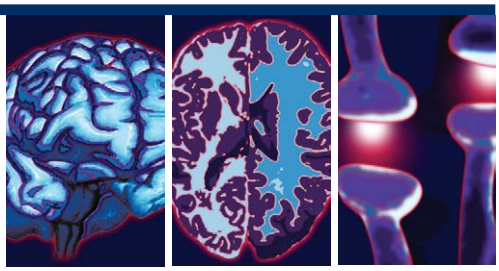
Review



Broad Impairment of Executive Functions in Patients with Parkinson's disease: A Meta-Analysis

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Abstract

Objective:

Executive functions (EF) impairments have been observed in patients with Parkinson's disease (PD). However, the pattern of EF deficits in this population remains unclear. This article aimed to examine the influence of PD on different EF domains through meta-analysis of published data.

Methods:

This article aimed to compare the EFs of PD patients with those of healthy controls (CON) in different EF domains. We searched electronic databases for articles reporting comparisons of EF performance between non-demented/non-depressed PD patients and CON. Accordingly, we identified 140 studies investigating 6 EF domains (attention, inhibition, planning, reasoning, shifting and working memory) in 4683 PD patients and 4247 CON.

Results:

Results showed that PD patients exhibited impaired attention (Hedges' g= -0.48), inhibition (Hedges' g=-0.48), planning (Hedges' g = -0.49), reasoning (Hedges' g = -0.31), shifting (Hedges' g = -0.55) and working memory (Hedges' g = -0.53). They exhibited a moderately impaired overall EF (Hedges' g = -0.49). EF deficits were not moderated by age, years of education, disease severity, motor deficits, disease duration, medication dose or global cognition.

Conclusions:

The findings suggest that among PD patients, EFs in which reasoning is least affected are broadly impaired.

Keywords

Executive functions, Meta-analysis, Movement disorder, Parkinson's disease

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopamine depletion subsequent to the loss of dopaminergic neurons in the substantia nigra pars compacta [1]. The most salient symptoms exhibited by PD patients are motor impairments, including bradykinesia, rigidity, resting tremor, gait problems and postural instability [2-4]. In industrialised countries, PD affects 1% of older adults (age > 60 years) [5], and estimates suggest that the population of PD patients will reach 8.7–9.3 million worldwide by 2030 [6]. This

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increase is expected to place significant burdens on caregivers and healthcare systems in the future.

Recent research has demonstrated that in addition to motor impairments, PD patients exhibit decreases in cognitive capabilities, particularly executive functions (EF) [7]. EFs comprise a set of inter-related, effortful cognitive processes directed toward goal-directed behaviors [8]. According to the unity/diversity model, 3 core EFs exist: inhibition, working memory and shifting [9]. Inhibition refers to the suppression and control of attention, thoughts and responses required to reach a goal. Working memory describes the ability to retain information temporarily for processing and manipulation [10]. Shifting is defined as changing between task sets or response rules. The core EFs serve as foundation for higher-order EFs, such as planning and reasoning [11]. Planning involves the identification and organization of a sequence of steps needed to achieve a goal [12], whereas reasoning describes the application of knowledge to draw logical inferences [13]. As EFs enable us to address a variety of everyday tasks in a flexible manner, EF impairments can reduce the quality of life and functional outcomes of PD patients.

In addition to declines in behavioral performances, EF dysfunctions exhibited by PD patients may be related to abnormal activity in the basal ganglia and dorsolateral prefrontal cortex [14-17]. As a result, compensatory brain activity is often observed in regions related to EFs. For instance, in the Tower of London task, PD patients can normally activate the prefrontal cortex, despite harbouring subcortical lesions, and can additionally activate the hippocampus as a compensatory mechanism [14]. Regarding set shifting, the behavioral performances of PD patients and healthy controls were comparable, although PD patients exhibited increased activation in the inferior parietal cortex and superior frontal gyrus that likely indicated certain neuro-compensatory mechanisms [18]. During the n-back task, PD patients exhibited reduced connectivity between the dorsolateral prefrontal cortex and other task-related regions, indicating deficits in the executive network. These findings suggested that hyperactivity in the dorsolateral prefrontal cortex, caudate nucleus and inferior parietal cortex plays a crucial role in counteracting decreases in the EF performance in PD patients [19]. Hence, EF dysfunctions in PD patients can be associated with dysfunctional frontostriatal loops caused by dopamine pathway abnormalities.

According to a previous meta-analysis, PD patients exhibited dysfunctional EFs with effect sizes (Hedges' *g*) ranging from -0.43 to -0.94 [7]. However, that meta-analysis failed to adequately address EF deficits in PD patients. First, the numbers of included studies related to different EF tasks were rather small ($k = 2–14$). Second, the authors did not report results for separate EFs, and thus it was difficult to compare the extents of deficits among different EFs. To overcome these limitations in our understanding, we conducted a meta-analysis to quantitatively summarize the existing results and compare different EFs between PD patients and healthy controls. Moreover, as a handful of studies have suggested the moderating effects of age, education, overall cognitive ability and PD-associated motor deficits on EF [20-24], we also examined the potential moderators of cognitive declines in PD patients. The results might provide insights for practitioners and clinicians that would allow them to focus on the most impaired cognitive abilities and devise suitable strategies to improve the functional abilities and quality of life of PD patients.

Methods

Inclusion and exclusion criteria

In this review, we included studies that measured EFs in PD patients and healthy controls. Inclusion was limited to English-language research articles published in peer-reviewed journals that provided sufficient data for effect size computation. Additionally, patients in the included studies should not have been clinically depressed or demented or exhibited other neurological diseases. Commentaries, review articles and studies including PD patients experiencing deep brain stimulation were excluded.

Literature search

The studies were identified by searching electronic databases and scanning the bibliographies of articles published from the first available date to May 10, 2016. The electronic databases Web of Knowledge, PubMed, Medline and PsycINFO were searched for literature using the term 'Parkinson's disease' in combination with the terms 'executive functions', 'working memory', 'cognitive control', 'inhibition', 'set shifting', 'flexibility', 'planning', 'reasoning' or 'task switching'.

■ Data extraction

We developed an electronic spreadsheet for data extraction. The screening and eligibility assessment was performed by 3 reviewers in a non-blinded, standardized manner. During training, the reviewers assessed 300 articles and achieved a rate of agreement above 90%. Disagreements between the reviewers were resolved by consensus. Subsequently, the remaining articles were divided into 3 groups and each was assigned to a reviewer who performed data extraction and coding. The spreadsheet completed by each reviewer was double-checked by another reviewer.

The following information was extracted from each included article: (1) participants' characteristics, including the mean age, years of education, global cognition (Mini-Mental State Examination score, MMSE) [25], disease severity (Hoehn and Yahr stage, HY) [26], motor deficits (motor score of the Unified Parkinson's Disease Rating Scale motor, UPDRS) [27], disease duration and dose of medication (levodopa equivalent daily dose, LEDD); (2) EF domain and tasks used and (3) behavioral outcomes (EF performance).

Statistical Analyses

EF was the primary outcome measure. Mean data were converted to Hedges' g for the meta-analysis. Multiple tests that assessed the same EF in one study were combined. The data analysis was conducted in Comprehensive Meta-Analysis 2.0. A random-effects model was used to account for variability among the samples and assessment tools across the included studies. A positive Hedges' g indicated a better EF performance among PD patients relative to healthy controls.

■ Heterogeneity

Cochran's Q test was used to assess heterogeneity. An I^2 statistic was included to quantify the proportion of heterogeneity across studies that could not be explained by chance (I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high heterogeneity, respectively) [28].

■ Publication bias

Publication bias was assessed through a visual inspection of funnel plots and Egger's asymmetry test [29]. In a funnel plot, asymmetry can result from the non-publication of null or negative results. In Egger's asymmetry test, the standardized effect estimate (effect size/standard error) is regressed on precision (1/standard error). A significant deviation of the y-intercept from zero might indicate the presence of publication bias. In addition, a fail-safe N test was also used to determine the number of hypothetical missing studies required to nullify the overall effects. A fail-safe N that exceeds the threshold ($N \geq 5k+10$) has been well accepted as an indicator of a meta-analytic result robust to publication bias [30]. The trim-and-fill method was used to calculate an adjusted effect size corrected for the effects of missing studies in asymmetrical funnel plots [31].

■ Meta-regression

The influences of age, years of education, disease severity, motor deficits, disease duration and global cognition and dose of medication on the study outcome were assessed through a mixed-effects meta-regression analysis based on an unrestricted maximum likelihood model.

Results

One hundred and forty articles involving 4639 PD patients and 4219 healthy controls were retrieved and included in the meta-analysis. **Figure 1** shows the number of studies retained at different stages of the literature search and screening process. Details of the individual studies are presented in **Table 1**. The mean ages of the PD patients and controls were 64.34 and 63.81 years, respectively. A total of 275 effect sizes were included in the meta-analysis: tapping on attention (k = 11, N_{PD} = 556, N_{CON} = 521), inhibition (k = 56, N_{PD} = 1837, N_{CON} = 1572), planning (k = 22, N_{PD} = 771, N_{CON} = 698), reasoning (k = 13, N_{PD} = 429, N_{CON} = 419), shifting (k = 82, N_{PD} = 2827, N_{CON} = 2648) and working memory (k = 91, N_{PD} = 2901, N_{CON} = 2650).

■ Pooled effect size

The pooled effect sizes, heterogeneity and publication bias results are summarized in **Table 2**. A summary forest plot of all the relevant EFs is presented in **Figure 2**. The pooled effect size suggested a fairly moderate deficit in overall EF among PD patients. Small to moderate effect sizes were observed for attention (Hedges' g = -0.48, 95% CI: -0.62 to -0.35), inhibition (Hedges' g = -0.48, 95% CI: -0.59 to -0.36), planning (Hedges' g = -0.49, 95% CI: -0.62 to -0.36), reasoning (Hedges' g = -0.31, 95% CI: -0.45 to -0.18), shifting (Hedges' g = -0.55,

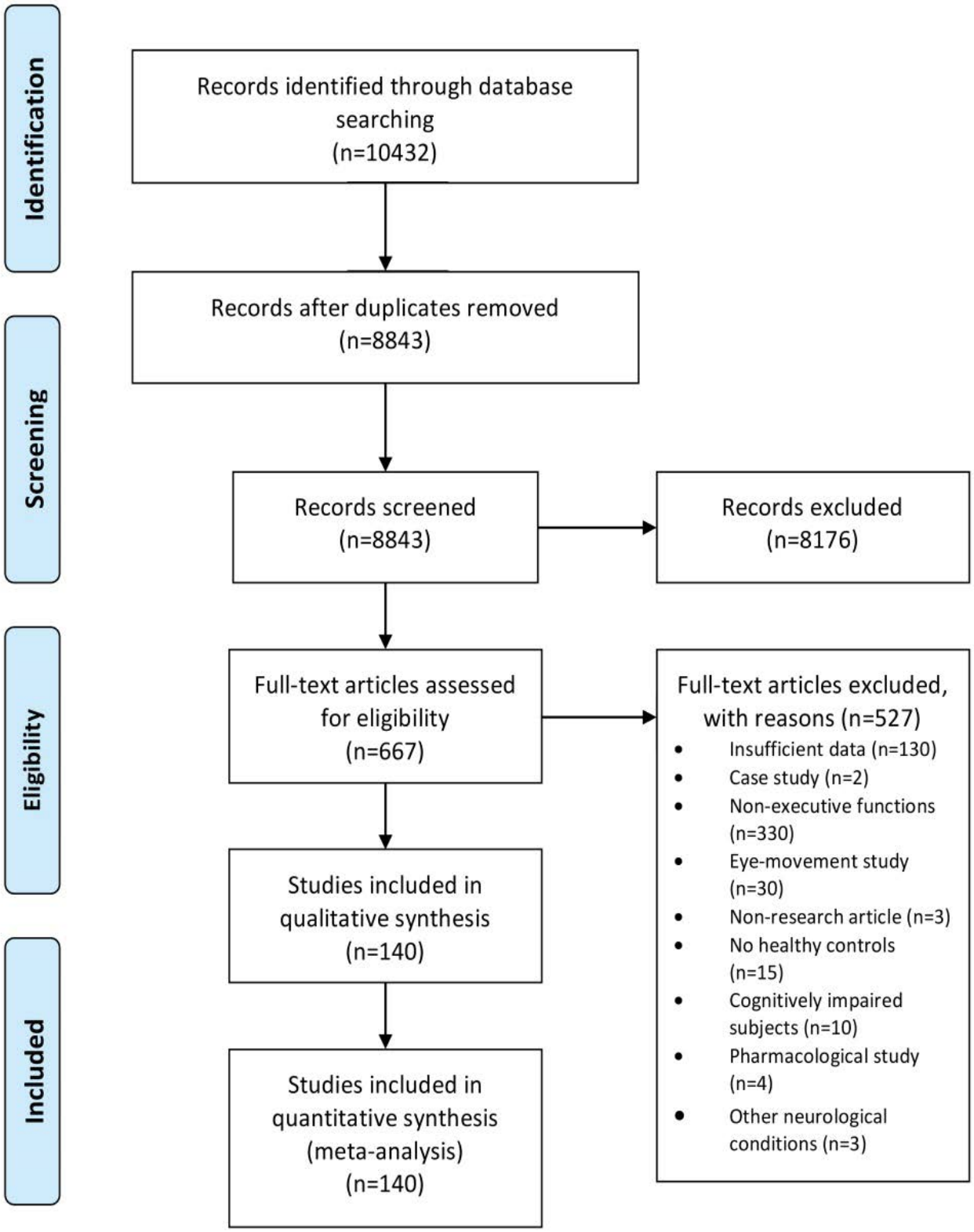

Figure 1: Flowchart of literature search.

Table 1: Summary of the included studies.

Study	Sample size (PD/ CON)	Age (PD/ CON)	Education (yrs)	MMSE	HY	UPDRS (motor)	Disease duration (Mo)	LEDD (mg)	Assessment	Outcome	Hedges' g (95% CI)
Attention											
Agosta et al. [39]	41/34	64/63	11	27.7	NA	27.1	85.2	NA	ACE-R	Test score	-0.80 (-1.27, -0.34)
Colman et al. [40]	27/25	61.39/62.93	13.21	28.11	1.79	15.68	72.48	786.94	Sustained Attention	Omissions	-0.42 (-0.97, 0.12)
Crescentini et al. [41]	19/14	66.7/65.6	8.1	29	2.05	26.2	76.8	540.3	Divided Attention	Omissions	-0.24 (-0.93, 0.44)
Crescentini et al. [42]	16/14	63.6/61.6	9.7	28.8	1.94	22.9	72	386.4	TAP-A	Omissions	-0.03 (-0.73, 0.67)
Duncan et al. [43]	125/50	66/65.8	12	29	2	26.8	6.15	175	CDR	Time of completion	-0.67 (-1.01, -0.34)
Elwan et al. [44]	19/25	61.84/56.35	NA	26.57	2.67	47.90	28.60	NA	PASAT	Test score	0.41 (-0.59, 1.41)
Ibarretxe-Bilbao et al. [45]	24/24	56.13/57.58	10.96	29.63	1.73	14.67	36.72	299.58	CCPT	Detectability	-0.68 (-1.25, -0.10)
Lord et al. [46]	121/184	67/69.4	NA	NA	1.94	25.5	NA	124.6	POA	Time of completion	-0.45 (-0.69, -0.22)
Murray and Rutledge, [47]	11/9	68.36/67.89	16	NA	NA	17.91	NA	NA	TEA	Composite score	-0.69 (-1.56, 0.18)
Poletti et al. [48]	103/100	66/66.8	9.20	27.90	NA	16.90	10.70	NA	Visual Search	Number of correct response	-0.32 (-0.60, -0.04)
Rodriguez-Ferreiro et al. [49]	50/42	72.92/74.08	7.04	26.94	1.96	NA	114.00	NA	Visual Search	Number of correct response	-0.77 (-1.19, -0.35)
Inhibition											
Abe et al. [50]	32/20	65.9/65.5	11.7	28.3	2.5	18.1	49.2	507	Stroop Task	Accuracy (incongruent)	-0.10 (-0.65, 0.46)
Anderson et al. [51]	27/16	63.8/65.4	NA	NA	2.7	24.9	NA	NA	Hayling Test	Accuracy	-0.21 (-0.82, 0.40)
Baggio et al. [52]	39/23	63.5/61	11.4	28.7	1.8	16.5	67.2	560.3	Stroop Task	Interference	-0.69 (-1.21, -0.17)
Baggio et al. [53]	43/36	64/63.4	10.8	29.35	1.58	14.1	73.2	646.7	Stroop Task	Interference	-0.26 (-0.70, 0.18)
Barnes and Boubert, [54]	20/20	63.73/68.54	NA	27.2	2.9	NA	116.64	465	Stroop Task	Interference	-0.82 (-1.46, -0.19)
Beste et al. [55]	15/17	66.8/65.2	NA	NA	NA	15.90	NA	NA	Flanker Task	Error (incongruent)	-0.22 (-0.89, 0.45)
Beyer et al. [56]	114/99	65.8/65	11.3	28.3	1.8	21	NA	NA	Stroop Task	Test score (incongruent)	-0.16 (-0.43, 0.10)
Bezdicek et al. [57]	46/41	57.7/60.78	14.84	NA	1.95	10.3	124.8	1029	Stroop Task	Interference	0.01 (-0.41, 0.42)
Bohlhalter et al. [58]	12/12	59.1/46.6	NA	NA	NA	16.5	92.4	766	Stroop Task	Interference	-0.29 (-1.07, 0.48)
Bohnen et al. [59]	13/14	70.8/69.7	NA	28.1	NA	26.4	70.8	NA	Stroop Task	Test score (incongruent)	-0.96 (-1.74, -0.19)
Broeders et al. [60]	59/40	62.5/61.4	11.60	27.90	1.70	16.00	17.50	153.90	Stroop Task	Time of completion (incongruent)	-0.64 (-1.05, -0.23)
Cohen et al. [61]	13/16	65.3/66.6	4.8	NA	2.1	29.9	78	714	Stroop Task	Interference	-0.28 (-1.00, 0.44)
Colman et al. [41]	27/25	61.39/62.93	13.21	28.11	1.79	15.68	72.48	786.94	Stroop Task	Time for color-word card divided by time for color card	-0.17 (-0.71, 0.37)
Crescentini et al. [42]	19/14	66.7/65.6	8.1	29	2.05	26.2	76.8	540.3	Stroop Task	Test score (incongruent)	0.46 (-0.23, 1.14)
Crescentini et al. [43]	16/14	63.6/61.6	9.7	28.8	1.94	22.9	72	386.4	Stroop Task	Test score (incongruent)	-0.69 (-1.41, 0.03)
Dujardin et al. [63]	18/18	60.17/59.5	11.56	NA	NA	17.58	11.33	NA	Stroop Task	Interference	-0.79 (-1.45, -0.12)
Edelstyn et al. [64]	17/17	65.4/64.5	NA	28	NA	NA	92.4	448.59	Hayling Test	Test score	-0.83 (-1.52, -0.15)
Ell, 2013 [65]	36/35	71.1/65.8	16.7	NA	2	NA	42	NA	DKEFS-CWI (inhibition)	Time of completion	-0.39 (-0.86, 0.08)
Fales et al. [66]	21/25	66.9/68.8	16.9	28.8	2	NA	69.6	NA	Stroop Task	Interference	0.26 (-0.31, 0.83)

Fling et al. [67]	15/12	65.5/66.7	NA	NA	2	29.3	76.8	485	Stroop Task	Time of completion (incongruent)	-0.41 (-1.16, 0.33)
Galtier et al. [68]	43/20	59.19/60.85	7.88	27.58	2.28	28.46	99.60	NA	Stroop Task	Interference	0.28 (-0.24, 0.81)
Gawrys et al. [69]	30/18	56.03/57.11	13.51	28.93	2	NA	NA	851.58	Stroop Task	Time of completion (subtest 3 - 1)	-0.74 (-1.34, -0.15)
Green et al. [70]	10/10	54.05/53.9	16.10	NA	1.30	9.20	NA	NA	Stroop Task	Interference	-0.06 (-0.90, 0.78)
Hausdorff et al. [71]	30/25	71.3/70	14.1	28.1	NA	18.1	NA	NA	Go/Nogo Task	Performance index	-0.71 (-1.26, -0.16)
Hsieh et al. [72]	26/27	63.3/63.48	9.07	NA	NA	NA	40.80	NA	Stroop Task	Interference	-0.52 (-1.05, 0.02)
Koerts et al. [73]	43/25	63.7/62.8	5.2	27.5	2.2	24.6	61.2	561.7	Stroop Task	Interference	-0.29 (-0.78, 0.20)
Koerts et al. [74]	88/65	62.5/61.9	NA	27.5	2	21.4	67.2	550.3	Stroop Task	Interference	-0.66 (-1.00, -0.32)
Koerts et al. [75]	43/25	63.6/62.8	5.30	27.50	2.20	24.60	63.60	583.70	Stroop Task	Interference	-1.07 (-1.59, -0.55)
Lewis et al. [76]	20/20	62.3/65.1	13.90	27.90	NA	23.30	70.80	806.30	Stroop Task	Time of completion	-0.37 (-0.98, 0.24)
Lord et al. [47]	121/184	67/69.4	NA	NA	1.94	25.5	NA	124.6	Hayling Test	Test score	-0.34 (-0.57, -0.11)
Marzinzik et al. [77]	11/11	70.1/72.4	9.1	28.6	1.6	13.7	70.8	300.4	Go/Nogo Task	Error (Nogo)	-0.12 (-0.93, 0.69)
McNamara et al. [78]	20/10	71.8/69	12.00	NA	NA	NA	96.00	NA	Stroop Task	Interference	-1.50 (-2.33, -0.67)
McNamara et al. [79]	22/22	73/70.5	12.8	27.5	NA	NA	NA	NA	Stroop Task	Interference	-0.83 (-1.45, -0.21)
McNamara et al. [80]	28/32	66.5/56.3	13.90	26.60	3.00	NA	NA	628.90	Stroop Task	Interference	-0.15 (-0.65, 0.35)
Miller et al. [81]	42/28	64.8/63.9	17.3	NA	2	20.1	80.4	356.5	Stroop Task	Number of correct response	-0.96 (-1.44, -0.48)
Mitchell and Barbosa Bouças [82]	33/33	63.6/66.9	15.2	NA	NA	NA	96	NA	Stroop Task	Accuracy (incongruent)	-0.51 (-0.99, -0.03)
Murray and Rutledge, [48]	11/9	68.36/67.89	16	NA	NA	17.91	NA	NA	Flanker Task	Accuracy (incongruent)	-0.72 (-1.60, 0.15)
Obeso et al. [83]	17/16	69.41/65.69	13.53	29.35	2.12	23.48	114	915.94	SST	Stop-signal reaction time	-1.23 (-1.96, -0.50)
O'Callaghan et al. [84]	50/27	63.8/65.6	13.4	28	2.1	NA	69.6	775.5	Hayling Test	Test score	-0.49 (-0.96, -0.03)
Pellicano et al. [85]	13/13	58.8/60.3	11.80	28.40	1.90	18.50	51.60	NA	Stroop Task	Interference	0.11 (-0.63, 0.86)
Pereira et al. [86]	20/20	64/59.1	NA	28.50	2.40	24.90	81.60	627.00	Stroop Task	Interference	-0.71 (-1.34, -0.08)
Pettit et al. [87]	18/19	68.8/66.2	14.06	NA	1.78	NA	78.36	NA	Hayling Test	Test score	-1.16 (-1.84, -0.47)
Pillon et al. [88]	20/14	62.4/64.3	11.00	28.90	2.50	18.10	97.20	630.30	Stroop Task	Interference	-3.71 (-4.81, -2.60)
Pillon et al. [89]	10/14	64.8/64.3	11.60	29.70	1.30	18.10	16.80	NA	Stroop Task	Interference	-0.32 (-1.12, 0.47)
Poletti et al. [49]	103/100	66/66.8	9.20	27.90	NA	16.90	10.70	NA	Stroop Task	Interference	-0.09 (-0.37, 0.18)
Ranchet et al. [90]	19/21	66.1/69.1	13	27.4	2.1	16.4	90	741.8	Stroop Task	Interference	-0.53 (-1.15, 0.09)
Raskin et al. [91]	54/34	61.9/61	14.7	NA	1.99	NA	NA	NA	Stroop Task	Interference	-0.53 (-0.96, -0.10)
Segura et al. [92]	43/32	60.77/64.69	12.02	29.47	1.7	13.16	74.76	692.81	Stroop Task	Interference	0.01 (-0.45, 0.46)
Stavitsky et al. [93]	35/18	66.2/64.4	16.8	NA	2	25.1	105.6	604.3	Stroop Task	Interference	-0.79 (-1.37, -0.21)
Theilmann et al. [94]	25/26	68/65.9	16.9	28.7	2.36	25.4	86.4	970.4	Stroop Task	Interference	0.04 (-0.51, 0.59)
van Spaendonck et al. [95]	51/24	53.9/52.7	NA	NA	NA	NA	39.60	NA	Stroop Task	Interference	-0.14 (-0.62, 0.34)
Wild et al. [96]	18/18	69.33/69.44	6.22	26.39	1.97	16.22	100.68	NA	Stroop Task	Interference	-1.33 (-2.04, -0.62)
Wylie et al. [97]	16/16	64.8/65.4	15.7	NA	1.8	NA	99.6	NA	Flanker Task	Reaction time (incongruent)	-0.48 (-1.16, 0.21)
Wylie et al. [98]	28/17	65.5/62.3	15.8	28.6	NA	19	NA	NA	Flanker Task	Time cost	-0.31 (-0.91, 0.28)
Zgaljardic et al. [99]	32/29	66.9/66.7	15.4	NA	1.92	NA	NA	NA	Stroop Task	Interference	-0.88 (-1.40, -0.36)
Zhang et al. [100]	42/36	62.2/62.7	9.8	27.59	2	20.02	50.4	298.2	Stroop Task	Time of completion (incongruent)	-0.51 (-0.96, -0.06)
Planning											
Altgassen et al. [101]	16/16	61.1/62.6	NA	NA	1.38	13.83	57.72	NA	TOL	Number of moves	-0.81 (-1.52, -0.11)
Broeders et al. [61]	59/40	62.5/61.4	11.60	27.90	1.70	16.00	17.50	153.90	TOL	Number of trials completed	-0.81 (-1.22, -0.39)
Cipresso et al. [102]	15/15	69/61.7	7.93	27	NA	NA	NA	NA	TOL	Test score	-0.83 (-1.56, -0.10)

Dujardin et al. [103]	12/12	65.92/59.25	10.25	NA	2.13	30.58	103	405	SSG	Number of sequence produced	-0.90 (-1.72, -0.09)
Engels et al. [104]	48/57	72.9/67.9	NA	26.14	NA	NA	NA	NA	BADS-KS	Test score	-0.66 (-1.06, -0.27)
Fales et al. [66]	21/25	66.9/68.8	16.9	28.8	2	NA	69.6	NA	TOL	Number of moves	-0.11 (-0.68, 0.47)
Foster et al. [105]	24/30	59/60	14.9	NA	NA	18.95	54	NA	TOL	Number of correct response	-0.02 (-0.55, 0.51)
Koerts et al. [73]	43/25	63.7/62.8	5.2	27.5	2.2	24.6	61.2	561.7	BADS-ZM	Test score	-0.21 (-0.70, 0.28)
Koerts et al. [74]	43/25	63.6/62.8	5.30	27.50	2.20	24.60	63.60	583.70	BADS-ZM	Hit-error	-0.26 (-0.75, 0.23)
Lord et al. [46]	121/184	67/69.4	NA	NA	1.94	25.5	NA	124.6	OTS	Problems solved	-0.52 (-0.76, -0.29)
McKinlay et al. [105]	30/30	65.77/66.43	14.08	28.9	2.3	27.13	87.6	NA	TOL	Accuracy	-0.65 (-1.18, -0.13)
McNamara et al. [77]	20/10	71.8/69	12.00	NA	NA	NA	96.00	NA	TOL	Time/move	-0.20 (-0.94, 0.55)
Miah et al. [106]	23/21	62.6/60.3	NA	NA	NA 2	17.09	64.18	397.69	OTS	Problems solved	-0.18 (-0.73, 0.37)
Monetta et al. [107]	11/11	67.1/71.2	16.60	NA	2.50	NA	109.20	NA	TOL	Number of moves	-1.30 (-2.21, -0.38)
Morris et al. [108]	12/18	64.58/63.72	9.5	NA	2.17	NA	NA	NA	TOL	Number of moves	0.16 (-0.55, 0.87)
Muslimovic et al. [109]	95/44	64.9/64.1	11.50	27.90	1.90	18.20	37.20	291.30	TOL	Number of correct response	-0.52 (-0.88, -0.16)
Parrao et al. [110]	44/17	63.5/63.1	11.2	NA	2.3	16.1	69.6	NA	TOL	Number of moves	-0.51 (-1.07, 0.06)
Pell et al. [111]	15/16	70.9/70.4	15.40	NA	NA	29.90	127.20	NA	TOL	Number of correct response	-0.93 (-1.67, -0.19)
Perfetti et al. [112]	25/24	69.8/72.9	8.70	27.00	2.20	19.90	NA	1210	TOL	Number of correct response	-0.83 (-1.41, -0.25)
Raskin et al. [90]	53/34	61.9/61	14.7	NA	1.99	NA	NA	NA	DKEFS-T	Total achievement	-0.47 (-0.90, -0.04)
Rosen et al. [113]	20/23	67.45/68.26	13.45	28.75	2.5	34.18	100.8	999.42	BADS-KS	Test score	-0.79 (-1.40, -0.18)
Schomaker et al. [114]	21/21	61.8/59.7	NA	28.81	NA	21.80	NA	851.10	TOH	Test score	0.06 (-0.53, 0.66)
Reasoning											
Basic et al. [115]	58/58	66.09/66.85	NA	26.10	NA	NA	77.76	NA	RPM	Test score	-0.12 (-0.48, 0.24)
Benke et al. [116]	22/18	58/60.9	9.9	NA	2.29	16.2	117.6	NA	RPM	Test score	-0.14 (-0.75, 0.47)
Bodden et al. [117]	21/21	63.7/58.5	14.6	29	2.5	NA	61.2	432.1	LPS (subtest 4)	Test score	-0.43 (-1.03, 0.17)
Brand et al. [118]	20/20	66.85/64	9.1	28.2	3	NA	106.05	NA	LPS (subtest 4)	Test score	-0.50 (-1.12, 0.12)
Costa et al. [119]	39/46	62.56/63.04	10.82	28.22	NA	9.09	81.48	NA	RPM	Test score	-0.46 (-0.89, -0.03)
Costa et al. [120]	33/20	63.4/66	12.6	29.4	NA	19.7	82.8	607	RPM	Test score	-0.30 (-0.85, 0.25)
Crescentini et al. [41]	19/14	66.7/65.6	8.1	29	2.05	26.2	76.8	540.3	RPM	Test score	-0.49 (-1.17, 0.20)
Euteneuer et al. [121]	21/23	67.6/64.4	11.1	29	2.5	17.7	85.7	487.69	LPS (subtest 4)	Test score	-0.38 (-0.97, 0.20)
Mioni et al. [122]	21/25	68.95/71.12	7.76	27.28	NA	10.92	68.4	NA	RPM	Test score	-0.63 (-1.22, -0.04)
Natsopoulosl et al. [123]	27/27	60.7/60.56	NA	29.41	NA	NA	75.96	NA	Modus Ponens	Test score	-0.25 (-0.77, 0.28)
Perfetti et al. [112]	25/24	69.8/72.9	8.70	27.00	2.20	19.90	NA	1210	Temporal Judgment	Test score	-0.65 (-1.22, -0.08)
Poletti et al. [48]	103/100	66/66.8	9.20	27.90	NA	16.90	10.70	NA	RPM	Test score	-0.16 (-0.43, 0.12)
Rosen et al. [113]	20/23	67.45/68.26	13.45	28.75	2.5	34.18	100.8	999.42	LPS (subtest 4)	Test score	-0.32 (-0.91, 0.27)
Shifting											
Abe et al. [50]	32/20	65.9/65.5	11.7	28.3	2.5	18.1	49.2	507	TMT	Time (B-A)	-0.61 (-1.18, -0.05)
Akamatsu et al. [124]	30/20	60.4/58.6	13.50	29.70	2.30	29.20	110.40	NA	TMT	Time (B)	-0.90 (-1.49, -0.32)
Aksan et al. [125]	39/77	74.58/75.4	15.00	NA	NA	NA	NA	NA	TMT	Time (B)	-1.04 (-1.45, -0.64)

Alonso-Recio et al. [126]	50/49	65.14/64.86	NA	29.00	NA	NA	77.40	NA	TMT	Time (B-A)	1.58 (1.13, 2.03)
Baggio et al. [52]	39/23	63.5/61	11.4	28.7	1.8	16.5	67.2	560.3	TMT	Time (B)	-0.33 (-0.84, 0.18)
Baggio et al. [53]	43/36	64/63.4	10.8	29.35	1.58	14.1	73.2	646.7	TMT	Time (B-A)	0.15 (-0.29, 0.59)
Bodden et al. [117]	21/21	63.7/58.5	14.6	29	2.5	NA	61.2	432.1	TMT	Time (B-A)	-0.15 (-0.74, 0.44)
Bogdanova and Cronin-Golomb, [127]	22/22	62.25/61.3	15.7	29.3	2	NA	98.4	486.35	TMT	Time (B)	-0.42 (-1.01, 0.17)
Bohnen et al. [59]	13/14	70.8/69.7	NA	28.1	NA	26.4	70.8	NA	TMT	Time (B-A)	-0.43 (-1.18, 0.31)
Bokura et al. [128]	13/14	71/71	9.80	NA	NA	29.23	86.77	NA	WCST	Number of category	-1.40 (-2.22, -0.57)
Brand et al. [118]	20/20	66.85/64	9.1	28.2	3	NA	106.05	NA	WCST	Perseverative error	0.67 (0.04, 1.29)
Broeders et al. [60]	59/40	62.5/61.4	11.60	27.90	1.70	16.00	17.50	153.90	WCST	Perseverative error	-0.53 (-0.93, -0.12)
Broussolle et al. [129]	27/30	55.88/52.9	NA	NA	2.61	14.72	83.91	471.30	WCST	Perseverative error	-0.28 (-1.16, 0.60)
Brown and Marsden [130]	16/16	59.2/56.1	11.30	NA	NA	NA	134.40	NA	WCST	Perseverative error	-1.04 (-1.77, -0.32)
Camicioli et al. [131]	29/16	60.5/57.9	14.3	28.6	NA	15.3	NA	NA	TMT	Time (B)	-0.81 (-1.43, -0.19)
Cohen et al. [61]	13/16	65.3/66.6	4.8	NA	2.1	29.9	78	714	TMT	Time (B-A)	-0.17 (-0.89, 0.55)
Colman et al. [40]	27/25	61.39/62.93	13.21	28.11	1.79	15.68	72.48	786.94	TMT/OMO	Time (B), error (OMO)	-0.66 (-1.21, -0.11)
Cooper et al. [132]	60/37	59.8/59.6	9.93	NA	NA	NA	15.75	NA	WCST	Perseverative error	-2.97 (-3.55, -2.39)
Costa et al. [119]	39/46	62.56/63.04	10.82	28.22	NA	9.09	81.48	NA	WCST	Perseverative error	-0.62 (-1.06, -0.19)
Costa et al. [120]	33/20	63.4/66	12.6	29.4	NA	19.7	82.8	607	WCST	Perseverative error	-1.08 (-1.67, -0.49)
Crescentini et al. [41]	19/14	66.7/65.6	8.1	29	2.05	26.2	76.8	540.3	TMT	Time (B)	-0.63 (-1.32, 0.06)
Crescentini et al. [42]	16/14	63.6/61.6	9.7	28.8	1.94	22.9	72	386.4	TMT	Time (B)	-0.56 (-1.27, 0.16)
Dalrymple-Alford et al. [133]	8/8	65.6/62.4	10.1	NA	2.13	NA	52.8	NA	WCST	Percentage of perseverative error	-0.13 (-1.06, 0.79)
Delazer et al. [134]	20/20	68.5/71.3	11.9	27.8	1.8	17.6	62.95	431	TMT	Time (B)	0.30 (-0.31, 0.91)
Drag et al., 2009	24/24	69.04/68.67	16.58	NA	1.86	14.4	64.62	NA	WCST	Number of category	-0.57 (-1.14, 0)
Dujardin et al. [135]	12/12	65.92/59.25	10.25	NA	2.13	30.58	103	405	WCST	Perseverative error	-0.61 (-1.41, 0.18)
Edelstyn et al. [63]	17/17	65.4/64.5	NA	28	NA	NA	92.4	448.59	Brixton Test	Test score	-0.83 (-1.52, -0.15)
Ell, 2013 [64]	36/35	71.1/65.8	16.7	NA	2	NA	42	NA	DKEFS-CWI (shifting)	Time of completion	-0.84 (-1.32, -0.36)
Elwan et al. [44]	5/12	61.84/56.35	NA	26.57	2.67	47.90	28.60	NA	TMT	Time (B)	-0.04 (-0.62, 0.55)
Engels et al. [103]	48/57	72.9/67.9	NA	26.14	NA	NA	NA	NA	BADS-RS	Number of correct response	-0.49 (-0.88, -0.10)
Euteneuer et al. [121]	21/23	67.6/64.4	11.1	29	2.5	17.7	85.7	487.69	WCST	Perseverative error	-0.58 (-1.18, 0.01)
Fales et al. [65]	21/25	66.9/68.8	16.9	28.8	2	NA	69.6	NA	WCST	Perseverative error	-0.27 (-0.84, 0.31)
Fama et al. [136]	20/38	63.1/65.3	16	27.4	NA	NA	81.6	NA	WCST	Perseverative error	-1.04 (-1.61, -0.47)
Galtier et al. [67]	43/20	59.19/60.85	7.88	27.58	2.28	28.46	99.60	NA	WCST	Number of category	-0.87 (-1.42, -0.33)
Gawrys et al. [68]	30/18	56.03/57.11	13.51	28.93	2	NA	NA	851.58	TMT	Time (B-A)	-1.06 (-1.67, -0.45)
Goebel et al. [137]	22/27	64.8/60.8	14	NA	1.27	NA	94.8	NA	TMT	Time (B)	-1.32 (-1.93, -0.70)
Hartikainen et al. [138]	22/26	66.5/65.5	NA	NA	1.9	NA	NA	NA	TMT	Time (B-A)	-0.34 (-0.90, 0.22)
Katzen et al. [139]	222/108	66.41/67.63	14.06	25.18	2.30	NA	79.08	NA	WCST	Number of category	-0.65 (-0.88, -0.41)
Kobayakawa et al. [140]	34/22	69.9/67.6	13.20	28.00	1.52	NA	76.80	391.00	WCST	Number of category	0.60 (0.06, 1.14)

Koerts et al. [72]	43/25	63.7/62.8	5.2	27.5	2.2	24.6	61.2	561.7	TMT	Time (B)	-0.36 (-0.85, 0.13)
Koerts et al. [73]	88/65	62.5/61.9	NA	27.5	2	21.4	67.2	550.3	TMT	Time (B)	-0.28 (-0.62, 0.06)
Koerts et al. [74]	43/25	63.6/62.8	5.30	27.50	2.20	24.60	63.60	583.70	TMT	Time (B)	-0.36 (-0.85, 0.13)
Lewis et al. [75]	20/20	62.3/65.1	13.90	27.90		23.30	70.80	806.30	TMT	Time (B)	-0.61 (-1.23, 0.02)
Lin et al. [141]	31/50	65.3/67.7	9.60	26.60	1.84	14.99	NA	NA	TMT	Time (B-A)	-0.06 (-0.51, 0.38)
Lord et al. [46]	121/184	67/69.4	NA	NA	1.94	25.5	NA	124.6	Brixton Test	Test score	-0.34 (-0.54, -0.14)
Miah et al. [106]	23/21	62.6/60.3	NA	NA	2	17.09	64.18	397.69	IED	Stages completed	-0.42 (-0.96, 0.13)
Miller et al. [80]	42/28	64.8/63.9	17.3	NA	2	20.1	80.4	356.5	TMT	Time (B)	-0.67 (-1.15, -0.18)
Mioni et al. [122]	21/25	68.95/71.12	7.76	27.28	NA	10.92	68.4	NA	TMT	Time (B-A)	0.40 (-0.19, 0.99)
Miura et al. [142]	32/25	67.8/66.9	12	28.5	2.72	NA	67.2	318.9	WCST	Perseverative error	-0.52 (-1.04, 0)
Monetta et al. [107]	11/11	67.1/71.2	16.60	NA	2.50	NA	109.20	NA	TMT	Time (B)	-0.92 (-1.77, -0.07)
Müller et al. [159]	20/20	55.3/55.7	10.7	NA	2.3	49.3	42.5	NA	WCST	Perseverative error	-0.63 (-1.26, 0)
Muslimovic et al. [109]	95/44	64.9/64.1	11.50	27.90	1.90	18.20	37.20	291.30	WCST	Perseverative error	-0.77 (-1.14, -0.4)
Parrao et al. [110]	44/17	63.5/63.1	11.2	NA	2.3	16.1	69.6	NA	WCST	Number of category	-1.15 (-1.74, -0.56)
Partiot et al. [144]	27/24	64.7/59.7	9.3	NA	NA	NA	93.6	NA	WCST	Number of category	-1.41 (-2.02, -0.80)
Pellicano et al. [84]	13/13	58.8/60.3	11.80	28.40	1.90	18.50	51.60	NA	WCST	Perseverative error	-1.08 (-1.89, -0.27)
Perfetti et al. [112]	25/24	69.8/72.9	8.70	27.00	2.20	19.90	NA	1210	TMT	Time (B-A)	-0.37 (-0.93, 0.19)
Pettit et al. [86]	18/19	68.8/66.2	14.06	NA	1.78	NA	78.36	NA	Brixton Test	Test score	-1.47 (-2.19, -0.76)
Pillon et al. [87]	20/14	62.4/64.3	11.00	28.90	2.50	18.10	97.20	630.30	WCST	Perseverative error	-2.87 (-3.82, -1.91)
Pillon et al. [88]	10/14	64.8/64.3	11.60	29.70	1.30	18.10	16.80	NA	WCST	Perseverative error	-3.41 (-4.66, -2.17)
Poletti et al. [48]	103/100	66/66.8	9.20	27.90	NA	16.90	10.70	NA	TMT	Time (B-A)	0.05 (-0.22, 0.33)
Ranchet et al. [89]	19/21	66.1/69.1	13	27.4	2.1	16.4	90	741.8	TMT	Time (B-A)	-0.61 (-1.23, 0.02)
Raskin et al. [90]	48/34	61.9/61	14.7	NA	1.99	NA	NA	NA	TMT	Test score	-1.48 (-1.96, -1.00)
Rosen et al. [113]	20/23	67.45/68.26	13.45	28.75	2.5	34.18	100.8	999.42	WCST	Perseverative error	-0.77 (-1.38, -0.16)
Sagar et al. [145]	37/32	60.2/58.5	9.80	NA	NA	NA	12.00	NA	WCST	Perseverative error	0.02 (-0.45, 0.49)
Schomaker et al. [114]	21/21	61.8/59.7	NA	28.81	NA	21.80	NA	851.10	TMT	Time (B/A)	-0.48 (-1.09, 0.12)
Segura et al. [91]	43/32	60.77/64.69	12.02	29.47	1.7	13.16	74.76	692.81	TMT	Time (B)	0.03 (-0.43, 0.48)
Stavitsky et al. [92]	35/18	66.2/64.4	16.8	NA	2	25.1	105.6	604.3	TMT	Time (B)	-0.96 (-1.55, -0.37)
Stolwyk et al. [146]	18/18	67.62/67.13	13.89	27.89	NA	11.67	80.04	470.84	TMT	Time (B)	-0.76 (-1.44, -0.08)
Tamura et al. [147]	24/24	60.9/61.7	12.7	28.5	2.21	NA	79.2	NA	TMT	Time (B-A)	-0.32 (-0.88, 0.24)
Theilmann et al. [93]	25/26	68/65.9	16.9	28.7	2.36	25.4	86.4	970.4	TMT	Time (B-A)	-0.25 (-0.80, 0.30)
Uc et al. [148]	79/151	65.9/65.3	14.80	28.30	2.10	24.10	67.20	577	TMT	Time (B-A)	-0.69 (-0.97, -0.41)
Uc et al. [149]	76/152	65.9/65.3	14.80	28.40	2.20	23.70	68.40	588.00	TMT	Time (B-A)	-0.69 (-0.97, -0.41)
Vandenbossche et al. [150]	14/14	NA/NA	20.21	28.79	2.43	35.64	98.52	NA	Brixton Test	Error	-0.77 (-1.52, -0.02)
Werheid et al. [151]	14/16	62.45/62.4	9.25	NA	NA	44.25	NA	NA	TMT	Time (B-A)	-0.92 (-1.65, -0.18)
Wild et al. [95]	18/18	69.33/69.44	6.22	26.39	1.97	16.22	100.68	NA	WCST	Perseverative error	-0.77 (-1.43, -0.11)
Yogev-Seligmann et al. [152]	20/20	70.3/70.9	15.9	NA	2.3	20.7	88.8	NA	TMT	Time (B-A)	-0.34 (-0.96, 0.27)
Yogev-Seligmann et al. [33]	18/15	68.7/75.4	15.9	NA	2.5	23.3	NA	NA	TMT	Time (B-A)	-0.05 (-0.72, 0.62)
Yu et al. [153]	55/30	62.47/64.2	12.33	28.29	1.46	16.65	43.44	NA	WCST	Perseverative error	0.16 (-0.28, 0.60)
Yu et al. [154]	39/40	62.7/61.9	11.4	27.9	1.6	18.9	51.6	562.9	WCST	Perseverative error	-0.06 (-0.49, 0.38)
Zamarian et al. [155]a	15/28	66.1/63.1	10.7	28.2	NA	NA	63.6	NA	TMT	Time (B)	-0.48 (-1.1, 0.15)
Zgaljardic et al. [98]	32/29	66.9/66.7	15.4	NA	1.92	NA	NA	NA	OMO	Test score	0.51 (0.01, 1.02)
Zhang et al. [99]	42/36	62.2/62.7	9.8	27.59	2	20.02	50.4	298.2	TMT	Time (B)	-0.64 (-1.09, -0.19)

Working Memory											
Abe et al. [50]	32/20	65.9/65.5	11.7	28.3	2.5	18.1	49.2	507	Digit Span	Span length	-0.08 (-0.63, 0.47)
Agosta et al. [39]	41/34	64/63	11	27.7	NA	27.1	85.2	NA	ACE-R	Test score	-0.41 (-0.86, 0.05)
Alonso-Recio et al. [126]	50/49	65.14/64.86	NA	29.00	NA	NA	77.40	NA	Digit Span	Span length	-0.53 (-0.93, -0.13)
Altgassen et al. [100]	16/16	61.1/62.6	NA	NA	1.38	13.83	57.72	NA	Digit Span	Span length	-0.56 (-1.26, 0.14)
Baggio et al. [52]	39/23	63.5/61	11.4	28.7	1.8	16.5	67.2	560.3	Digit Span	Span length	-0.22 (-0.73, 0.29)
Barnes and Boubert, [54]	20/20	63.73/68.54	NA	27.2	2.9	NA	116.64	465	2-back Task	%hits-%false alarm	-1.32 (-2.00, -0.64)
Basic et al. [115]	58/58	66.09/66.85	NA	26.10	NA	NA	77.76	NA	Digit Span	Span length	-0.78 (-1.15, -0.40)
Beato et al. [156]	18/21	52.7/	13.8	NA	3	37.6	139.2	902	n-back Task	Number of correct response	-0.67 (-1.31, -0.03)
Benito-León et al. [157]	46/138	78.1/76.5	NA	NA	2.4	NA	22.8	NA	Immediate Free Recall	Items recalled	-0.17 (-0.50, 0.16)
Benke et al. [116]	22/18	58/60.9	9.9	NA	2.29	16.2	117.6	NA	MGT	Test score	0.07 (-0.54, 0.68)
Bezdicek et al. [57]	46/41	57.7/60.78	14.84	NA	1.95	10.3	124.8	1029	Digit Span	Span length	-0.26 (-0.68, 0.15)
Bodden et al. [117]	21/21	63.7/58.5	14.6	29	2.5	NA	61.2	432.1	Memo Test	Test score	-0.42 (-1.02, 0.18)
Bogdanova and Cronin-Golomb [127]	22/22	62.25/61.3	15.7	29.3	2	NA	98.4	486.35	Digit Span	Span length	-0.50 (-1.09, 0.09)
Bohlhalter et al. [58]	12/12	59.1/46.6	NA	NA	NA	16.5	92.4	766	Working Memory Span	Span length	-0.92 (-1.73, -0.10)
Bohnen et al. [59]	13/14	70.8/69.7	NA	28.1	NA	26.4	70.8	NA	CVLT	Test score	-0.21 (-0.95, 0.52)
Bott et al. [20]	21/21	63.7/66.4	16.5	NA	NA	27.1	NA	NA	EXAMINER	Test score	-0.65 (-1.26, -0.04)
Brand et al. [118]	20/20	66.85/64	9.1	28.2	3	NA	106.05	NA	Immediate Recall	Items recalled	-2.02 (-2.77, -1.27)
Breitenstein et al. [158]	6/16	70.45/68.6	NA	29.2	NA	22.5	37.65	281	Digit Span	Span length	-0.34 (-1.17, 0.49)
Broeders et al. [60]	59/40	62.5/61.4	11.60	27.90	1.70	16.00	17.50	153.90	RAVLT	Items recalled	-0.57 (-0.98, -0.16)
Bublak et al. [159]	14/14	55.1/55.2	NA	28.9	2.3	NA	47.3	NA	Working Memory Span	Span length	-0.58 (-1.33, 0.16)
Camicioli et al. [131]	29/16	60.5/57.9	14.3	28.6	NA	15.3	NA	NA	DOT	Span length	-1.15 (-1.79, -0.50)
Cipresso et al. [101]	15/15	69/61.7	7.93	27	NA	NA	NA	NA	Cors Block Test	Span length	-0.69 (-1.41, 0.03)
Cohen et al. [61]	13/16	65.3/66.6	4.8	NA	2.1	29.9	78	714	Digit Span	Span length	0.07 (-0.64, 0.78)
Colman et al. [40]	27/25	61.39/62.93	13.21	28.11	1.79	15.68	72.48	786.94	Digit Span	Span length	-0.36 (-0.90, 0.18)
Cooper et al. [132]	60/37	59.8/59.6	9.93	NA	NA	NA	15.75	NA	DOT	Span length	-2.43 (-2.97, -1.90)
Costa et al. [119]	39/46	62.56/63.04	10.82	28.22	NA	9.09	81.48	NA	Immediate Visual Memory	Items recalled	-0.42 (-0.85, 0.01)
Costa et al. [120]	33/20	63.4/66	12.6	29.4	NA	19.7	82.8	607	Word List Recall	Items recalled	0 (-0.55, 0.55)
Crawford et al. [160]	25/18	63/75	11.76	28.8	2.12	NA	NA	NA	Digit Span	Span length	0.17 (-0.43, 0.77)
Crescentini et al. [41]	19/14	66.7/65.6	8.1	29	2.05	26.2	76.8	540.3	Digit Span	Span length	-0.54 (-1.22, 0.15)
Crescentini et al. [42]	16/14	63.6/61.6	9.7	28.8	1.94	22.9	72	386.4	Digits Span	Span length	-0.93 (-1.69, -0.17)
Dalrymple-Alford et al. [133]	8/8	65.6/62.4	10.1	NA	2.13	NA	52.8	NA	Digit Span	Span length	0 (-0.93, 0.93)
Delazer et al. [134]	20/20	68.5/71.3	11.9	27.8	1.8	17.6	62.95	431	Digit Span	Span length	-0.66 (-1.28, -0.03)
Drag et al. [135]	24/24	69.04/68.67	16.58	NA	1.86	14.4	64.62	NA	Digit Span	Span length	-0.42 (-0.99, 0.14)
Dujardin et al. [102]	12/12	65.92/59.25	10.25	NA	2.13	30.58	103	405	Digit Span	Span length	-0.95 (-1.77, -0.13)
Dujardin et al. [62]	18/18	60.17/59.5	11.56	NA	NA	17.58	11.33	NA	LNS	Cost index	-0.60 (-1.25, 0.05)
Ell, [64]	36/35	71.1/65.8	16.7	NA	2	NA	42	NA	Digit Span	Span length	-0.93 (-1.41, -0.44)
Engels et al. [103]	48/57	72.9/67.9	NA	26.14	NA	NA	NA	NA	Digit Span	Span length	-0.53 (-0.91, -0.14)
Euteneuer et al. [121]	21/23	67.6/64.4	11.1	29	2.5	17.7	85.7	487.69	Word List Recall	Items recalled	-0.56 (-1.15, 0.03)
Fama et al. [136]	20/38	63.1/65.3	16	27.4	NA	NA	81.6	NA	Immediate Recall	Items recalled	-0.57 (-1.12, -0.03)

Foster et al. [104]	24/30	59/60	14.9	NA	NA	NA	NA	NA	Letter Maintenance	Accuracy	-0.43 (-0.97, 0.10)
Fournet et al. [161]	15/15	66.1/66.6	9.7	NA	1.93	21.8	96	NA	Verbal Span	Span length	-1.01 (-1.75, -0.26)
Gawrys et al. [68]	30/18	56.03/57.11	13.51	28.93	2	NA	NA	851.58	Digit Span	Span length	-0.87 (-1.47, -0.27)
Gilbert et al. [162]	14/14	66.29/65.79	12.21	29.14	2.14	NA	87.48	NA	Alphabetical Recall	Items recalled	-0.20 (-0.93, 0.52)
Goebel et al. [163]	14/22	66.17/62.06	NA	29.29	NA	NA	106.8	NA	Digit Span	Span length	-0.68 (-1.36, -0.01)
Goebel et al. [137]	22/27	64.8/60.8	14	NA	1.27	NA	94.8	NA	Digit Span	Span length	-0.68 (-1.25, -0.11)
Hartikainen et al. [138]	22/26	66.5/65.5	NA	NA	1.9	NA	NA	NA	DSST	Test score	-0.34 (-0.90, 0.22)
Hsieh et al. [71]	26/27	63.3/63.48	9.07	NA	NA	NA	40.80	NA	Digit Span	Span length	-0.47 (-1.01, 0.07)
Ibarretxe-Bilbao et al. [45]	24/24	56.13/57.58	10.96	29.63	1.73	14.67	36.72	299.58	RAVLT	Items recalled	-0.05 (-0.61, 0.51)
Koerts et al. [72]	43/25	63.7/62.8	5.2	27.5	2.2	24.6	61.2	561.7	Digit Span	Span length	-0.62 (-1.12, -0.12)
Koerts et al. [73]	88/65	62.5/61.9	NA	27.5	2	21.4	67.2	550.3	Immediate Recall	Items recalled	-0.38 (-0.72, -0.04)
Koerts et al. [74]	43/25	63.6/62.8	5.30	27.50	2.20	24.60	63.60	583.70	Digit Span	Span length	-0.63 (-1.13, -0.13)
Koivisto et al. [164]	8/12	72.9/69.3	7	22.9	2.5	NA	115.2	NA	Object Recall	Items recalled	-1.56 (-2.56, -0.57)
Lee et al. [165]	19/12	64.11/67.61	9	NA	NA	NA	94.32	NA	PLM	Accuracy	-0.88 (-1.61, -0.14)
Lee et al. [166]	21/28	66.71/68.57	14.29	28.50	1.98	NA	80.40	NA	Working Memory Span	Span length	-0.80 (-1.38, -0.22)
Lord et al. [46]	121/184	67/69.4	NA	NA	1.94	25.5	NA	124.6	Digit Span	Span length	-0.38 (-0.58, -0.18)
Martin et al. [167]	16/22	65.4/68	15.10	29.10	NA	7.90	NA	NA	SDMT	Test score	-2.22 (-3.03, -1.42)
Miah et al. [106]	23/21	62.6/60.3	NA	NA	2	17.09	64.18	397.69	Spatial Span	Span length	-0.32 (-0.87, 0.23)
Miller et al. [80]	42/28	64.8/63.9	17.3	NA	2	20.1	80.4	356.5	Digit Span	Span length	-0.59 (-1.07, -0.11)
Mioni et al. [122]	21/25	68.95/71.12	7.76	27.28	NA	10.92	68.4	NA	Word List Recall	Items recalled	-0.25 (-0.84, 0.34)
Mitchell and Barbosa Bouças, [81]	33/33	63.6/66.9	15.2	NA	NA	NA	96	NA	n-back Task	Accuracy	-0.47 (-0.95, 0.01)
Miura et al. [142]	32/25	67.8/66.9	12	28.5	2.72	NA	67.2	318.9	Digit Span	Span length	-0.49 (-1.01, 0.03)
Monetta et al. [107]	11/11	67.1/71.2	16.60	NA	2.50	NA	109.20	NA	Working Memory Span	Span length	0.47 (-0.34, 1.29)
Müller et al. [159]	20/20	55.3/55.7	10.7	NA	2.3	49.3	42.5	NA	Digit Span	Span length	-1.07 (-1.73, -0.42)
Murray and Rutledge, [47]	11/9	68.36/67.89	16	NA	NA	17.91	NA	NA	Sentence Reading Span	Span length	-1.34 (-2.28, -0.40)
Owen et al. [168]	7/7	53.9/56.47	NA	NA	2.56	NA	NA	NA	Working Memory Span	Span length	0.06 (-0.94, 1.06)
Parrao et al. [110]	44/17	63.5/63.1	11.2	NA	2.3	16.1	69.6	NA	Digit Span	Span length	-0.78 (-1.35, -0.21)
Peavy et al. [169]	16/30	64.2/63	15.40	NA	NA	NA	140.40	NA	Digit Span	Span length	-0.39 (-0.99, 0.21)
Peigneux et al. [170]	17/17	63.2/63	11.30	NA	2.53	30.42	105.88	NA	Digit Span	Span length	0.37 (-0.30, 1.03)
Pell et al. [111]	15/16	70.9/70.4	15.40	NA	NA	29.90	127.20	NA	Digit Span	Span length	-0.64 (-1.35, 0.06)
Pellicano et al. [84]	13/13	58.8/60.3	11.80	28.40	1.90	18.50	51.60	NA	RAVLT	Items recalled	-0.98 (-1.77, -0.19)
Pereira et al. [85]	20/20	64/59.1	NA	28.50	2.40	24.90	81.60	627.00	Digit Span	Span length	-1.09 (-1.75, -0.44)
Perfetti et al. [112]	25/24	69.8/72.9	8.70	27.00	2.20	19.90	NA	1210	Jigsaw Puzzle Test	Test score	-1.07 (-1.67, -0.48)
Poletti et al. [48]	103/100	66/66.8	9.20	27.90	NA	16.90	10.70	NA	Digit Span	Span length	-0.34 (-0.62, -0.07)
Poliakoff and Smith-Spark [171]	24/24	62.6/62.8	12.30	29.40	2.21	21.00	88.56	NA	Digit Span	Span length	-0.17 (-0.73, 0.39)
Pollux [172]	18/18	58.27/61.05	NA	28.38	2.5	NA	103.32	NA	Digit Span	Span length	-0.57 (-1.22, 0.09)
Ranchet et al. [89]	19/21	66.1/69.1	13	27.4	2.1	16.4	90	741.8	Benton Test	Test score	-0.13 (-0.74, 0.48)
Raskin et al. [90]	54/34	61.9/61	14.7	NA	1.99	NA	NA	NA	Digit Span	Span length	0.59 (0.15, 1.03)
Rodriguez-Ferreiro et al. [49]	50/42	72.92/74.08	7.04	26.94	1.96	NA	114.00	NA	Immediate Recall	Items recalled	-0.45 (-0.86, -0.04)
Segura et al. [91]	43/32	60.77/64.69	12.02	29.47	1.7	13.16	74.76	692.81	RAVLT	Items recalled	-0.26 (-0.71, 0.19)

Siepel et al. [173]	339/158	61.1/59.4	15.5	NA	NA	21	NA	NA	HVLT-R	Items recalled	-0.35 (-0.54, -0.16)
Stavitsky et al. [92]	35/18	66.2/64.4	16.8	NA	2	25.1	105.6	604.3	Digit Span	Span length	-0.28 (-0.84, 0.28)
Stebbins et al. [174]	16/16	68.56/69.19	14.8	28.81	2.75	NA	NA	NA	Free Recall	Items recalled	-0.80 (-1.51, -0.10)
Stolwyk et al. [146]	18/18	67.62/67.13	13.89	27.89	NA	11.67	80.04	470.84	Digit Span	Span length	-0.12 (-0.77, 0.53)
Tamura et al. [147]	24/24	60.9/61.7	12.7	28.5	2.21	NA	79.2	NA	Digit Span	Span length	-0.63 (-1.20, -0.06)
Theilmann et al. [93]	25/26	68/65.9	16.9	28.7	2.36	25.4	86.4	970.4	Digit Span	Span length	-0.52 (-1.07, 0.03)
van Spaendonck et al. [94]	51/24	53.9/52.7	NA	NA	NA	NA	39.60	NA	RAVLT	Items recalled	-0.37 (-0.86, 0.11)
Werheid et al. [151]	14/16	62.45/62.4	9.25	NA	NA	44.25	NA	NA	Digit Span	Span length	-0.53 (-1.25, 0.18)
Xu et al. [175]	20/20	65.9/68.9	12.40	27.60	1.40	26.60	72.00	622.25	DSST	Reaction time for correct response	-0.48 (-1.09, 0.14)
Zamarian et al. [155]	15/28	66.1/63.1	10.7	28.2	NA	NA	63.6	NA	Digit Span	Span length	-0.72 (-1.36, -0.09)
Zgaljardic et al.[98]	32/29	66.9/66.7	15.4	NA	1.92	NA	NA	NA	Digit Span	Span length	-1.10 (-1.64, -0.57)
Zhang et al. [99]	42/36	62.2/62.7	9.8	27.59	2	20.02	50.4	298.2	Digit Span	Span length	-0.25 (-0.70, 0.19)

Note. Mean results of age, year of education, MMSE, HY, UPDRS motor score and LEDD were presented. ACE-R, Addenbrooke's Cognitive Assessment Revised; ANT, Attention Network Test; BADS-KS, Behavioural Assessment of the Dysexecutive Syndrome (Key Search); BADS-RS, Behavioural Assessment of the Dysexecutive Syndrome (Rule Shift Test);BADS-ZM, Behavioural Assessment of the Dysexecutive Syndrome (Zoo Map); CCPT-II, Conners' Continuous Performance Test II; CDR, Cognitive Drug Research Battery;CI, confidence interval; CON, controls; CVLT, California Verbal Learning Task;DKEFS-CWI, Delis-Kaplan Executive Function System (Color-Word Interference Subtest);DKEFS-T, Delis-Kaplan Executive Function System (Tower Subtest);DOT, Digit Ordering Task;DSST, Digit Symbol Substitution Task;EXAMINER, Measures and Instruments for Neurobehavioral Evaluation and Research;HVLT-R, Hopkins Verbal Learning Test-Revised;HY, Hoehn and Yahr stage;IED, Intra-dimensional/Extra-dimensional Shift Task;LEDD, levodopa equivalent daily doses; LNS, Letter Number Sequencing Task;LPS, Leistungsprüfsystem;MGT,Münchner Gedachtnistest;MMSE, Mini Mental State Examination; NA, not available; OMO, Odd-Man-Out Task;OTS, One Touch Stocking Task;PASAT, Paced Auditory Serial Addition Test;PD, Parkinson' patients; PLM, Prose Learning and Memory Test;POA, Power of Attention Test;RAVLT, Rey Auditory Verbal Learning Test;RPM, Raven's Progressive Matrices;SDMT, Symbol Digit Modalities Test;SSG, Spatial Sequences Generation Test;SST, Stop Signal Task;TAP-A, Test for Attentional Performance (Alertness);TEA, Test of Everyday Attention;TMT, Trail Making Test;TOH, Tower of Hanoi;TOL, Tower of London;WCST, Wisconsin Card Sorting Test; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2: Summary of the meta-analytic results.

EF domain	N (PD/CON)	k	Hedges' g (95% CI)	Heterogeneity test		Publication bias test		
				Q	I^2	FSN	Egger's test t-value	ES_{adj} (95% CI)
Attention	556/521	11	-0.48 (-0.62, -0.35)***	12.56	12.44	134	0.56	-0.48 (-0.62, -0.35)
Inhibition	1837/1572	56	-0.48 (-0.59, -0.36)***	135.85***	59.51	2287	2.80**	-0.33 (-0.46, -0.20)
Planning	771/698	22	-0.49 (-0.62, -0.36)***	27.97	24.92	411	0.097	-0.47 (-0.61, -0.34)
Reasoning	429/419	13	-0.31 (-0.45, -0.18)***	6.44	0	66	2.99**	-0.20 (-0.32, -0.08)
Shifting	2827/2648	82	-0.55 (-0.68, -0.42)***	414.86***	80.48	6662	2.02*	-0.31 (-0.45, -0.17)
Working memory	2901/2650	91	-0.53 (-0.62, -0.44)***	215.28***	58.19	7527	2.64**	-0.38 (-0.48, -0.28)
Overall	4639/4219	275	-0.49 (-0.53, -0.44)***	820.94***	66.50	67088	3.93***	-0.36 (-0.42, -0.30)

Note. CI, confidence interval; EF, executive function; ESadj, adjusted effect size (Hedges' g) by trim-and-fill method; FSN, fail-safe N. *p<0.05, **p<0.01, ***p<0.001.

95% *CI*: -0.68 to -0.42) and working memory (Hedges' g = -0.49, 95% *CI*: -0.53 to -0.44).

Heterogeneity

Heterogeneity was significant among the studies of overall EF (Cochran's Q = 820.94, p< 0.001). After grouping by domain, however, significant heterogeneity was not observed among studies of attention (Cochran's Q = 12.56, p= 0.32), planning (Cochran's Q = 27.97, p = 0.14) and reasoning (Cochran's Q = 6.44, p= 0.89), but remained significant among studies of inhibition (Cochran's Q = 135.85, p< 0.001), shifting (Cochran's Q = 414.86, p< 0.001) and working memory (Cochran's Q = 215.28, p< 0.001). Heterogeneity was moderate for inhibition (I^2 = 59.51%), working memory (I^2 = 58.19%) and overall EF (I^2 = 66.5%), but high for shifting (I^2 = 80.48%).

Publication bias

The fail-safe N exceeded the thresholds for all EF domains except reasoning, indicating that the meta-analytic results were generally robust to publication bias. Funnel plot asymmetry appeared to be present for all EF domains **(Figure 3)**. However, Egger's asymmetry test yielded significant results only for inhibition (t = 2.80, p < 0.01), reasoning (t = 2.99, p < 0.01), shifting (t = 2.02, p < 0.05), working memory (t = 2.64, p < 0.01) and overall EF (t = 3.93, p < 0.001). After a trim-and-fill procedure, the adjusted effect sizes

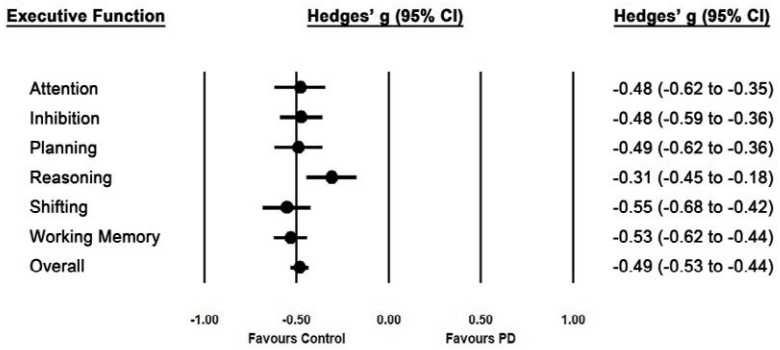

Figure 2: Meta-analysis results for different executive functions. Positive effect size indicates better behavioral performance of Parkinson's patients (PD).

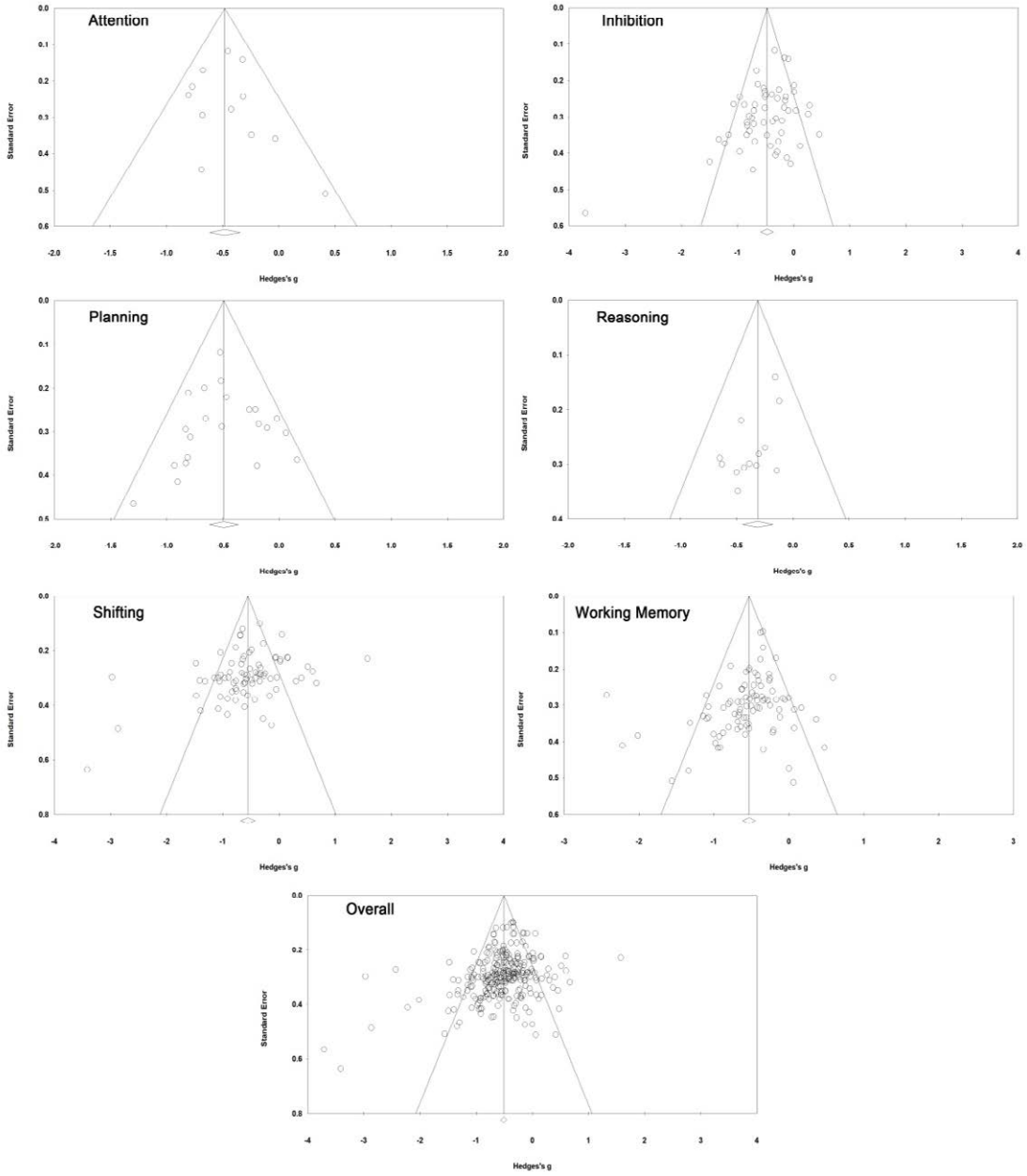

Figure 3: Funnel plots of executive functions.

generally decreased, and no significant measure became non-significant. On average, the mean effect size (Hedges' *g*) decreased (i.e., became less negative) in the trimmed analyses by a value of 0.13 (Table 2).

■ Meta-regression

The results of meta-regression analyses showed that age (β = -0.0046, p = 0.44), years of education (β = -0.0036, p = 0.83), Hoehn and Yahr stage (β = -0.11, p = 0.32), disease duration (β = -0.0025, p = 0.15), UPDRS motor score (β = -0.0046, p = 0.44), MMSE (β = 0.065, p = 0.21) and LEDD (β = 0.000009, p = 0.54) did not significantly predict the study outcomes.

Discussion

■ Summary of evidence

This meta-analysis quantitatively compared the EFs of PD patients and healthy controls. A fairly moderate impairment of overall EF was observed among PD patients, consistent with the results of a previous meta-analysis [7]. The smaller effect size observed in this meta-analysis might have resulted from the inclusion of a greater number of studies. Small to moderate effect sizes were observed in different EF domains (Hedges' g = -0.31 to -0.55), among which reasoning skill was the least affected. This finding was compatible with the results of an earlier study in which abstract thinking was demonstrated to be less affected than attentional control in PD patients [32]. Other EF domains were similarly affected to a similar extent. Furthermore, the EF deficits experienced by PD patients were not found to be influenced by age, years of education, disease severity, motor deficits, disease duration, medication dose or global cognition.

■ Heterogeneity

Moderate heterogeneity was observed for overall EF. After grouping by EF domain, however, high heterogeneity was observed for shifting, whereas moderate heterogeneity was observed for inhibition and working memory. Heterogeneity may have resulted from variability among the assessment tools and performance indexes used by the included studies. In addition, the constructs of inhibition, shifting and working memory could possibly be divided into heterogeneous sub-constructs. For instance, PD patients might exhibit impairment in only one type of working memory. Thus, heterogeneity may arise if the different types of inhibition, shifting and working memory are treated as single constructs.

■ Publication bias

According to Egger's asymmetry test, the overall EF was subject to publication bias. Even after grouping by EF domain, obvious publication bias remained for inhibition, reasoning, shifting and working memory, suggesting that null results or results indicating better EF among PD patients may not have been published. The fail-safe N indicated that the meta-analytic results for attention, inhibition, planning, shifting and working memory were robust to publication bias. However, the fail-safe N for reasoning was smaller than the threshold, indicating that the meta-analytic results for this domain were susceptible to publication bias. The effect sizes generally decreased after the trim-out-fill procedure was applied, but remained significantly different from zero. Hence, broad EF impairments were observed in PD patients, and reasoning remained the least affected EF domain.

■ Implications

The current meta-analysis provided evidence indicating that PD patients exhibit substantial dysfunctions across different EF domains. In this population, the impairments in the attention, inhibition, planning, and reasoning, shifting and working memory domains were not moderated by age, years of education, disease severity, motor deficits, disease duration, medication dose or global cognition. These results better enable us to understand the EF profiles of PD patients, and this information will assist clinicians and caregivers with devising suitable strategies to improve the functional outcomes and quality of life of PD patients.

EFs are essential for performing daily tasks; accordingly, impairments in these domains can greatly degrade a PD patient's quality of life and functional capability [33]. The existing literature suggests that EF can be altered through deliberate training and intervention. For instance, physical exercise has been shown to improve inhibition, planning and working memory in PD patients [34-36]. Computerized cognitive training and video games were also found to improve EF in PD patients [37,38]. The selection of an appropriate remedial approach could halt a decline in or even improve the EF of PD patients, thus reducing the challenges faced during daily life and the burdens placed on caregivers.

■ Limitations and future research direction

This meta-analysis was limited to studies

published in peer-reviewed journals. Although this criterion ensured the quality of the included studies, we risked missing relevant studies that had been published elsewhere. Additionally, some identified studies were excluded from the meta-analysis because they contained insufficient data for an effect size computation. This reduced the number of included studies and potentially introduced a non-random bias.

In addition, the selection of EF domains and tasks may have been arbitrary. According to an existing consensus, inhibition, working memory and shifting are the core EFs [9]. Although attention, planning and reasoning are crucial for goal-directed behaviors, their inclusion in EF is debatable. For instance, reasoning may depend on one's prior knowledge and experience, rather than the ability to follow rules of logic. Moreover, more than one performance index (such as reaction time, accuracy and error rate) might apply to an EF task, and the index selection may be subjective. To ensure that the included performance indices were representative of the assessed EFs, we attempted to select the most appropriate indicators based on suggestions in the literature.

Furthermore, as most included studies failed to report the medication statuses of PD patients during testing, it was difficult to determine whether performance was affected by medication. Therefore, future reports should provide more details about the medication statuses of PD patients, which would allow a decoupling of genuine EF deficits from medication-influenced performance.

Conclusions

PD patients exhibit impairments in the EF domains of attention, inhibition, planning, reasoning, shifting and working memory; of these, reasoning is the least affected. Furthermore, these deficits are not influenced by age, years of education, disease severity, motor deficits, disease duration, medication dose or global cognition. However, as the results for reasoning were more susceptible to publication bias, compared to other EF domains, additional studies of this domain should be conducted and included in future meta-analyses. Finally, although numerous studies have demonstrated the plasticity of EF in PD patients, the efficacies of remediate EF training and intervention strategies require further verifications.

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Conflict of Interest

No conflict of interest is to be disclosed.

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