderate-efficacy DMT

Cognitive Slope Comparison Between High-Efficacy DMT vs Low-/Moderate-Efficacy DMT

In the DMT cohort, 396 individuals who had available data and did not switch DMT class during the evaluated period were included. Of these, 96 (24.2%) were on high-efficacy DMT (high-efficacy group) and 300 (75.8%) were on low- to medium-efficacy DMT (low-/moderate-efficacy group). The clinical characteristics of the DMT cohort are summarized in **TABLE S2**. After matching, 95 high-efficacy DMT and 298 low-/moderate-efficacy DMT patients were included in the matched cohort. The summary of the linear regression model fitted to the matched cohort for prediction of cognitive slope is shown in Table 2. None of the variables except education, including being on high-efficacy DMT compared to low-/moderate-efficacy DMT, were found to have statistically significant estimates in predicting the cognitive slope (**FIGURE 1B**).

Post-Match MRI Analysis

When available, the average MRI metrics for the duration of monitoring were compared across the DMT vs non-DMT cohorts, as well as high-efficacy vs low-/moderate-efficacy cohorts as shown in **TABLE S3**. Patients in the DMT cohort had higher GMF, higher T2LV, and lower thalamic volumes when compared with the non-DMT cohort. No other statistically significant differences were found.

($P < .001$), less disability ($P \leq .011$), and a higher predominance of relapsing disease ($P \leq .001$). After matching, 537 individuals on DMT and 102 individuals not on DMT were included in the matched group. The summary of the linear regression model fitted in the matched cohort for prediction of cognitive slope is shown in **TABLE 2**. Cognitive slope was defined as the change in PST over time. Cognitive slope was determined to be positive in both the DMT and non-DMT groups. There was no significant difference in cognitive slope across the 2 groups (**FIGURE 1A**). The only variable with a statistically significant relationship was the initial zPST score, which correlated negatively with the cognitive slope. Older age, male sex, and increased disease duration showed negative point estimates for PST slope, although these did not reach statistical significance. The estimate for being on or off DMT was not found to be statistically significant.

DISCUSSION

We conducted a large-scale, single-center, retrospective analysis investigating the association between DMT and cognitive function in a cohort of individuals with MS. After controlling for age, level of education, MS phenotype, disease severity, physical disability, and baseline PST score, our study did not find a significant difference in PST scores between treated and untreated patients with MS. Importantly, study participants were matched based on their initial PST score after a 2-year period either on or off DMT, and no significant longitudinal difference in average PST score was revealed. Similarly, when individuals on DMT were divided into high-efficacy DMT and low-/moderate-efficacy DMT cohorts, no significant difference in average PST score slope was found, a finding similarly described in prior literature.[22] As expected, older age, male sex, and increased disease duration, each of which is considered a

positive predictor of increased disease severity, were all negatively associated with PST score. Higher initial PST score was negatively associated with PST slope. While the reason for this is not entirely clear, it may suggest that patients at a higher cognitive baseline have more opportunity for future decline or may represent a regression to the mean effect.

The cognitive slopes calculated for both cohorts were positive, suggesting that PST scores improved during the 2-year period observed. This is likely due to confounding by the practice effect, in which individual testing inevitably leads to performance enhancement on future tests.[11,25] The limited length of time observed and number of PSTs recorded are possible contributors to this finding. Nonetheless, DMT status did not appear to be associated with the absolute value of the cognitive slope.

We interrogated MRI measures in relation to DMT status, as these measures may be associated with cognitive function in MS. Our analysis showed no significant difference in WBF between the DMT and non-DMT cohorts across an average of 5 years, suggesting the cohorts were well matched. In the DMT cohort, GMF and T2LV were both significantly higher, suggesting that these values are not necessarily negatively correlated, and ThalF was significantly lower and is likely related to greater T2LV.

As previously mentioned, a meta-analysis conducted by Landmeyer et al in 2020 that evaluated the effects of DMT on cognitive test performance concluded that there is a small to moderate effect size of both platform and escalation therapies on processing speed.[22] Notably, there was no difference between escalation and platform therapies.[22] There are several reasons why our results may have differed. Many of the studies included in the meta-analysis were uncontrolled observational studies that evaluated cognition as a secondary or tertiary outcome.[22] Additionally, the sample sizes evaluated in several of these studies were small; only 1 study reached a cohort of 1000, and the majority included less than 100 participants.[22] Underreporting of negative results in studies with smaller samples was also noted, which may have led to publication bias.[22] Furthermore, the included studies used the SDMT as well as the Paced Auditory Serial Addition Test, which may have led to increased variability. In our study, approximately 24% of individuals in the DMT cohort were on high-efficacy DMT, which included ocrelizumab, alemtuzumab, natalizumab, and rituximab. In the prior meta-analyses, 1 sample each of alemtuzumab (21 individuals) and rituximab (75 individuals) were included, and neither ocrelizumab nor natalizumab was featured. Similar to the prior meta-analysis, our study further emphasizes a lack of a robust response to DMT despite the use of escalation therapies with high potency, which suggests that there may be a secondary pathophysiological mechanism in MS-related cognitive decline.

Recent literature implicating the role of gray matter pathology and neurodegeneration in MS-related cognitive decline may provide further insight into our findings. Gray matter involvement in MS has been well documented, with demyelination occurring in the cerebral cortex and deep gray structures.[26,27] While gray matter destruction and associated cerebral atrophy are more commonly seen in primary progressive MS, these findings are variably present in relapsing and secondary progressive disease as well.[26,28] Furthermore, both gray matter inflammation and atrophy may be present early in MS disease activity and also can occur in CIS.[26]

The relationship between gray matter disease and acute white matter lesions in MS remains unclear. Cortical atrophy is not always a reliable predictor of white matter lesion burden on MRI.[29] This is evidenced by large autopsy studies evaluating MS pathology, which have not shown a clear association between white matter and gray matter disease involvement.[28] Furthermore, similar levels of CI have been measured across CIS and early RRMS, despite a significantly higher level of MRI T2 lesion burden in RRMS,[29] and the frequency and severity of CI may be similarly debilitating across both populations.[29] These findings suggest that cognitive deficits in MS may be at least partially independent of acute MS relapse and focal white matter lesion development.[29] Finally, cognitive deficits can be present in patients with minimal physical disability, resulting in a weak correlation between the Expanded Disability Status Scale (EDSS) score and CI.[29] This may help to explain why DMT administration, which is highly efficacious in preventing acute relapse activity and preserving EDSS, may result in a weaker association with cognitive preservation.

Our study has several limitations, many of which are common to observational studies. Our study was performed at a single center, which limits its generalizability to other populations, especially outside of the United States. As with any retrospective analysis, the possibility of confounders may have affected the outcome, and although efforts were made to control for major confounders as previously detailed, some residual confounders persist. Indication bias in the study may have removed treatment effects from our results. While all patients

PRACTICE POINTS

Cognitive impairment in multiple sclerosis is prevalent and disabling.

In the current study, choice of disease-modifying therapy did not appear to be a significant predictor of information processing speed.

In isolation, information processing speed may not be sufficient to evaluate for cognitive impairment in individuals with multiple sclerosis. ■

seen at our center take the PST prior to their appointment, those with more active disease likely take more PSTs, which could result in a detection bias. Excluding individuals with less than 2 PSTs may have also led to a degree of selection bias.

Our dichotomization of 2 years on treatment and 2 years off treatment was intended to maximize the ability to demonstrate an effect while maintaining statistical power based on sample size, but this decision may have influenced the results. It is possible that 2 years may not be a long enough time period to identify a significant difference in processing speed across the 2 cohorts. Furthermore, the timing of DMT also may have differential effects at different stages of the disease course. Studying a cohort of patients who are stable on a particular DMT for the duration of 2 years suggests overall disease stability and excludes patients with breakthrough disease who might be more cognitively affected. This is an inherent challenge in evaluating the effect of DMT on progressive symptoms in MS in a real-world observational study. Furthermore, despite attempts to match patients based on disease severity and duration, our cohort had extensive variability, with a subset of individuals who likely had a high level of disease burden at the time of evaluation. There were also differences in sample size between our DMT and non-DMT cohorts, with our high-efficacy and low-/moderate-efficacy subgroups limited in size, especially given that those who switched treatment groups or were exposed to high-efficacy therapy prior to being on low-/moderate-efficacy therapy were excluded from our analysis.

As noted earlier, due to limitations in length of monitoring and number of PSTs completed, our study could not avoid practice effect confounding. This is a common problem with the use of the SDMT.[25] The suitability of SDMT or PST to monitor long-term treatment effects in an observational cohort is still to be determined, but it may require even larger sample sizes and more prolonged follow-up. Previous studies have demonstrated that several different cognitive phenotypes exist in MS, and processing speed may only be impaired in a minority of patients early in the disease state.[30,31] Over time, the number of cognitive domains affected by MS increases.[31] Damasceno et al demonstrated that 47.5% of individuals with MS showed multiple cognitive domains affected at 2 years, with that number rising to 62.2% after 6 years. Thus, the use of a brief monodomain cognitive screen, rather than comprehensive neuropsychological testing or brief neuropsychological batteries, may not be sufficient on its own to truly identify CI, particularly over a brief period of time. This may have contributed to the absence of observed DMT effect in our study. Taken together, our data may suggest that evaluating processing speed in isolation may not be a sensitive treatment outcome biomarker in clinical practice.

Large-scale multicenter prospective studies are needed to further evaluate the effect of DMT on long-term cognitive outcomes in MS. Ideally, future studies should account for acute relapses across DMT and non-DMT cohorts and compare MRI volumetric data longitudinally, evaluating whether cognitive decline occurs at similar rates despite significant differences in acute relapse rate. Future prospective studies should also focus on evaluating the association of DMT and CI in individuals with early RRMS, who often start DMT near the time of their MS diagnosis. A recent study investigating the effect of a highly effective DMT (ie, ocrelizumab) compared with platform therapies (ie, beta-1a interferon) highlighted the significance of steady progression independent of relapse activity (PIRA) on disability accumulation and revealed that highly effective therapies may be significantly more effective in preventing PIRA.[32] Although CI was not evaluated, investigating the effects of various DMT on PIRA in relation to CI may prove to be important.

CONCLUSIONS

This single-center retrospective analysis examined the association of DMT and processing speed and did not find a significant difference between individuals with MS on a DMT vs those not on a DMT for at least 2 years, after controlling for age, level of education, MS phenotype, disease severity, physical disability, and baseline PST score. Additional multicenter longitudinal prospective studies are needed to further support these findings. Future studies should evaluate the rate and magnitude of cognitive decline across multiple cognitive domains in individuals with MS deemed to have clinically stable disease, as this may allow clinicians a sensitive and effective tool in measuring progression independent of relapse activity. ■

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REFERENCES

1. Evans C, Beland SG, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology*. 2013;40(3):195-210. doi:10.1159/000342779
2. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler*. 2020;26(14):1816-1821. doi:10.1177/1352458520970841
3. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol*. 2008;7(12):1139-1151. doi:10.1016/S1474-4422(08)70259-X.
4. Langdon DW. Cognition in multiple sclerosis. *Curr Opin Neurol*. 2011;24(3):244-249. doi:10.1097/WCO.0b013e328346a43b
5. Johnen A, Landmeyer NC, Bürkner PC, Wiendl H, Meuth SG, Holling H. Distinct cognitive impairments in different disease courses of multiple sclerosis-a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;83:568-578. doi:10.1016/j.neubiorev.2017.09.005

6. Oh J, Suthiphosuwan S, Sati P, et al. Cognitive impairment, the central vein sign, and paramagnetic rim lesions in RIS. *Mult Scler*. 2021;27(14):2199-2208. doi:10.1177/13524585211002097
7. Glanz BI, Holland CM, Gauthier SA, et al. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. *Mult Scler*. 2007;13(8):1004-1010. doi:10.1177/1352458507077943
8. Benedict RHB, DeLuca J, Enzinger C, Geurts JJG, Krupp LB, Rao SM. Neuropsychology of multiple sclerosis: looking back and moving forward. *J Int Neuropsychol Soc*. 2017;23(9-10):832-842. doi:10.1017/S1355617717000959
9. Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler*. 2017;23(8):1123-1136. doi:10.1177/1352458517694432
10. Clemens L, Langdon D. How does cognition relate to employment in multiple sclerosis? a systematic review. *Mult Scler Relat Disord*. 2018;26:183-191. doi:10.1016/j.msard.2018.09.018
11. Portaccio E, Stromillo ML, Goretti B, et al. Neuropsychological and MRI measures predict short-term evolution in benign multiple sclerosis. *Neurology*. 2009;73(7):498-503. doi:10.1212/WNL.0b013e3181b351fd
12. Razzolini L, Portaccio E, Stromillo ML, et al. The dilemma of benign multiple sclerosis: can we predict the risk of losing the "benign status"? a 12-year follow-up study. *Mult Scler Relat Disord*. 2018;26:71-73. doi:10.1016/j.msard.2018.08.011
13. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol*. 2020;19(10):860-871. doi:10.1016/S1474-4422(20)30277-5
14. Baddeley A. Working memory. *Science*. 1992;255(5044):556-559. doi:10.1126/science.1736359
15. Macaron G, Baldassari LE, Nakamura K, et al. Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment and magnetic resonance imaging metrics. *Eur J Neurol*. 2020;27(7):1238-1249. doi:10.1111/ene.14239
16. Bergendal G, Fredrikson S, Almkvist O. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *Eur Neurol*. 2007;57(4):193-202. doi:10.1159/000099158
17. Chiaravalloti ND, Stojanovic-Radic J, DeLuca J. The role of speed versus working memory in predicting learning new information in multiple sclerosis. *J Clin Exp Neuropsychol*. 2013;35(2):180-191. doi:10.1080/13803395.2012.760537
18. Sumowski JF, Benedict R, Enzinger C, et al. Cognition in multiple sclerosis: state of the field and priorities for the future. *Neurology*. 2018;90(6):278-288. doi:10.1212/WNL.0000000000004977
19. Rao SM, Losinski G, Mourany L, et al. Processing speed test: validation of a self-administered, iPad-based tool for screening cognitive dysfunction in a clinic setting. *Mult Scler*. 2017;23(14):1929-1937. doi:10.1177/1352458516688955
20. Rudick RA, Miller D, Bethoux F, et al. The Multiple Sclerosis Performance Test (MSPT): an iPad-based disability assessment tool. *J Vis Exp*. 2014;(88):e51318. doi:10.3791/51318
21. Mowry EM, Bermel RA, Williams JR, et al. Harnessing real-world data to inform decision-making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). *Front Neurol*. 2020;11:632. doi:10.3389/fneur.2020.00632
22. Landmeyer NC, Bürkner PC, Wiendl H, et al. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: a meta-analysis. *Neurology*. 2020;94(22):e2373-e2383. doi:10.1212/WNL.0000000000009522
23. Ontaneda D, Tallantyre EC, Raza PC, et al. Determining the effectiveness of early intensive versus escalation approaches for the treatment of relapsing-remitting multiple sclerosis: the DELIVER-MS study protocol. *Contemp Clin Trials*. 2020;95:106009. doi:10.1016/j.cct.2020.106009
24. Baldassari LE, Nakamura K, Moss BP, et al. Technology-enabled comprehensive characterization of multiple sclerosis in clinical practice. *Mult Scler Relat Disord*. 2020;38:101525. doi:10.1016/j.msard.2019.101525
25. Jia X, Gao C, Cui L, Guo C. Neurophysiological evidence for the retrieval practice effect under emotional context. *Int J Psychophysiol*. 2020;147:224-231. doi:10.1016/j.ijpsycho.2019.12.008
26. Klaver R, De Vries HE, Schenk GJ, Geurts JJG. Grey matter damage in multiple sclerosis: a pathology perspective. *Prion*. 2013;7(1):66-75. doi:10.4161/pri.23499
27. Mahajan KR, Nakamura K, Cohen JA, Trapp BD, Ontaneda D. Intrinsic and extrinsic mechanisms of thalamic pathology in multiple sclerosis. *Ann Neurol*. 2020;88(1):81-92. doi:10.1002/ana.25743
28. Vercellino M, Plano F, Votta B, Mutani R, Giordana MT, Cavalla P. Grey matter pathology in multiple sclerosis. *J Neuropathol Exp Neurol*. 2005;64(12):1101-1107. doi:10.1097/01.jnen.0000190067.20935.42
29. Khalil M, Enzinger C, Langkammer C, et al. Cognitive impairment in relation to MRI metrics in patients with clinically isolated syndrome. *Mult Scler*. 2011;17(2):173-180. doi:10.1177/1352458510384009
30. Leavitt VM, Tosto G, Riley CS. Cognitive phenotypes in multiple sclerosis. *J Neurol*. 2018;265(3):562-566. doi:10.1007/s00415-018-8747-5
31. Damasceno A, Pimentel-Silva LR, Damasceno BP, Cendes F. Cognitive trajectories in relapsing-remitting multiple sclerosis: a longitudinal 6-year study. *Mult Scler*. 2020;26(13):1740-1751. doi:10.1177/1352458519878685
32. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol*. 2020;77(9):1132-1140. doi:10.1001/jamaneurol.2020.1568