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ARTICLE

Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis

A meta-analysis

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Abstract

Objective

Disease-modifying treatments (DMTs) are the gold standard for slowing disability progression in multiple sclerosis (MS), but their effects on cognitive impairment, a key symptom of the disease, are mostly unknown. We conducted a systematic review and meta-analysis to evaluate the differential effects of DMTs on cognitive test performance in relapsing-remitting MS (RRMS).

Methods

PubMed, Scopus, and Cochrane Library were searched for studies reporting longitudinal cognitive performance data related to all major DMTs. The standardized mean difference (Hedges *g*) between baseline and follow-up cognitive assessment was used as the main effect size measure.

Results

Forty-four studies, including 55 distinct MS patient samples, were found eligible for the systematic review. Twenty-five studies were related to platform therapies (mainly β-interferon [n = 17] and glatiramer acetate [n = 4]), whereas 22 studies were related to escalation therapies (mainly natalizumab [n = 14] and fingolimod [n = 6]). Reported data were mostly confined to the cognitive domain processing speed. A meta-analysis including 41 studies and 7,131 patients revealed a small to moderate positive effect on cognitive test performance of DMTs in general (g = 0.27, 95% confidence interval [CI] = [0.21–0.33]), but no statistically significant differences between platform (g = 0.27, 95% CI = [0.18–0.35]) and escalation therapies (g = 0.28, 95% CI = [0.19–0.37]) or between any single DMT and β-interferon.

Conclusions

DMTs are effective in improving cognitive test performance in RRMS, but a treatment escalation mainly to amend cognition is not supported by the current evidence. Given the multitude of DMTs and their widespread use, the available data regarding differential treatment effects on cognitive impairment are remarkably scant. Clinical drug trials that use more extensive cognitive outcome measures are urgently needed.

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Glossary

ARR = annualized relapse rate; **CI** = confidence interval; **DMT** = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **OSF** = Open Science Framework; **PASAT** = Paced Auditory Serial Addition Test; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting MS; **SDMT** = Symbol Digits Modalities Test.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS, characterized by progressive neuroaxonal degeneration and cerebral gray matter atrophy.[1,2] Cognitive impairment is regarded a key symptom of MS, with a prevalence up to 60%.[3] Patients with MS with cognitive impairment have lower employment rates, engage in fewer social activities, and are at a greater risk of developing comorbid psychiatric illnesses,[4] underlining the clinical and socioeconomic significance of cognitive impairment as a relevant marker of disease severity.[5]

Today, the use of disease-modifying treatments (DMTs) with immunomodulatory or immunosuppressive effects is the gold standard in MS therapy. To evaluate the benefits of these drugs, researchers have focused on diverse outcomes including annualized relapse rate (ARR), neurologic disability measured by the Expanded Disability Status Scale (EDSS), or MRI metrics of disease burden (e.g., lesion activity and load). Several meta-analyses of randomized (placebo) controlled trials (RCTs) substantiated the general efficacy of the currently available DMTs regarding these outcome parameters.[6] In general, escalation therapies such as natalizumab or alemtuzumab have a greater impact on disability worsening, lesion activity, and load than platform therapies such as β-interferon.[7]

Unfortunately, we know only little about the effects of DMTs on cognition in patients with MS. The sparse evidence available hints toward an overall beneficial effect on cognitive functioning for a range of DMTs.[8,9] However, it remains unclear whether more potent escalation treatments have a systematically greater impact on slowing and stabilizing cognitive decline compared with platform therapies. To our knowledge, this is the first systematic review and meta-analysis that specifically gathers and evaluates the available evidence regarding the effects of DMTs on cognitive test performance to provide clinicians with unbiased advice for treating cognitive impairment in MS.

Methods

Search strategy

To be included in the present systematic review, articles had to (1) be written in English, French, Spanish, or German language; (2) report on an adult relapsing-remitting MS (RRMS) sample; (3) assess the effects of (at least) 1 DMT in a longitudinal design; and (4) report data on (at least) 1 standardized cognitive test performed at baseline and follow-up, as (5) either mean and SDs or in an equivalent format (e.g., z values). In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[10] and the Population Intervention Comparison Outcome framework, an elaborate search strategy (192 search terms) was developed. The DMTs that were included in the systematic search were β-interferon, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, cyclophosphamide, laquinimod, daclizumab, ocrelizumab, cladribine, azathioprine, rituximab, and ozanimod. To increase search sensitivity, different synonyms were used for the clinical condition (e.g., "multiple sclerosis," "relapsing-remitting multiple sclerosis," and "RRMS"), the DMTs (e.g., "natalizumab" and "Tysabri"), and the cognitive outcomes (e.g., "SDMT" and "symbol digit modalities test"). The complete search algorithm that was deployed in all database searches is given in the Open Science Framework (OSF) online repository osf.io/ujdhw/. PubMed, Scopus, and Cochrane databases were searched, looking at the period from inception date to July 30, 2018. In addition, ECTRIMS and ACTRIMS conference abstracts and reference lists of published articles were screened for further studies.

Selection of articles

One author (N.C.L.) performed initial abstract screening. Two authors (N.C.L. and A.J.) retrieved and independently examined the full articles with regard to the inclusion criteria. In cases of incompletely reported data, the authors and/or pharmaceutical companies sponsoring the research were contacted with a formal request to provide additional data. In a consensus meeting, 4 authors (N.C.L., A.J., S.G.M., and T.R.) made the final decision on study inclusion.

Data extraction

We used a tailor-made standardized data extraction spreadsheet that captured (1) demographic information (treatment duration, age, sex, education, disease duration, and baseline EDSS score), (2) study information (e.g., number of patients and length of the treatment period in months), (3) DMT type, and (4) cognitive tests. To evaluate the quality of included studies, we rated all articles using a modified version of the Downs and Black checklist (see the OSF online repository for details).[11] This checklist assesses study quality regarding reporting, external validity, and internal validity with a maximum achievable score of 27. The reported neuropsychological outcomes were organized into 7 cognitive domains: cognitive processing speed, verbal memory, visual memory, attention, visuospatial processing, executive functions, and multiple domain screenings. Reported treatments were broadly grouped into platform therapies and escalation therapies (table 1 for details).

Table 1 Number of patient samples reported and total number of patients grouped by treatment

Treatment	k	n	No. of RCT samples (%)
Platform therapies	32	4,490	10 (31.25)
β-interferon	21	2,314	6 (28.57)
Glatiramer acetate	7	375	3 (42.86)
Dimethyl fumarate	3	801	1 (33.33)
Teriflunomide	1	1,000	0 (0.00)
Escalation therapies	23	2,693	4 (17.39)
Natalizumab	14	600	1 (7.14)
Fingolimod	6	1988	3 (50.00)
Alemtuzumab	1	21	0 (0.00)
Ocrelizumab	NA	NA	NA
Cladribine	NA	NA	NA
Rituximab[a]	1	75	0 (0.00)
Cyclophosphamide[a]	1	9	0 (0.00)
Mitoxantrone[a]	NA	NA	NA
Laquinimod[a]	NA	NA	NA
Azathioprine[a]	NA	NA	NA
Ozanimod[a]	NA	NA	NA

Abbreviations: k = number of samples; n = number of patients; NA = not available; RCT = randomized controlled trial.
[a] Third-line or unapproved therapy in some countries. One study reported longitudinal data on daclizumab,[15] which has been omitted here because the drug was withdrawn from the market (for details, see the OSF online repository).

Statistical analysis

The metafor package[12] of R software[13] was used to perform a multilevel meta-analysis. Hedges *g* was computed as the main summary effect size, representing differences between baseline and follow-up cognitive assessment, divided by the pooled SD for the respective cognitive outcome. Positive effect sizes indicate an improvement of test performance from baseline to follow-up. Moderator analyses were conducted to assess potentially confounding influences of clinical and demographic variables. A priori, treatment duration, baseline EDSS score, sex, age, disease duration, years of education, and study quality score were specified as potential moderator variables. Publication bias was investigated by inspecting funnel plots and by using the Egger regression test[14] and the trim-and-fill method.[15]

Data availability

All analyses and supplementary material, including e-references, are accessible via OSF (osf.io/ujdhw/). Additional data will be shared by request from any qualified investigator.

Results

Results of the systematic review

Figure 1 shows an overview of the study selection process. The initial search yielded a total of 1,861 hits. After removing duplicates, 1,276 articles were screened for eligibility. The authors and pharmaceutical companies, as the rightsholders of another 95 potentially relevant articles, were contacted with a formal request to provide additional data, but only 8% submitted additional data that led to the inclusion of the article. The final sample of the systematic review consisted of 44 studies (n = 7,183 patients from k = 55 treatment samples), which each reported at least 1 longitudinally assessed cognitive outcome specifically related to treatment with a DMT.

Distribution of treatments

Table 1 shows the distribution of DMTs among the 44 eligible studies. Platform therapies were investigated in 25 independent studies (k = 32 samples), whereas escalation therapies were researched in 22 studies (k = 23). The most commonly studied DMT was β-interferon, followed by natalizumab, glatiramer acetate, and fingolimod. One article evaluated the effect of daclizumab,[16] but because the drug has been withdrawn from the market, it was omitted from all further analysis. No articles reported longitudinal cognitive outcomes for the following DMTs: cladribine, ocrelizumab, mitoxantrone, laquinimod, azathioprine, and ozanimod.

Study characteristics and quality indices

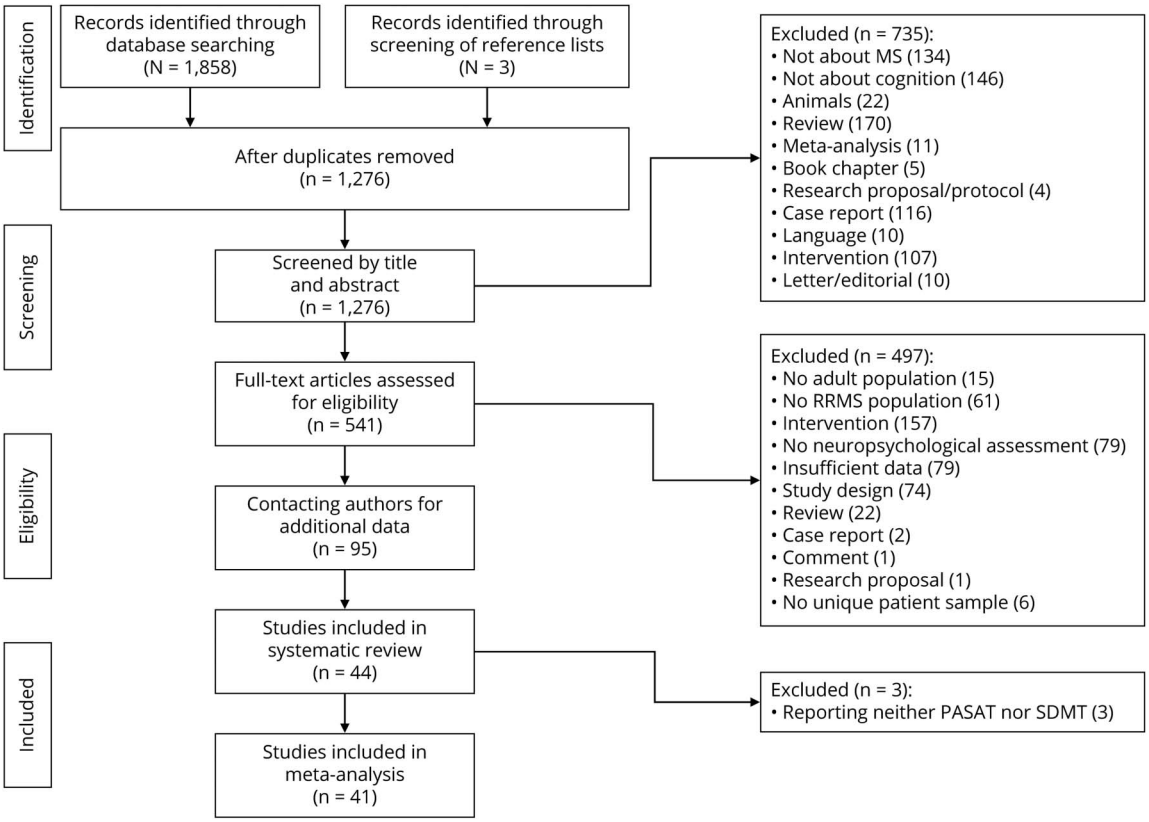
The average treatment duration with DMTs was 1.21 (±0.51) years across all studies. Only 14 of the 55 treatment samples were part of RCTs. Overall, the number and proportion of RCTs (as opposed to uncontrolled studies) were lower for escalation (k = 4, 28.57% of all escalation samples) compared with platform therapies (k = 10, 71.43%). Only 17 of the 44 studies (38.64%) addressed potential practice effects of cognitive tests, for example, by reporting the use of parallel forms and/or by parallel longitudinal assessment of a control group. The majority of studies (25 of 44) reported 3 or less cognitive tests, whereas only 19 reported more than 3 and up to 21 cognitive test results (table 2). The most commonly investigated neurocognitive domain was processing speed, which was reported in 41 studies (k = 52). The Paced Auditory Serial Addition Test (PASAT 3s k = 36, PASAT 2s k = 17) and the Symbol Digits Modalities Test (SDMT) (k = 26) were the most frequently reported individual tests (see the OSF online repository for details on all other reported cognitive domains and tests). Given the limited number of cognitive domains other than processing speed and the dominance of the PASAT and SDMT, we based our meta-analysis on studies that included either one or both of these 2 tests (41 studies, k = 52).

Results of the meta-analysis

Patient group characteristics

Demographic and clinical characteristics of the combined full RRMS sample from all 41 studies and of the subsamples of patients on platform therapies and on escalation therapies are

Figure 1 Flowchart illustrating the screening and study selection process for the systematic review and meta-analysis



MS = multiple sclerosis; n = number of articles; PASAT = Paced Auditory Serial Addition Test; RRMS = relapsing-remitting MS; SDMT = Symbol Digits Modalities Test.

shown in table 3. To summarize, the full sample (n = 7,131) had a mean age of 36.56 (±4.33) years; a female proportion of 67.21% (±11.09); a mean disease duration of 6.81 (±3.36) years; and an average years of education of 12.47 (±0.80). Mild to moderate physical disability was reported in the full patient sample, with a mean baseline EDSS score of 2.66 (±0.88). The treatment groups differed significantly regarding years of education ($M_{platform}$ = 13.02 [±0.63], $M_{escalation}$ = 12.12 [±0.72]), disease duration ($M_{platform}$ = 5.64 [±3.46], $M_{escalation}$ = 8.13 [±2.75]), and EDSS score ($M_{platform}$ = 2.30 [±0.57], $M_{escalation}$ = 3.13 [±0.99]), pointing toward more active disease characteristics and greater disease burden in the escalation group samples. No other differences regarding patient characteristics were found between treatment groups.

Treatment effects between baseline and follow-up

Escalation and platform therapy groups both improved in cognitive test performance between baseline and follow-up with a small to moderate effect size ($g_{platform}$ = 0.27, 95% confidence interval [CI] = [0.18–0.35]; $g_{escalation}$ = 0.28, 95% CI = [0.19–0.37]) (figure 2; see the OSF online repository for single-study effect sizes). SD between studies (τ_s) was 0.12, and SD between outcomes (τ_o) was 0.08, indicating that approximately 50% of the total variance was due to heterogeneity across studies. There were no significant group differences, indicating that escalation therapies were not more effective than platform therapies in improving cognitive test performance (figure 2). Critically, also no single DMT improved cognitive test performance more effectively than β-interferon ($g_{\beta\text{-interferon}}$ = 0.30, 95% CI = [0.19–0.41]; figure 2 and table 4).

Influence of study quality

Taking into account the potential influence of study quality, we conducted a sub–meta-analysis including only RCTs with the highest quality score (a total of 9 studies). However, this analysis also showed no statistically significant differences between platform ($g_{platform}$ = 0.27, 95% CI = [0.12–0.43]) and escalation therapies ($g_{escalation}$ = 0.28, 95% CI = [0.07–0.48]). The SD between studies (τ_s) was 0.12 and between outcomes was (τ_o) 0.12. Here, 66.73% of the total variance was due to heterogeneity across studies.

Moderator analysis and assessment of potential publication bias

To test the influence of potentially confounding covariates on our results, moderator analyses were conducted. We found none of the considered moderator variables (treatment duration, baseline EDSS score, sex, age, disease duration, study quality score, and years of education) to have a significant

Table 2 Overview of the 44 studies and investigated cognitive domains included in the systematic review

Study	QS	n	DMT	Investigated cognitive domains (no. of reported outcomes)
Zivadinov et al.[17]	14	27	β-IFN	MDS (1)
Kleiter et al.[18]	16	116	β-IFN	PS (1)
Benesova et al.[19]	16	272	β-IFN	PS (1)
Flechter et al.[20]	11	16	β-IFN	EF (1)
Mokhber et al.[21]	20 (RCT)	65	β-IFN	PS (3), VeM (2), ViM (2), EF (1)
Cinar et al.[22]	15	161	β-IFN, GA	PS (1), ViM (1), VeM (1)
Utz et al.[23]	14	40	β-IFN, NTZ, FMD	ATT (5), ViM (2), EF (4), PS (1), VeM (1)
Barak and Achiron[24]	13	23	β-IFN	PS (2), EF (1), VeM (1), ViM (1)
Patti et al.[25]	14	459	β-IFN	PS (2), EF (1), VeM (3), ViM (2)
Comi et al.[26]	19 (RCT)	108	β-IFN, FMD	PS (3), VeM (3), ViM (2), EF (1)
Gerschlager et al.[27]	16	14	β-IFN	PS (2), VeM (2), ViM (2), ATT (1), EF (1)
Benedict et al.[16]	21 (RCT)	922	β-IFN	PS (1)
Baier et al.[28]	15	137	β-IFN	PS (1)
Amato et al.[29]	13	49	β-IFN	PS (3), VeM (3), ViM (2), EF (2)
Tomassini et al.[30]	14	26	β-IFN	PS (1)
Lacy et al.[31]	16	9	β-IFN	EF (5), VeM (2), ViM (2)
Davydovskaya et al.[32]	14	26	β-IFN	PS (1)
Zecca et al.[33]	21 (RCT)	19	β-IFN, NTZ	PS (1)
Boiko et al.[34]	19 (RCT)	122	GA	PS (1)
Weinstein et al.[35]	18 (RCT)	125	GA	PS (3), VeM (3), ViM(2), EF(1)
Ziemssen et al.[36]	16	72	GA	PS (1)
Al-iedani et al.[37]	14	20	DF	PS (1)
Giovannoni et al.[38]	21 (RCT)	769	DF	PS (1)
Montes Diaz et al.[39]	12	12	DF	PS (1)
Coyle et al.[40]	17	1,000	TFD	PS (1)
Rorsman et al.[41]	13	21	NTZ	PS (3), VeM (2), ViM (2), EF (2), VP (1)
Allali et al.[42]	14	9	NTZ	PS (4), EF (11), VeM(3), ATT (3)
Iaffaldano et al.[43]	16	100	NTZ	PS (3), VeM (3), EF (2), ViM (2)
Kunkel et al.[44]	13	51	NTZ	ATT (4), PS (3), EF (3)
Planche et al.[45]	14	48	NTZ	EF (3), PS (2), VeM (2), ATT (1)
Mattioli et al.[46]	12	39	NTZ	EF (6), PS (2), ATT (2), VeM (1), ViM (1), VP (1)
Lang et al.[47]	14	29	NTZ	VeM (7), ViM (3), PS (3), ATT (1)
Mattioli et al.[48]	16	24	NTZ	EF (6), PS (2), ATT (2), VeM (1), VP (1), ViM (1)
Talmage et al.[49]	14	15	NTZ	PS (1)
Svenningsson et al.[50]	13	195	NTZ	PS (2)
Novakova et al. (2015)[e1]	13	31	NTZ	PS (1)
Mattioli et al. (2011)[e2]	14	17	NTZ	EF (5), PS (2)
Langdon et al. (2016)[e3]	10	716	FMD	PS (1)

Continued

Table 2 Overview of the 44 studies and investigated cognitive domains included in the systematic review *(continued)*

Study	QS	n	DMT	Investigated cognitive domains (no. of reported outcomes)
Petsas et al. (2019)[e4]	14	32	FMD	PS (2)
Kappos et al. (2016)[e5]	21 (RCT)	783	FMD	PS (1)
Cree et al. (2018)[e6]	15 (RCT)	355	FMD	PS (2)
Riepl et al. (2018)[8]	15	21	ALZ	VeM (4), PS (3), EF (4), ATT (1), VP (1), ViM (1)
de Flon et al. (2017)[e7]	15	75	RIX*	PS (1)
Krishnan et al. (2008)[e8]	16	9	CP*	PS (1)

Abbreviations: ALZ = alemtuzumab; ATT = attention; β-IFN = β-interferon; CP = cyclophosphamide; DF = dimethyl fumarate; DMT = disease-modifying treatment; EF = executive function; FMD = fingolimod; GA = glatiramer acetate; n = number of patients; MDS = Multiple Domain Screening; NTZ = natalizumab; OSF = Open Science Framework; PS = processing speed; QS = study quality score assessed using a modified version of the Downs and Black checklist with a maximum of 27 points; RCT = randomized controlled trial; RIX = rituximab; VeM = verbal memory; ViM = visual memory; VP = visuospatial processing; TFD = teriflunomide.
One additional study reported longitudinal data on daclizumab,[15] which has been omitted here because the drug was withdrawn from the market (study details are given in the OSF online repository). No studies were found reporting cognitive data related to the following DMTs: ocrelizumab, cladribine, mitoxantrone*, laquinimod*, azathioprine*, ozanimod*; * = third-line or unapproved therapy in some countries.

impact on treatment effects regarding cognitive outcomes on a meta-analytic level (table 5 for details). Inspection of the funnel plots and using the trim-and-fill method hinted toward several missing outcomes on the left side, indicating a potential publication bias by underreporting of null or negative test results in studies with small sample sizes (see the OSF online repository for details).

Discussion

Despite the widespread use of different DMTs in MS, there is no consensus as to which therapy effectively improves cognitive impairment, one of the most frequent and debilitating symptoms of the disease.[e9] Currently, no clinical guidelines exist on whether cognitive impairment or its longitudinal progression presents the need in its own right for changing the DMT.[e10] Although previous studies hint toward beneficial effects of DMTs on cognitive impairment, the size and robustness of these effects are unclear.[e11] Particularly, whether more potent escalation therapies with superior impact on clinical and paraclinical measures of disease activity and burden also exert a greater impact on cognitive performance compared with platform therapies is unknown. With the current systematic review and multilevel meta-analysis, we aimed at combining the current body of evidence regarding change of cognitive test performance related to the intake of different DMTs.

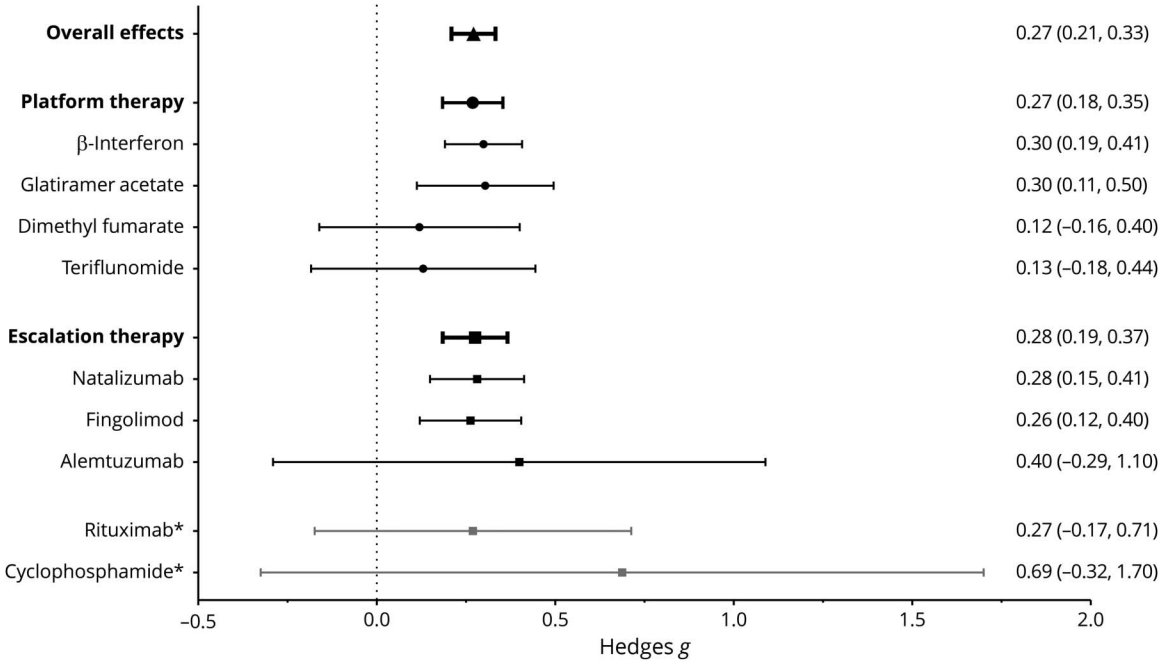
Our systematic review showed that a considerable number of articles assessed longitudinal cognitive effects of a range of commonly applied platform and escalation DMTs (particularly β-interferon and natalizumab). With regard to differential cognitive effects in platform vs escalation therapies, several drugs were, however, underrepresented (e.g., alemtuzumab and teriflunomide), and data on cognitive outcomes related to some newer drugs are currently missing (e.g., ocrelizumab and cladribine). Most of the included studies examined cognitive performance with a very limited number of neuropsychological tests, which were mostly confined to the domain of processing

Table 3 Demographics of the full patient sample included in the meta-analysis, split by type of treatment

	Full patient sample			Platform therapy only			Escalation therapy only		
	n = 7,131	41 studies	k = 52	n = 4,438	22 studies	k = 29	n = 2,693	22 studies	k = 23
	Mean	SD	k	Mean	SD	k	Mean	SD	k
Age, y	36.56	4.33	51	35.65	4.99	29	37.76	2.98	22
Female %	67.21	11.09	49	68.05	9.78	27	66.19	12.67	22
Education, y	12.47	0.80	13	13.02	0.63	5	12.12	0.72	8
Disease duration, y	6.81	3.36	47	5.64	3.46	25	8.13	2.75	22
EDSS score at baseline	2.66	0.88	51	2.30	0.57	29	3.13	0.99	22
Treatment duration, y	1.20	0.51	52	1.30	0.59	29	1.08	0.38	23

Abbreviations: EDSS = Expanded Disability Status Scale; k = number of treatment samples; n = number of patients.

Figure 2 Forest plot visualizing the mean effect sizes of longitudinal improvement of cognitive processing speed under different DMTs



Effect sizes are presented as Hedges *g*. Positive effect sizes indicate an improvement of cognitive performance between baseline and follow-up. Confidence intervals crossing the zero line indicate no significant effect of the respective treatment on cognition. Larger error bars (confidence intervals) reflect that only few samples and/or participants treated with the respective drug were included in the meta-analysis. One study further reported longitudinal data on daclizumab,[15] which has been omitted here because the drug was withdrawn from the market. For an overview of all single-study and population effect sizes, see the OSF online repository; *third-line or unapproved therapy in some countries. DMT, disease-modifying treatment; OSF = Open Science Framework.

speed. Only a minority of the included articles were RCTs, and most of these studies investigated older platform therapies only. In contrast, the majority of studies were uncontrolled observational studies and/or cognition was evaluated only as a secondary or even tertiary outcome. Unfortunately, the authors and rightsholders, particularly drug companies, were found overly restrictive in providing additional data. Despite these methodologic difficulties, our applied meta-analysis on longitudinal cognitive changes in tests of processing speed revealed a robust, small to moderately sized positive effect of DMTs overall. This result underlines current clinical guidelines advising DMTs for all newly diagnosed patients with RRMS.[e12] Apart from DMTs, the effectiveness of other drugs for improving cognitive impairment in MS has been evaluated previously.[e13] A recent meta-analysis of the available placebo-controlled trials in patients with MS, however, showed no superior effects of add-on acetylcholinesterase inhibitors or neurostimulants (including methylphenidate, modafinil, L-amphetamine sulfate, and lisdexamfetamine dimesylate) on cognitive performance.[e14] There is also growing evidence that neuropsychological rehabilitation programs, in addition to DMTs, may have a positive effect on cognitive impairment in MS.[e15] These programs are generally computer assisted and target a variety of cognitive domains (including memory, attention, visuospatial functions, and executive functions). As trainings are typically fitted to a patient's individual needs, there is a substantial heterogeneity regarding their content, duration, and frequency of administration. Consequently, a recent meta-analysis found effect sizes ranging from d = 0.15 to d = 0.54.[e15] As cognitive rehabilitation is still underrepresented in clinical care in many countries, and most patients additionally receive a DMT, a head-to-head comparison of the effect sizes of cognitive rehabilitation programs vs DMTs appears inadequate at this point.

Table 4 Improvement of cognitive performance grouped by single treatment compared with β-interferon

Treatment	Estimate	95% CI	*p* Value
Glatiramer acetate	0.005	−0.21 to 0.22	0.96
Teriflunomide	−0.17	−0.50 to 0.16	0.31
Natalizumab	−0.02	−0.19 to 0.15	0.83
Fingolimod	−0.04	−0.21 to 0.14	0.67
Cyclophosphamide[a]	0.39	−0.63 to 1.41	0.45
Alemtuzumab	0.10	−0.60 to 0.80	0.78
Rituximab[a]	−0.03	−0.49 to 0.43	0.90

Abbreviations: CI = confidence interval; DMT = disease-modifying treatment. No single DMT improved cognitive test performance more effectively than β-interferon ($g_{\beta\text{-interferon}}$ = 0.30, 95% CI = [0.19–0.41]); positive effect size estimates indicate greater (but not statistically significant) improvement regarding cognitive performance compared with β-interferon.
[a] Third-line or unapproved therapy in some countries.

Table 5 Moderator analysis

Moderator	Estimate	95% CI	*p* Value	k
Age	−0.006	−0.02 to 0.01	0.44	51
Sex	0.002	−0.006 to 0.01	0.60	49
Education	−0.02	−0.22 to 0.18	0.84	13
Disease duration	−0.01	−0.03 to 0.01	0.34	47
EDSS score	−0.03	−0.12 to 0.05	0.44	51
Treatment duration	−0.002	−0.01 to 0.01	0.73	52
Quality score	−0.005	−0.03 to 0.02	0.61	52

None of the considered moderator variables showed to have a significant impact on treatment effects regarding cognitive outcomes on a meta-analytic level. k = number of populations in which the respective moderator variable was reported.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale.

A second major finding of our meta-analysis is that escalation DMTs show no greater benefit for cognitive performance changes than platform therapies. The currently available body of evidence thus does not argue in favor of escalating treatment when cognitive performance is the main clinical target, as risks of serious adverse effects (e.g., progressive multifocal leukoencephalopathy related to natalizumab)[e16] appear too large compared with the potential benefits regarding cognitive performance. This result is particularly surprising, given the superior potency of escalation therapies concerning other clinical parameters of disease severity (e.g., EDSS score and ARR). The primary mode of action of escalation DMTs targets inflammatory processes of RRMS pathology.[e17,e18] In contrast, recent evidence suggests that cognitive impairment may be primarily driven by neurodegeneration, concomitant brain atrophy, and functional network collapse.[e19] Global brain atrophy in MS can in part progress independently from inflammatory processes, as mirrored by clinical relapses or new lesions on MRI.[e20,e21] The available evidence of close associations between cognitive impairment and regional atrophy of deep GM structures (e.g., hippocampus and nuclei of the basal ganglia) in MS further underlines the importance of the neurodegenerative component of the disease for cognitive performance.[e22] Taken together, the superior impact of escalation therapies on the inflammatory component of the disease may simply not lead to superior effects on cognitive test performance, as the latter may be primarily driven by neurodegeneration.[e19] Another potential explanation for measuring similar cognitive effects in platform vs escalation therapies is the influence of cognitive reserve and intellectual enrichment on standard tests of cognitive performance.[e23] Recently, the term "cognitive clinico-radiological paradox" has been established to describe weak associations between cognitive test performance and MRI metrics, particularly in young patients with less advanced physical disability and in early disease stages.[e24] Brain injury in these patients may still be compensated until a certain threshold is reached and performance differences become measurable with standard neuropsychological tests.[e24] In conclusion, although a superior effect of escalation therapies on cognitive performance is not visible in our analysis, it cannot be excluded. Specific characteristics of the investigated samples (i.e., relatively early disease stages in most pivotal studies), insensitive cognitive outcome measures, and the overall limited available body of evidence, especially for newer escalation therapies, may cloud such an effect.

Meta-analyses assemble and combine the available evidence and thus fully depend on the quantity and quality of published data. We focused our search on published, peer-reviewed studies and conference abstracts of ACTRIMS and ECTRIMS meetings that were written in English, Spanish, French, or German language. It is therefore possible that not all potentially relevant articles were included. Critically, our meta-analysis was underpowered to reliably assess the cognitive effects of several individual drugs that were represented by too few studies (e.g., alemtuzumab). However, by aggregating all available studies into platform and escalation therapies, the estimated pooled effect sizes for these broad treatment categories seem fairly accurate, given the relatively large number of included studies. Importantly, although processing speed is often regarded as the core domain of cognitive impairment in RRMS, differential effects of DMTs on other cognitive domains remain uninvestigated. Deficits in episodic memory, for example, are also frequent in MS[e25] and may play a crucial and independent role in everyday functioning of patients (e.g., in the occupational context). Evidence suggests that deficits in processing speed are more pronounced in early stages but advance slower compared with memory deficits.[e26] With regard to biological underpinnings, slowed processing speed is often attributed to diffuse lesions, axonal damage related to these lesions, and total brain volume loss. In contrast, deficits in episodic memory are seen as a result of disruptions in specific deep gray matter structures, most notably the hippocampi.[e27] Considering these distinctions, defining such a complex symptom like cognitive impairment based on only 1 domain remains disputable.

Furthermore, articles generally do not provide sufficient information on the prevalence and definitions of cognitive impairment in their samples. Thus, although we find an average improvement in longitudinal cognitive test performance from baseline to follow-up, we cannot provide estimations on the rate of alleviation of cognitive impairment or whether the observed mean changes are clinically meaningful in individual patients. Finally, because of the lack of studies that report longitudinal cognitive data from clinical placebo groups, a potential influence of practice effects on the improvement of cognitive test performance cannot be excluded. Although practice effects have been shown to be relatively small in tests for processing speed, and especially in the SDMT when using parallel forms,[e28] this issue has

been considered only in an unsatisfactory manner by most of the included studies. Despite that, available research hints at a protective effect of DMTs on cognition that exceeds the influence of potential effects of retesting.[e29] This is further supported by findings that show a clear cognitive decline in patients with RRMS and a reduced benefit of retesting compared with healthy controls.[e19,e30] Considering this, we are convinced that the observed changes in mean cognitive performance are not solely explainable by practice effects.

The current meta-analysis reveals a robust, small to moderately sized positive effect of DMTs on longitudinal cognitive test performance in RRMS. This result underlines the current recommendation to treat all patients with RRMS with DMTs after initial diagnosis. Nevertheless, we found no superior effects of escalation therapies compared with platform therapies regarding longitudinal gains in cognitive performance. Therefore, the currently published body of evidence does not favor an escalation of treatment on the basis of cognitive test performance alone. Notably, longitudinal data on cognitive performance during treatment with several newer DMTs (ocrelizumab and cladribine) are missing so far, and the overall quality of the currently available studies is low. The assessment of cognitive outcomes is still vastly underrepresented in RCTs evaluating DMTs. Although completed trials of, for example, ozanimod promise superior effects regarding cognitive impairment compared with β-interferon, these studies could not be included due to data unavailability at the time of the analysis.[e31]

Taken together, the field urgently needs large-scale RCTs, looking at cognitive outcomes in a range of already established drugs simultaneously, while controlling for the heterogeneity of the disease (differences in disease durations, physical disabilities, education, and prevalence of cognitive impairment). Pivotal drug trials need to include change-sensitive standardized multiple domain cognitive batteries (e.g., BICAMS).[e32] While controlling for potential practice effects by using adequate retesting intervals, parallel test versions, and longitudinal assessments in clinical control groups. Finally, drug companies need to be less restrictive with already available data and should advance toward a publicly open science concept to facilitate the urgently needed research in this area.

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Continued

Appendix *(continued)*

Name	Location	Contribution
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Heinz Holling, PhD	Department of Statistics, Faculty of Psychology, Westphalian-Wilhelms-University Münster, Germany	Critical revision of the manuscript for intellectual content
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Andreas Johnen, PhD	Clinic of Neurology with Institute of Translational Neurology, University Hospital Münster, Westphalian-Wilhelms-University Münster, Germany	Study concept and design, study selection, coding of studies and data extraction, data analysis and interpretation, and drafting of the manuscript

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Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: A meta-analysis

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