Neuroscience and Biobehavioral Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Distinct cognitive impairments in different disease courses of multiple sclerosis—A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Multiple sclerosis
Neuropsychological assessment
Meta-Analysis
Cognition
PPMS
RRMS

ABSTRACT

Cognitive impairment (CI) is common and debilitating in patients with multiple sclerosis. However, little is known about how different disease courses affect CI, impeding prognosis and disease management. Here, we contrasted the magnitude and profile of CI measured with standardized neuropsychological tests in patients with primary progressive multiple sclerosis (PPMS) against relapsing-remitting multiple sclerosis (RRMS) while considering potentially confounding demographic and clinical differences. Systematic literature review and meta-analysis was performed finding 47 eligible studies (N = 4460 patients). Effect-sizes for 12 cognitive domains were calculated as Hedges' *g*. Results indicated more severe CI overall ($g = -0.37, p < .001$) and in each single cognitive domain ($g = -0.28$ to $-0.65, p < .001$) in patients with PPMS despite comparable degrees of fatigue and depression. Moderator analyses revealed that these differences were not fully attributable to clinical heterogeneity between disease courses (e.g., age, disability). Particularly verbal learning and memory differentiated PPMS and RRMS independent from demographic differences. Results imply that, previously underrecognized, PPMS patients display severe degrees of CI and need more specialized disease management than RRMS patients.

1. Introduction

Cognitive impairment (CI) affects up to 70% of patients with multiple sclerosis (MS) partly independent from the course and stage of the disease (Amato et al., 2006; Chiaravalloti and DeLuca, 2008; Langdon, 2011). CI has adverse implications for patient's quality of life, rate of employment, engagement in social activities and prevalence of comorbid psychiatric disorders (Goverover et al., 2007; Mitchell et al., 2005; Rao et al., 1991b). A vast body of neuropsychological data on the degree and profile of CI in MS has been assembled in the past: In order of reported prevalence, the cognitive domains processing speed, episodic memory (visual memory slightly more than verbal memory) and executive functions have been identified to be affected already in the earliest clinical stages (Amato et al., 2006; Chiaravalloti and DeLuca, 2008; Diker et al., 2016; Patti et al., 2009; Pokryszko-Dragan et al., 2016; Rao et al., 1991a). Despite that, there is only limited research contrasting the profiles and the degree of CI in different disease courses. Patients with progressive forms i.e., secondary-progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) are generally found to display more severe CI, probably due to an additive neurodegenerative pathogenic component and more severe cortical gray matter atrophy (Aviv et al., 2012; Riccitelli et al., 2011; Vollmer et al., 2016). However, as SPMS is always preceded by a usually lengthy phase of relapsing-remitting multiple sclerosis (RRMS), this disease phenotype is inherently associated with more severe disability, longer disease duration, a higher lesion load and thus more severe CI than RRMS is not surprising (Giovannoni, 2004). Confounding factors such as a longer disease duration however, cannot per se account for differences in CI between RRMS and PPMS given that PPMS does not incorporate a preceding phase of RRMS. Whether PPMS and RRMS differ in a distinct pattern of cognitive deficits remains inconsistent across studies: Whereas some evidence suggests that PPMS patients show a non-specific pattern of greater CI across cognitive domains, other findings point to more distinct disturbances only in specific domains (e.g. language, visuospatial skills; Connick et al., 2013; Denney et al., 2005; Gaudino et al., 2001; Planche et al., 2016; Ruet et al., 2013). The

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http://dx.doi.org/10.1016/j.neubiorev.2017.09.005
Received 16 May 2017; Received in revised form 2 September 2017; Accepted 4 September 2017

role of moderating factors influencing differences in CI between PPMS and RRMS is inconclusive: Like in SPMS, some researchers argue that differences in CI between RRMS and PPMS are primarily related to demographic and clinical differences between subtypes, i.e., that higher levels of physical disability, longer disease duration, older age or more severe depressive symptoms sufficiently explain more severe CI in patients with PPMS (Achiron et al., 2013; Borghi et al., 2013; Huijbregts et al., 2004; Lynch et al., 2005; Ruano et al., 2016). Other evidence however, indicates that differences in CI between these subtypes persist even after statistically controlling for some of these variables and that rather unique pathogenic factors in PPMS account for them (Ruet et al., 2013).

To date, no meta-analysis focussing on potential differences in CI between PPMS and RRMS subtypes exists. The primary goal of this systematic review is thus to 1) quantify the magnitude of overall CI in patients with PPMS and RRMS by integrating all previously reported evidence, 2) identify and validate single cognitive domains and tests eligible to differentiate between subtypes and 3) explore the confounding influences of demographic and clinical differences (e.g., age, sex, education, disease duration, depression, fatigue, physical disability, manual dexterity) on potential between-group differences regarding CI.

2. Methods

For conducting this meta-analysis, we followed the PRISMA guidelines (Moher et al., 2009). Articles were independently screened for eligibility by two of the authors (AJ and NCL).

2.1. Inclusion criteria

Studies had to meet the following criteria to be included:

a Reporting results of at least one neuropsychological test (including fatigue and/or depression questionnaires) separately for PPMS and RRMS patient groups as described in the 1996 consensus paper (Lublin et al., 1996) diagnosed according to McDonald or Poser criteria (McDonald et al., 2001; Polman et al., 2005; Poser et al., 1983).
b Reporting sample characteristics and demographic variables for both groups (i.e., age, sex, expanded disability status scale (EDSS; Kurtzke, 1983), disease duration, education).
c Reporting neuropsychological test data and clinical questionnaires as unadjusted means and standard deviations, or in an equivalent format.

Criteria a was mandatory for inclusion. If criteria b and c were not met, authors were contacted for additional data. If only insufficient information was provided, studies were ultimately excluded. No disagreements between raters regarding inclusion of studies emerged.

2.2. Search strategy

We searched Pubmed, Scopus, and PsycINFO between September 1st and October 1st 2016 for relevant articles written in English or German language. The used search terms were: “primary progressive relapsing remitting multiple sclerosis” or “primary progressive multiple sclerosis” or “PPMS RRMS” or “PPMS” in conjunction with different keywords, e.g.; “cognition”; “neuropsychology”. The same search strategy was applied to relevant journals (eTable 1). Furthermore; reference lists of published articles were screened for additional studies to be included.

2.3. Data extraction

We used a tailor-made, standardized data extraction spreadsheet for all eligible studies. Demographic variables and patient characteristics from the articles were extracted. In accordance with other meta-analytic reviews investigating CI in MS as well as standard textbooks of neuropsychological assessment, we classified the neuropsychological test data into cognitive domains prior to extraction (Lezak et al., 2012; Prakash et al., 2008; Zakzanis, 2000). Based on the reported neuropsychological tests, data were categorized into 12 cognitive domains: working memory (holding and manipulating information for brief periods), processing speed (response times from speeded cognitive tasks), verbal learning (learning efficiency for verbal material over multiple iterations), immediate verbal memory (free and/or cued recall of verbal material after short delays), delayed verbal memory (free and/or cued recall of verbal material after delays > 20 min), visual memory (free and/or cued recall of visual material after variable delays), cognitive fluency (number of correct responses on tasks on divergent thinking), higher executive functions (planning efficiency, decision making, habit-inhibition, set-shifting, reasoning) visuospatial function (tasks with high demands on space perception and visuoconstruction e.g., figure copying or block-assembly), multiple domain screenings (short screening tests that incorporate various cognitive domains) and language (naming of objects, grammar and vocabulary knowledge) as well as the non-cognitive domains manual dexterity (tests stressing accurate motor performance), anxiety & depression and fatigue (both clinical questionnaire scores). Table 1 displays the most frequent tests and measures representing each domain. The complete allocation of tasks and test parameters to domains can be found in Appendix A.

2.4. Statistical analysis

The *metafor* (Viechtbauer, 2010) package of the R programming language (Team R.C., 2016) was used to perform the statistical analysis. Effect-sizes for neuropsychological data were computed as Hedges' g representing mean differences between PPMS and RRMS patients, divided by the pooled standard deviation for the respective cognitive domain. Negative effect-sizes indicate a poorer performance of patients with PPMS, compared to patients with RRMS. A multilevel meta-analysis was used to compute the average weighted effect-sizes across cognitive domains. This model allows estimating the between-study variance τ_s^2 to account for differences regarding the employed neuropsychological tests between studies, as well as the residual variance τ_e^2 to account for differences in effect-sizes within studies (Noortgate et al., 2014; for a detailed model-specification see Appendix A). To evaluate the significance of the results, confidence intervals ($\alpha = .05$) were considered. To ensure the validity of our results, cognitive domains reported in less than $k = 5$ studies were excluded from further analysis. Effect-sizes were interpreted as small ($d \geq .2$), moderate ($d \geq .5$) or large ($d \geq .8$) in accordance with Cohen's conventions. To assess the influence of confounders on CI, meta-regression analyses were performed. A priori, *age*, *sex*, *education*, *disease duration*, *fatigue, EDSS, manual dexterity* and *anxiety & depression* were classified as potentially moderating variables. To evaluate the risk of publication bias, funnel plots combined with Egger's regression test were applied (Sterne and Egger, 2001; Egger et al., 1997). In addition, the trim and fill method was used to quantify how many studies on either the left or right side of the funnel were missing to obtain symmetry (Duval and Tweedie, 2000).

3. Results

The study selection process is visualized in Fig. 1. Literature search delivered 4943 hits in total. After removing duplicates, 1004 studies were screened for eligibility. After full-text evaluation (N = 603) authors of 101 studies were contacted to provide additional data. 38% of the contacted authors replied and 27% could provide sufficient information. Ultimately, 47 studies were included in this meta-analysis (Table 2).

Table 1
Frequencies and effect-sizes of all cognitive and non-cognitive domains and most frequently used neuropsychological tests.

Cognitive Domain & Tests	% total outcomes	*k*	*n*	Hedges' *g*	95%-CI	*p*
Working Memory	15%	32	3057	−.33	−.47 to −.19	< .001
PASAT 2s	3%	8	695	−.43	−.66 to −.19	< .001
PASAT 3s	8%	26	2749	−.29	−.45 to −.13	< .001
Processing Speed	13%	27	1836	−.56	−.72 to −.41	< .001
SDMT	6%	20	1389	−.82	−1.01 to −0.64	< .001
Verbal Learning	3%	10	556	−.65	−.91 −.38	< .001
CVLT – Verbal Learning	1%	5	363	−.59	−.93 to −.25	< .001
Immediate Verbal Memory	4%	9	574	−.51	−.74 to −.28	< .001
CVLT – Immediate Recall	2%	3	188	−.58	−.92 to −.23	.001
RAVLT – Immediate Recall	1%	3	153	−.45	−.93 to .02	.06
Delayed Verbal Memory	12%	20	1415	−.53	−.69 to −.38	< .001
SRT – LTS	3%	9	783	−.66	−.89 to −.42	< .001
SRT – CLTR	2%	8	746	−.67	−.90 to −.43	< .001
SRT – DR	2%	8	746	−.55	−.79 to −.31	< .001
Visual Memory	7%	14	1074	−.42	−.60 to −.25	< .001
10/36 SPART – IR	2%	8	744	−.49	−.73 to −.25	< .001
10/36 SPART – DR	2%	7	644	−.39	−.64 to −.14	.002
Cognitive Fluency	8%	16	1205	−.32	−.50 to −.13	< .001
COWAT	3%	5	370	−.46	−.72 to −.20	< .001
Word List Generation Test	3%	8	633	−.14	−.39 to .10	.25
Higher Executive Functions	11%	12	710	−.28	−.44 to −.11	< .001
Stroop Test – Part C	1%	5	326	−.19	−.48 to .10	.21
Visuospatial Function	2%	6	336	−.43	−.74 to −.11	.008
RCFT – Copy Trial	1%	3	159	−.35	−.75 to .05	.08
Manual Dexterity	6%	14	1258	−.73	−.94 to −.52	< .001
Nine Hole Peg Test	6%	13	1244	−.76	−.96 to −.56	< .001
Anxiety & Depression	10%	26	1910	−.09	−.26 to .07	.26
Beck Depression Inventory	2%	6	421	−.51	−.82 to −.20	.001
Fatigue	7%	17	1088	−.14	−.35 to .07	.18
Fatigue Severity Scale	2%	8	600	−.19	−.48 to .10	.20

Note: Frequencies and effect-sizes for cognitive domains (in bold) and most often reported neuropsychological tests (in regular font). Negative effect-sizes indicate more impairment in the PPMS vs. RRMS group.% total outcomes = percentage that the respective domain or test accounts for out of the total outcomes; *k* = number of studies with outcomes from this domain/test; *n* = number of patients with outcomes from this domain/test; Hedges' *g* = effect-size comparing RRMS against PPMS; 95%-CI = confidence interval for Hedges' g effect-size; *p* = p value for Hedges' g effect-size; PASAT 2s = Paced auditory serial addition test 2 s interval; PASAT 3s = Paced auditory serial addition test 3 s interval; RCFT = Rey Complex Figure Test; SDMT = Symbol digit modalities test; SRT – LTS = Selective reminding test – long term storage; SRT – CLTR = Selective reminding test – consistent long-term retrieval; SRT – DR = Selective reminding test – delayed recall; 10/36 SPART – IR = Spatial recall test – immediate recall; 10/36 SPART – DR = Spatial recall test – delayed recall; COWAT = Controlled Oral Word Association Test.

3.1. Study and patient group characteristics

Data of 4460 patients with MS (1004 PPMS, 3456 RRMS) and 345 outcomes/tests (per disease phenotype) were recorded. Table 3 shows the clinical and demographic characteristics of the PPMS and RRMS patient groups. No significant difference was found for years of *education* (mean difference ≈ 3.5 months, $p = .41$). The mean *age* of the PPMS patients was significantly higher compared to the RRMS patients (mean difference ≈ 10.5 years, $p < .001$). There were less *females* in the PPMS group (mean difference ≈ 18%, $p < .001$) and patients with PPMS had a significantly longer *disease duration* compared to patients with RRMS (mean difference ≈ 15 months, $p = .02$). In addition, PPMS patients showed a significantly greater disability as measured by the *EDSS* compared to patients with RRMS (mean difference 2.69 points, $p < .001$).

3.1.1. Effect-sizes of neuropsychological tests

Table 1 provides an overview of the frequencies of reported tests and domains across studies. The most frequently examined cognitive domains within the included studies were: *working memory*, reported in $k = 32$ studies, *processing speed* ($k = 27$) and *anxiety & depression* ($k = 26$). Most commonly used neuropsychological tests were the Paced Auditory Serial Addition Test (PASAT 3s; Gronwall, 1977) ($k = 26$), the Symbol Digit Modalities Test (SDMT; Smith, 1968) ($k = 20$) and the Nine-Hole Peg Test (9-HPT; Goodkin et al., 1988) reported in $k = 13$ articles each (see Table 1 for details on effect-sizes of neuropsychological domains and single test outcomes).

3.2. Global differences in cognition between PPMS and RRMS

Overall effect-sizes for each included study are presented in Table 2: In total, 37 of the 47 included articles showed more impairment in the PPMS group ($g < 0$). The difference between PPMS and RRMS on overall neuropsychological performance (excluding the non-cognitive domains *anxiety & depression, fatigue* and *manual dexterity*) was significant: PPMS patients performed moderately worse compared to RRMS patients ($g = -0.37$, $p < .001$, see Fig. 2). Variance between studies (τ_s^2) was .125 and residual variance (τ_e^2) was .038. Given this heterogeneity, we would expect that only 11% of the studies and 14% of the cognitive test results indicate greater CI in RRMS than in PPMS ($g > 0$).

3.3. Effect-sizes categorized by cognitive domain

To investigate whether specific domains are differentially impaired in PPMS, we calculated effect-sizes for between-group differences for cognitive and non-cognitive domains (Fig. 2). No significant differences were found for *anxiety & depression* ($g = -0.09$, $p = .26$) and *fatigue*

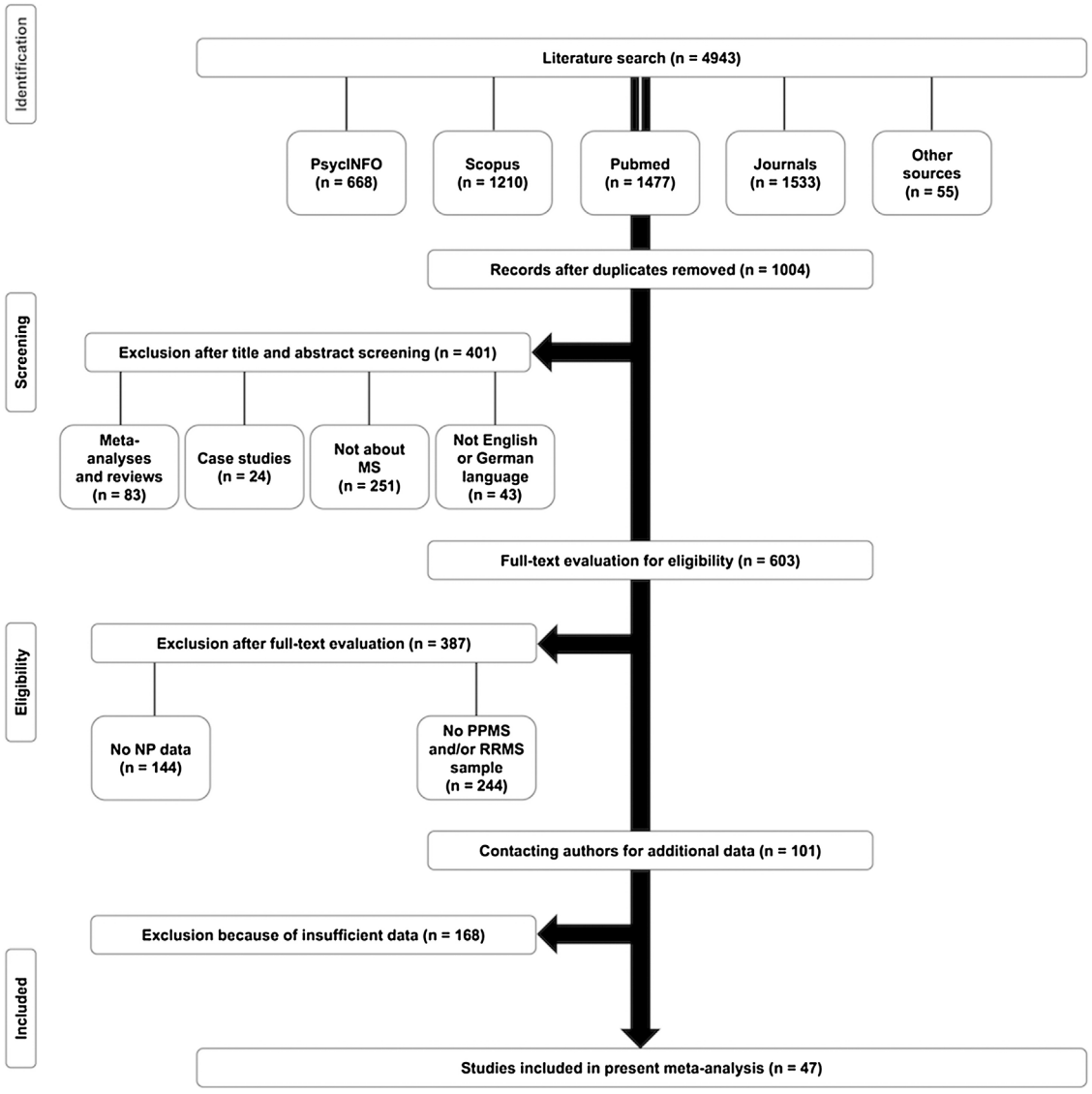

Fig. 1. Flowchart illustrating the study selection process in accordance with the PRISMA guidelines for meta-analyses. MS = multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis; NP = neuropsychological.

($g = -0.14$, $p = .18$). However, PPMS patients showed significantly more impairment in every other reviewed domain compared to RRMS patients. Moderate effect-sizes ($g = 0.5$ to 0.8) were found for the domains *processing speed, verbal learning, immediate verbal memory, delayed verbal memory* as well as for *manual dexterity*. Effect-sizes for *working memory, visuospatial function, visual memory, cognitive fluency* and *higher executive functions* were small ($g < = 0.5$). *Language* and *multiple domain screenings* were excluded due to a too small data basis (k < 5 studies reported these domains).

3.4. Moderator analysis

To facilitate interpretation, we only present significant results of mean differences of moderator variables between RRMS and PPMS here. For a more detailed analysis also exploring differential moderating effects for both groups separately, see eTable 2.

Group differences in *sex*, *education, disease duration, manual dexterity* and *fatigue* showed no significant moderating influences on any cognitive or non-cognitive domain.

Mean age difference between groups significantly moderated the cognitive domains *processing speed* ($b = -0.06$, $p = .001$) and *working memory* ($b = -0.04$, $p = .02$). Age sufficiently explained performance discrepancies between PPMS and RRMS for *processing speed* ("corrected g" = 0.03, 95%-CI = −0.35 to 0.42) and *working memory* ("corrected g" = 0.09, 95%-CI = −0.26 to 0.44) but not for other cognitive domains (eTable 2). When correcting for mean age difference, effect-sizes for the other cognitive domains decreased by $g = 0.12$ on average.

Mean *EDSS* difference only significantly moderated the non-cognitive domain *manual dexterity* (b = −0.42, p < .001). Statistically correcting for between-group *EDSS* differences consequently resulted in lower between-group discrepancy of *manual dexterity* performance ("corrected g" = 0.46, 95%–CI = −0.24 to 1.16) but did not significantly influence any cognitive domain (average decrease by $g = 0.14$). A small moderating effect was also found for the between-group difference of *anxiety & depression* ($b = -0.12$, p < .001): Correcting for between-group differences in *anxiety & depression* resulted in lower between-group differences regarding *processing speed* ("corrected g" = −0.48; 95%–CI = −0.72 to 0.25).

3.5. Sensitivity analysis

Inspection of funnel plots and Egger's test and trim and fill method (Table 4, Fig. 3) revealed no systematic publication bias. Only the domain *delayed verbal memory* showed evidence for asymmetric

Table 2
Effect-sizes for overall neuropsychological impairment for each included study.

Author (year)	Hedges' *g*	95%-CI	*n*	*p*
Ruet et al. (2013)	−.50	−.82 to −.19	101	.002
Rodrigues et al. (2011)	−.59	−.92 to −.25	66	< .001
Luo et al. (2014)	−1.24	−1.79 to −.69	20	< .001
Denney et al. (2005)	−.007	−.39 to .37	40	.97
Kraus et al. (2005)	−.19	−.51 to .13	47	.24
Potagas et al. (2008)	−.41	−.76 to −.06	98	.02
Gaudino et al. (2001)	−.19	−.59 to .20	39	.33
Yaldizli et al. (2016)	−.25	−.65 to .15	111	.22
van de Pavert et al., 2016	−.34	−.68 to .002	55	.05
Dackovic et al. (2016)	−1.34	−1.69 to −.99	100	< .001
Riccitelli et al. (2011)	.13	−.27 to .52	44	.53
Inglese et al. (2007)	.22	−.26 to .70	22	.37
Giovannoni et al. (2001)	.03	−.54 to .60	29	.92
Montel and Bungener (2007)	.59	−.10 to 1.28	82	.09
Wakefield et al. (2013)	.18	−.33 to .69	91	.49
Kroencke et al. (2000)	−.28	−.75 to .20	182	.25
Holper et al. (2010)	−.03	−.67 to .61	145	.92
Bergendal et al. (2007)	−.70	−1.14 to −.27	14	.002
Lapshin et al. (2014)	.19	−.20 to .59	59	.34
Wen et al. (2015)	−.68	−1.26 to −.11	20	.02
Hesse et al. (2014)	−.38	−1.17 to .41	21	.34
Denney et al. (2004)	.08	−.25 to .42	71	.62
Goldsmith et al. (2011)	−.36	−.92 to .21	93	.21
Jonkmann et al. (2015)	−.18	−.56 to .21	57	.36
Ysrraelit et al. (2008)	−1.41	-1.86 to −.97	132	< .001
Tavazzi et al. (2007)	−1.70	−2.44 to −.96	309	< .001
Rosti-Otajärvi et al. (2014)	−.60	−.94 to −.26	164	< .001
Kalkers et al. (2001a,b)	.05	−.75 to .86	42	.90
Miletić-Drakulić et al. (2006)	.05	−.45 to .55	92	.85
Kiy et al. (2011)	−.24	−.58 to .11	72	.18
Sepulcre et al. (2006)	−.47	−.83 to −.12	48	.01
Kalkers et al. (2000)	−.43	−.90 to .03	176	.07
Sepulcre et al. (2009)	−.28	−.70 to .14	33	.19
Ozcan et al. (2014)	−.51	−1.07 to .04	37	.07
Huijbregts et al. (2004)	−.61	−.94 to −.27	163	< .001
Horowski et al. (2011)	−.07	−.62 to .48	32	.80
Roosendaal et al. (2011)	.13	−.46 to .71	707	.67
Hughes (2013)	−.83	−1.20 to −.46	30	< .001
Scherer et al. (2007)	−.47	−.98 to .03	84	.06
Zivadinov et al. (2016)	−.47	−.96 to .02	118	.06
Kalkers et al. (2001a, 2001b)	−.53	−1.06 to −.01	93	.04
Kavcic and Scheid (2011)	−.53	−1.27 to .21	12	.16
Gao et al. (2014)	−.54	−1.10 to .01	59	.05
D'Orio et al. (2012)	−.41	−.77 to −.05	69	.03
Vellinga et al. (2009)	−.72	−1.18 to −.25	260	.003
Pinto et al. (2012)	−.12	−.54 to .29	53	.56
Papadopoulou et al. (2013)	−.002	−.55 to .55	68	.99

Note. All 47 studies included in the meta-analysis with effect-sizes (Hedges' *g*) for overall differences in neuropsychological test data between PPMS and RRMS. Negative effect-sizes indicate more severe impairment in PPMS. 95%-CI = confidence interval; *n* = participants included in the study; *p* = significance of between-group differences.

Table 3
Demographic and clinical sample data averaged over all 47 included articles.

Demographic Data	PPMS (*n* = 1004)		RRMS (*n* = 3456)			
	Mean	Range	Mean	Range	*p*	*k*
Age, y	51.17	40.90–56.10	40.67	34.30–49.40	< .001	46
Female No. (%)	18.02 (54.82)	0–36 (0–83)	157.68 (73.08)	4.00–469 (40.0–90.0)	< .001	46
Education, y	13.10	3.00–15.70	13.39	4.10–16.20	.41	23
Disease duration, y	9.92	2.33–20.20	8.66	3.40–19.70	.02	42
EDSS	5.01	2.17–6.60	2.32	1.50–4.20	< .001	36

Note. PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; *k* = number of studies reporting the variable; y = years; all means are weighted for sample size, *p* values from unmatched *t*-tests comparing means; EDSS = expanded disability status scale.

distribution across studies: Trim and fill method indicated 14 missing outcomes on the left side thus possibly even underestimating impairment of patients with PPMS in this domain.

4. Discussion

To date, differences in CI between RRMS and PPMS patients have not yet been systematically contrasted on a meta-analytic level. Although previous evidence hint at more severe CI in patients with PPMS, it is unclear whether certain cognitive domains are differentially affected (Connick et al., 2013; Gaudino et al., 2001; Denney et al., 2004). Moreover, it remains inconclusive whether potentially confounding demographic and clinical differences can account for differences between the two groups (Borghi et al., 2013; Lynch et al., 2005; Ruano et al., 2016). With the current systematic review including 47 original articles and using multilevel meta-analytic regression models on neuropsychological test data, we aimed to address these questions.

4.1. Global differences in cognition between PPMS and RRMS

A robust result of this meta-analysis is an overall greater CI of patients with PPMS compared to RRMS ($g = -0.37$). This result is in line with current literature indicating greater CI in PPMS, potentially due to a neurodegenerative pathogenic component and more gray matter atrophy in this disease subtype (Gaudino et al., 2001; Huijbregts et al., 2004; Vollmer et al., 2016). The clarity and magnitude of the effect was however, unexpected: Effect-sizes of CI in patients with PPMS as compared to RRMS were comparable to previously reported effect-sizes comparing patients with RRMS to healthy controls ($g = -0.54$; Prakash et al., 2008). Judging only from previously reported effect-sizes from meta-analyses on CI, our results imply that patients with PPMS in fact display a degree of CI comparable to other debilitating neurological diseases with much more recognized cognitive involvement, including non-demented Parkinson's disease, vascular cognitive impairment, and amyotrophic lateral sclerosis (Beeldman et al., 2016; Kudlicka et al., 2011; Vasquez and Zakzanis, 2015). These results strongly suggest that patients with PPMS need more specialized disease management and assistance to overcome obstacles imposed by CI on everyday life since effective symptomatic pharmaceutical treatment has not been established for this patient group to date (Comi, 2013). Reported prevalence of CI in MS in general is quite heterogeneous ranging from 30% up to 75% (Amato et al., 2006; Chiaravalloti and DeLuca, 2008). Considering the large differences in the degree of CI between subtypes of MS, previous data on cognitive functioning from mixed study samples (i.e., RRMS and progressive subtypes) may have come to imprecise conclusions, possibly overestimating the prevalence of cognitive impairments in MS in general but underestimating differences between disease courses. Our results suggest that, disease course or associated differences in pathogenic factors have a strong impact on the degree of CI in MS, warranting critical consideration of studies with mixed cohorts.

4.2. Is there a specific pattern of cognitive dysfunction in PPMS?

Patients with PPMS showed significantly greater CI than patients with RRMS in every reviewed cognitive domain. This finding is in line with literature indicating a broad cognitive dysfunction in PPMS when compared against RRMS (Planche et al., 2016; Ruet et al., 2013). Although the data basis for some cognitive domains was too small for a final appraisal (e.g., language; Renauld et al., 2016), results of this meta-analysis do not support the notion of subtype-specific disturbances in isolated cognitive domains (Connick et al., 2013; Gaudino et al., 2001; Denney et al., 2004). However, the overrepresentation of some neuropsychological domains and tests in the data and, in some instances, the heterogeneity of the measures within domains may open the possibility that more distinct cognitive dysfunction patterns exist but that the used measures and the methodology of a meta-analysis are

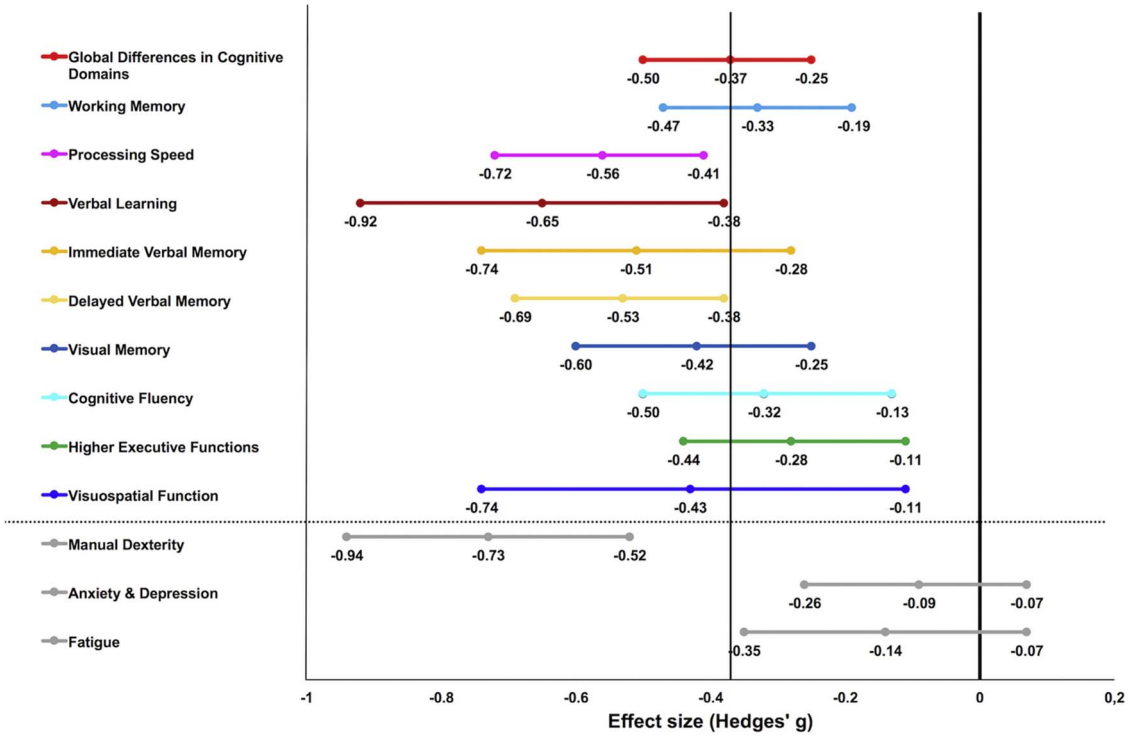

Fig. 2. Forest plot indicating effect-sizes for each cognitive domain. Effect-sizes are expressed as Hedges' g; Negative effect-sizes indicate greater impairment in patients with PPMS compared to RRMS; Dashed horizontal line seperates cognitive from non-cognitive domains; Solid vertical line indicates average level of cognitive differences (excluding the non-cognitive domains manual dexterity, anxiety & depression and fatigue) between PPMS and RRMS. RRMS = relapsing-remitting multiple sclerosis; PPMS = primary progressive multiple sclerosis.

not adequately accounting for this possibility.

4.3. Domains with the greatest discrepancies between PPMS and RRMS

Although CI was not restricted to single domains in PPMS, some domains were considerably more impaired and may thus be considered suggestive for the PPMS phenotype in neuropsychological assessments: Deficits in *verbal learning*, *processing speed*, *immediate* and *delayed verbal memory* exceeded the average CI difference between PPMS and RRMS: Regarding differential impairments in *processing speed* and *verbal memory*, our results are in line with previous evidence showing a greater deficit for both, cognitive speed and acquisition of new verbal material in PPMS vs. RRMS (Gaudino et al., 2001; Jonkman et al., 2015; Bergendal et al., 2007). Here, we found almost equally pronounced impairments on *delayed* and *immediate verbal memory recall,* supporting current evidence that the core of memory deficits in MS may be reduced performance in acquisition and encoding of new information(*verbal learning*) rather than an accelerated rate of forgetting (Gaudino et al., 2001). In line with this interpretation, some previous studies indicate that impairments in word list learning are closely linked to reduced *processing speed* in patients with MS (Gaudino et al., 2001; Archibald and Fisk, 2000). Taken together, our findings imply that neuropsychological assessment of patients with MS should incorporate in-depth examinations with tests for *processing speed*, *verbal learning* and *verbal memory* to best discriminate between disease subtypes. Particularly the latter two were also not associated with age-differences between RRMS and PPMS.

4.4. No differences in anxiety & depression or fatigue

We found no difference between PPMS and RRMS in the domain *anxiety & depression*. This is rather unintuitive considering the greater cognitive and physical disability in PPMS compared with RRMS (Rao et al., 1991b). Previous studies contrasting depressive symptoms

Table 4
Publication bias in single cognitive domains.

Cognitive Domain	Egger's regression test	Trim and fill
Working Memory	$t(51) = -.27$, $p = .79$	0 missing outcomes
Processing Speed	$t(42) = -.59$, $p = .56$	7 missing outcomes on the right side
Verbal Learning	$t(8) = -.62$, $p = .55$	3 missing outcomes on the right side
Immediate Verbal Memory	$t(11) = -.41$, $p = .69$	2 missing outcomes on the right side
Delayed Verbal Memory	$t(41) = 2.56$, $p = .01$	14 missing outcomes on the left side
Visual Memory	$t(23) = 1.42$, $p = .17$	6 missing outcomes on the left side
Cognitive Fluency	$t(24) = -.72$, $p = .48$	0 missing outcomes
Manual Dexterity	$t(20) = -.001$, $p = .99$	0 missing outcomes on the right side
Higher Executive Functions	$t(37) = 1.27$, $p = .21$	11 missing studies on the right side
Visuospatial Function	$t(4) = -.68$, $p = .53$	0 missing outcomes
Anxiety & Depression	$t(31) = .91$, $p = .37$	10 missing outcomes on the left side
Fatigue	$t(22) = 1.52$, $p = .14$	3 missing outcome on the left side

Note: Publication bias assessed for cognitive domains reported in k ≥ 5 studies; For Egger's regression test t-values and p-values are reported.

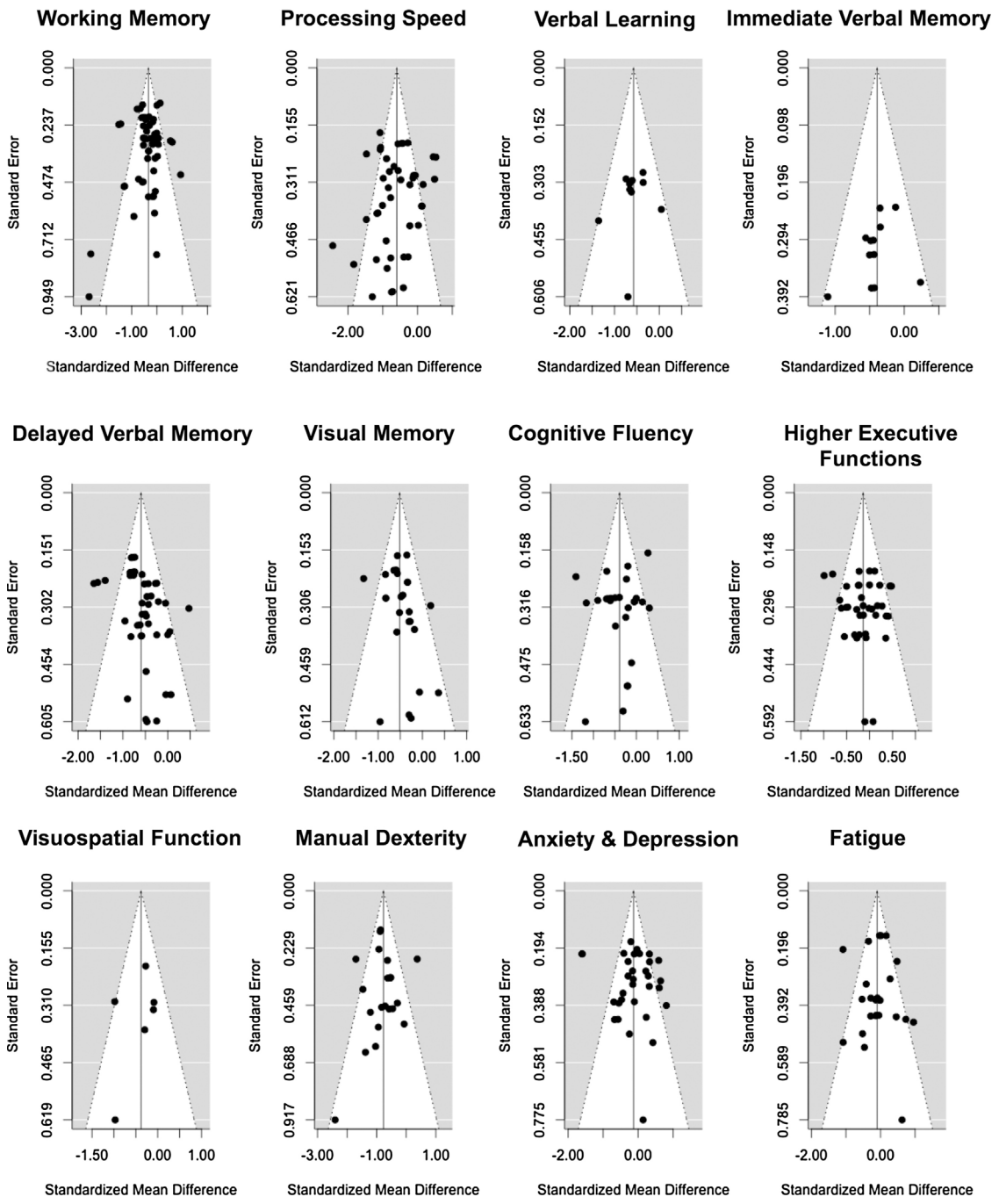

Fig. 3. Funnel-plots of Hedges' g effect-sizes for all cognitive domains, displaying standardized mean differences (x-axis) against the standard error (y-axis) for each outcome measure per cognitive domain and aligned for the overall mean. Points represent individual outcome measures (studies). Lack of symmetry can be interpreted as indicative of publication bias.

between PPMS and RRMS revealed conflicting results: Whereas some studies indicate that PPMS patients exhibit more severe depressive symptoms than patients with RRMS (Jones et al., 2012) others suggest a lower lifetime prevalence of major depression as well as fewer depressive symptoms in PPMS (Zabad et al., 2005; Montel and Bungener, 2007). One explanation for this may be differences regarding the use of elaborated coping strategies: In contrast to patients with RRMS who experience dynamic progression and remissions between relapses, patients with PPMS suffer from a constant worsening of their condition from onset of the disease and may thus have more needs and more time to adjust to the challenges CI imposes on their lives (Montel and Bungener, 2007; Zabad et al., 2005). Regarding *fatigue*, results of this meta-analysis also showed no evidence for differences between subtypes, although some previous studies report higher levels of *fatigue* in PPMS (Ruet et al., 2013; Kroencke et al., 2000; Lerdal et al., 2003). However, research focusing on *fatigue* and its interactions with different MS disease courses is sparse. Similar to depression, evidence suggests a significant influence of early psychological coping strategies on perceived fatigue (Lerdal et al., 2003).

4.5. Influences of moderating factors on cognition

A shortcoming of many studies on CI in MS is that demographic and clinical factors that may interact with cognition are not routinely analyzed (Costa et al., 2016). Here, we addressed this issue by performing meta-regression analyses with demographic and clinical

variables commonly reported. Interestingly our results showed no moderating effect on any cognitive domain for the factors *sex*, *years of education*, *disease duration, manual dexterity* and *fatigue.* These findings are of major clinical importance since e.g., *disease duration* has been referred to as a main contributor to cognitive decline in PPMS (Bergendal et al., 2007). Although our PPMS sample had a significantly longer *disease duration*, the mean difference was only 15 months and could not explain differences in CI between the two subtypes. In line with our findings, previous evidence also suggests only a limited influence of total *disease duration* on cognition in MS when considered in isolation (Ruet et al., 2013; Smestad et al., 2010).

A potential influence of formal *education* on cognition in MS is frequently discussed within the framework of cognitive reserve or intellectual enrichment, referring to functional compensation of CI despite structural brain damage (Sumowski and Leavitt, 2013). There is a general notion that more years of formal *education* may lead to more cognitive reserve and thus constitute a protective factor against CI (Benedict and Zivadinov, 2011; Luerding et al., 2016). However, years of *education* is only an indirect proxy for the concept of cognitive reserve and more closely related measures e.g., premorbid intelligence, reading activity, physical activity or job demands on cognitive flexibility were not routinely assessed within studies. Cultural diversity of the included patients and profoundly differing school systems between countries may further explain why we found no significant moderating influence of years of education on cognitive domains in the current meta-analysis.

Age had a significant moderating influence on the cognitive domains *processing speed* and *working memory* and controlling for age differences equalized between-group differences in these domains. As the impact of *age* on these two subdomains was almost equal in PPMS and RRMS, this finding likely represents a general, sample-related age-effect which is not specific for MS or for specific subtypes (although interactions between age and reduced brain-network plasticity in subtypes of MS are discussed; Schoonheim et al., 2010). Moderating effects of age on other cognitive domains were non-significant. Notably, the estimation of the influence of *age* on between-group differences was interpolated from a limited set of studies that included age-matched RRMS and PPMS patients.

Differences in *EDSS* also explained a considerable proportion of variance in the statistical model for overall performance. The moderating effect of the *EDSS* was however significantly driven by its association with the non-cognitive domain *manual dexterity*. A higher *EDSS* was associated with moderate performance deterioration in *manual dexterity* resulting in smaller differences between both groups. Importantly, although not absent, the moderating effect of *EDSS* was non-significant in all reviewed cognitive domains. Associations between global CI and higher *EDSS* have previously been reported when considered within large study populations (Lynch et al., 2005; Ruano et al., 2016). A major problem of the *EDSS* however, is its lack of reliability in measuring disability which needs to be considered when interpreting such results (Meyer-Moock et al., 2014).

Similar to *age*, we found a moderating influence of *anxiety & depression* on CI which was restricted to the domain *processing speed* and only of a small magnitude. The complex interplay between depressive symptoms and processing speed has previously been thoroughly investigated in MS (Diamond et al., 2008). Importantly, no significant group differences between patients with RRMS and PPMS were found for *anxiety & depression* here. Thus, although established associations between depression and cognitive domains such as *processing speed* were reflected in our results, in line with other studies we found that depression was not systematically related to disease subtype and could not account for between-group differences regarding CI (Amato et al., 2006; Thornton and Raz, 1997; Denney et al., 2004).

In conclusion, *age* and *EDSS* showed evidence for moderating between-group differences for the domains *processing speed*, *working memory* and *manual dexterity*. However, considering clinical and demographic heterogeneity provided no sufficient explanation for the vast differences found in a multitude of cognitive domains (e.g., *verbal learning, verbal memory*) between PPMS and RRMS.

4.6. Limitations

Meta-analyses depend on published research results. Similar to previous reports, we found that many studies examining cognition in MS failed to report results for PPMS and RRMS groups separately (Costa et al., 2016). Despite our efforts to obtain these data, not every potentially relevant article could be included. Only one cognitive domain however, was suspicious for a publication bias, underscoring the validity of our analyses. Secondly, meta-analyses only evaluate data on study level in terms of means, since individual values of subjects are not available. This may become an issue in moderator analysis, when influences of demographic variables that vary on patient level are evaluated. Different outcomes on study level compared to patient level may occur: A recent study has for example also found age and disability significantly moderating CI across MS subtypes but contrary to our results, these variables explained more variance than subtype per se (Ruano et al., 2016). More research in age- and EDSS- matched samples from different MS subtypes is highly needed.

The categorization of neuropsychological test data into broader cognitive domains can be ambiguous since domains are interrelated and overlapping (e.g., working memory and processing speed) and single tests may tap into numerous domains. A different allocation of test parameters into domains may have subsequently yielded slightly different results. Moreover, cognitive domains presented here may differ in terms of the heterogeneity of the included tests (e.g., *higher executive functions* incorporates quite heterogeneous cognitive tasks). More studies and primary data are needed to focus on potential between-group differences within those domains, that we subsumed here. Finally, despite the robustness of the found effect of an overall greater CI in PPMS, our results also show a noteworthy amount of heterogeneity: As expected from estimated between-study variance, 15% of all cognitive test results (i.e., 44 out of 288 excluding non-cognitive domains) indicated greater disturbances in the RRMS group.

4.7. Conclusions

Findings of this meta-analysis including 47 original studies underline that the magnitude of CI differs profoundly between PPMS and RRMS subtypes. PPMS patients exhibit significantly more CI in almost every cognitive domain: Particularly *verbal learning* and all measures of *verbal memory* discriminated between PPMS and RRMS, whereas no significant differences emerged for either *anxiety & depression* or *fatigue*. Importantly the differences in cognitive functioning between subtypes of MS persisted in large parts independent from demographic and clinical between-group differences: Influences of reviewed clinical moderator variables on cognition were either absent (i.e., *disease duration, sex, education, fatigue, manual dexterity)* or restricted to a limited number of domains: *Age* and *EDSS* significantly interacted with the cognitive domains *processing speed* and *working memory* as well as with *manual dexterity* to varying degrees, explaining some but not all of the differences regarding CI between PPMS and RRMS. Since these moderating influences were not systematically related to disease course, other pathogenic (e.g., degree of cortical or deep gray matter atrophy, genetics) or sample-related (e.g., cognitive reserve/intellectual enrichment, medication status, comorbidities) differences between MS subtypes may drive the remaining differences in CI. Regardless of this, our results imply that patients with PPMS may need more specialized treatment and disease management strategies for CI than patients with RRMS. Future studies on the degree and profile of CI in MS need to refrain from reporting mixed samples of patients with PPMS and RRMS to account for the vast differences between subtypes and to prevent an overestimation of CI in MS in general.

Author disclosures

AJ, NCL, P-CB and HH have no disclosures to report. SGM has received honoraria for lecturing, travel expenses for attending meetings and financial research support from Almirall, Bayer Health Care, Biogen, Diamed, Genzyme, Merck Serono, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Teva. HW receives honorarium for acting as a member of Scientific Advisory Boards and as consultant for Biogen Idec, Behring, Fresenius Medical Care, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva, and receives research support from the German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation.

Author contributions

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Paul-Christian Bürkner, analysis and interpretation of data

Heinz Wiendl, critical revision of manuscript for medical content

Sven G. Meuth, study supervison, critical revision of manuscript for intellectual content

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Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.09.005.

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