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Review

Computerized cognitive training in Parkinson's disease: A systematic review and meta-analysis

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ABSTRACT

Cognitive impairment is a central non-motor symptom of Parkinson's disease (PD), and there are no established treatments. Computerized cognitive training (CCT) is a safe and efficacious strategy but its efficacy in PD is unclear. We aimed to investigate the efficacy of CCT on cognitive, psychosocial and daily function, and assess potential effect moderators in people with PD without dementia. Randomized controlled trials of CCT were included in multivariate meta-analyses and meta-regressions. Seventeen studies (16 trials) encompassing 679 participants were included. The pooled effect of CCT relative to control was small and statistically significant for overall cognitive function (g=0.16; 95% CI 0.02–0.29). There was robust evidence for benefit on clinical measures of global cognition across 10 trials (g=0.33; 95% CI 0.19–0.48), especially in PD with mild cognitive impairment (PD-MCI), as well as on individual cognitive domains. Greater CCT dose and PD-MCI population were associated with larger effect sizes, but no statistically significant differences were found between subgroups. There was no significant difference in the efficacy of home-based compared to supervised training. Our findings suggest that CCT is associated with cognitive benefits in PD, including when delivered remotely. Larger, well-powered trials are warranted to examine what specific CCT regimens are most likely to promote cognitive and everyday functioning in the long-term.

1. Introduction

Cognitive impairment is a central non-motor symptom in Parkinson's disease (PD), associated with significant impact on quality of life (Svenningsson et al., 2012) and largely unresponsive to pharmacotherapy (Aarsland et al., 2017). Approximately 20% of people with PD present with mild cognitive impairment (MCI) at diagnosis, with a higher age-standardized risk of conversion to MCI and dementia as the disease progresses (Aarsland et al., 2017). Developing and implementing interventions that could effectively prevent or delay cognitive decline is therefore a critical and unmet need for PD care (Aarsland et al., 2017; Goldman et al., 2018).

Expert panels (Aarsland et al., 2017; Goldman et al., 2018) and clinical guidelines (Müller et al., 2020) have pointed to cognitive training as a safe and efficacious non-pharmacological intervention to prevent cognitive decline in PD, either as a stand-alone intervention or as part of a multicomponent strategy. Computerized cognitive training (CCT) has several advantages over traditional cognitive interventions, including the potential to adapt training to individual needs, inexpensive delivery at home, and real-time feedback on performance to patients and clinicians (Walton et al., 2017). Yet conversely to robust evidence for efficacy in older adults (Hill et al., 2017; Lampit et al., 2014b), a Cochrane review did not find reliable evidence for CCT efficacy on global cognition based on seven trials in people with PD and MCI or dementia (Orgeta et al., 2020). Other systematic reviews (Couture et al., 2019; Lawrence et al., 2017; Leung et al., 2015; Nousia et al.,

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2020; Svaerke et al., 2020) have reported mixed results, typically on the basis of a small pool of studies mixing CCT with other cognitive interventions as well as randomized controlled trials (RCTs) with other study designs. Thus, whether and how CCT should be implemented in clinical practice for people with PD remain largely unclear (Goldman et al., 2018; Kalbe et al., 2018). In light of preliminary expert panel recommendations and a sharp increase in trials of CCT in the past several years, we aimed to update the randomized evidence for CCT and examine potential effect moderators that could guide clinical implementation.

2. Methods

2.1. Protocol and registration

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) statement (Page et al., 2021) and was prospectively registered with PROSPERO (CRD42020185386). The review protocol has been published (Gavelin et al., 2020).

2.2. Eligibility criteria

We included RCTs studying the effects of CCT on one or more cognitive, psychosocial or functional outcome in patients with PD (any age and etiology), as compared to an active (e.g., sham CCT, recreational activities) or passive (wait-list, no-contact) control group. Study participants could be either cognitively healthy, with subjective cognitive impairment (PD-SCI) or mild cognitive impairment (PD-MCI); studies including only participants with PD dementia (PDD) were excluded as CCT is unlikely to be efficacious past dementia onset (Hill et al., 2017; Orgeta et al., 2020). Studies that included mixed samples (e.g., PDD and PD-MCI) were included if separate results were reported or could be obtained for the eligible population. CCT was defined as minimum of 4 h of practice on standardized computerized tasks or video games with clear cognitive rationale, administered on personal computers, mobile devices or gaming consoles (Hill et al., 2017; Lampit et al., 2014b; Leung et al., 2015). Studies that combined CCT with other interventions (e.g., physical exercise) were eligible as long as the adjacent intervention was provided similarly to the experimental and control groups. In multi-arm studies, all experimental and control conditions meeting the eligibility criteria were included. Eligible outcomes were change from baseline to post-intervention in non-trained measures of cognition, assessed through one or more standardized neuropsychological tests or close equivalents (Hill et al., 2017; Lampit et al., 2014b; Leung et al., 2015). Additional outcomes included subjective cognitive complaints, psychosocial function (e.g., depression, quality of life) and everyday functioning (e.g., instrumental activities of daily living). Outcomes from longitudinal follow-ups were also included. The primary outcome was overall cognitive performance. Secondary outcomes were global cognition, domain-specific cognitive performance, subjective cognition, psychosocial function and functional abilities.

2.3. Search strategy and study selection

We searched MEDLINE, EMBASE and PsycINFO from 1 January 2015 through July 27, 2021 to identify articles published since the date of the search in our previous meta-analysis of cognitive training in PD (Leung et al., 2015). No restrictions on language or type of publication were applied. Records from the updated search were combined with eligible studies identified in the original version of the review. Three studies included in our previous review were excluded as they provided paper-based cognitive training (Pena et al., 2014; Petrelli et al., 2014) or sports games with limited cognitive challenge (Pompeu et al., 2012). The electronic search was complemented by hand searching the references of included articles and previous reviews, clinical trial registries and communication with investigators of ongoing studies. The full search strategy is provided in Appendix A. Two independent reviewers (HMG and MD) conducted duplicate initial screening of titles and abstracts as well as full-text screening of potentially relevant articles. We attempted to locate the associated full-text through manual searches or obtain data from authors of potentially eligible conference abstracts or unpublished trials.

2.4. Data extraction and coding

Data extraction and coding was conducted by one reviewer (MD or IL) and another reviewer (HMG) checked all data entry. Missing or incomplete data were requested from the corresponding authors of the studies. Coding of outcomes into cognitive domains was conducted according to the Cattell-Horn-Carroll and Miyake (CHC-M) taxonomy (Webb et al., 2018). Following this framework, each cognitive outcome was classified as representing a broad cognitive domain (e.g., *Executive Function*) as well as a more specific, narrow ability (e.g., *Inhibition*). Global cognitive screening instruments, such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), were classified as global cognition. The classification of outcomes by domain is presented in Appendix B. Data were extracted as means and standard deviations (SD) for each group and time-point or, when this was not available, as mean change and SD (Zimmermann et al., 2014) or mean difference and 95% confidence interval (CI) (Walton et al., 2018). Intention-to-treat data were preferred if reported.

2.5. Risk of bias assessment

Two independent reviewers (MD, IL or HMG) assessed the risk of bias of individual RCTs using the revised Cochrane Risk of Bias tool (RoB 2) (Sterne et al., 2019). Disagreements were resolved by consensus or by a senior reviewer (AL). Studies with "some concerns" or "high" risk of bias in domain 3 (bias due to missing outcome data) or 4 (bias in measurement of the outcome) were considered as having some concerns or high risk of bias overall, and coded as a single group (Hill et al., 2017; Lampit et al., 2014b; Leung et al., 2015).

2.6. Data synthesis

Analyses were based on robust variance estimation (Hedges et al., 2010) using the R packages robumeta (Fisher et al., 2017) and clubSandwich (Pustejovsky, 2020). Between-group differences in eligible outcomes measures were converted to standardized mean differences and calculated as Hedges' g with 95% CI. Pooling of outcomes across studies was conducted using multivariate models with robust variance estimation in order to account for non-independence of multiple effect sizes within studies (Hedges et al., 2010). Analyses were conducted for overall cognition, comprising of all cognitive outcomes combined, followed by separate analyses for each cognitive domain, and for psychosocial, functional and subjective cognitive outcomes. For the primary outcome, a sensitivity analysis was conducted by comparing results from correlated and hierarchical effects models. Heterogeneity across studies was quantified using tau^2 and further expressed as a proportion of overall observed variance using the I^2 statistic (Borenstein et al., 2017). Prediction intervals were calculated to assess the dispersion of true effects across settings (Riley et al., 2011).

To investigate potential moderators of overall cognitive efficacy, the following pre-specified subgroup analyses were performed using robust variance estimation meta-regression models: cognitive status (normal/PD-SCI or PD-MCI), CCT type (single or multi-domain), delivery (supervised or home-based), dose (total training hours) and type of control (active intervention, sham or passive control). Potential interactions between moderators were planned but not conducted due to insufficient number of studies to power multivariable meta-regressions. Small-study effect was assessed by visually inspecting funnel plots of effect size vs

standard error (Sterne et al., 2011) and formally tested using the Egger's test (Egger et al., 1997). Finally, we performed subgroup analysis of the overall cognitive outcome by risk of bias, study source and preregistration.

3. Results

3.1. Study selection

After removal of duplicates, the updated literature search yielded 1521 articles, of which 1391 were excluded based on titles and abstracts. Subsequently, we assessed 130 full-text articles for eligibility and ten of these fulfilled inclusion criteria. A list of the excluded studies with reasons is provided in Appendix C. Records were combined with four eligible studies from our previous review (Cerasa et al., 2014; Edwards et al., 2013; París et al., 2011; Zimmermann et al., 2014) and two additional studies were identified through manual search (NCT01156714; van de Weijer et al., 2020). One study that compared outcomes for CCT with or without transcranial direct current stimulation (tDCS) was split into two separate comparisons with three independent arms each (Lawrence et al., 2018), resulting in a total of 17 RCTs in the meta-analysis (Fig. 1). We identified one secondary outcome article (Giehl et al., 2020b) which was combined with the other manuscript from the same study (Ophey et al., 2020). The authors of seven studies (Bernini et al., 2021; De Luca et al., 2019; Ferraz et al., 2018; Maggio et al., 2018; NCT01156714; Ophey et al., 2020; van de Weijer et al., 2020) were contacted with requests for additional summary data, of which five provided data (Bernini et al., 2021; De Luca et al., 2019; Ferraz et al., 2018; Maggio et al., 2018; Ophey et al., 2020).

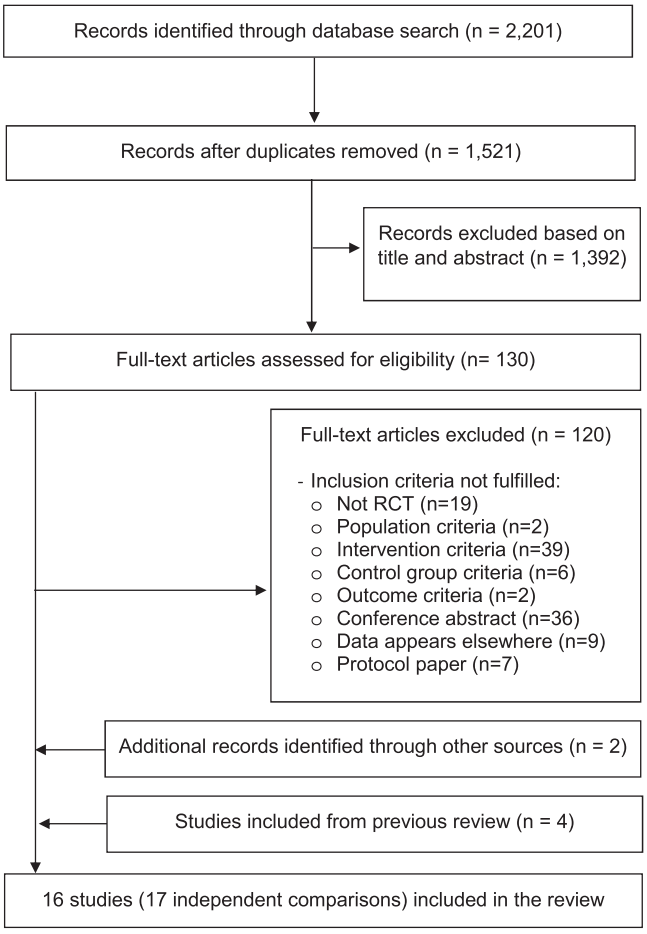

Fig. 1. Flowchart of study selection process.

3.2. Characteristics of included studies

The included studies encompassed 679 participants with mean age ranging from 59.7 to 71.4 years. Participant disease severity ranged from Hoehn & Yahr stages 1–4. Nine studies focused on participants with cognitive impairment (Bernini et al., 2019, 2021; Cerasa et al., 2014; De Luca et al., 2019; Lawrence et al., 2018; Maggio et al., 2018; París et al., 2011; van de Weijer et al., 2020; Vlagsma et al., 2020). Five studies were from Italy (Bernini et al., 2019, 2021; Cerasa et al., 2014; De Luca et al., 2019; Maggio et al., 2018), two were from Australia (Lawrence et al., 2018; Walton et al., 2018), the Netherlands (van de Weijer et al., 2020; Vlagsma et al., 2020) and the United States (Edwards et al., 2013; NCT01156714) and the remaining studies were from Brazil (Ferraz et al., 2018), Finland (Fellman et al., 2018), Germany (Ophey et al., 2020), Switzerland (Zimmermann et al., 2014) and Spain (París et al., 2011). Six studies (38%) had a high risk of bias, seven (44%) had some concerns and three (19%) had a low risk of bias (Table 1, Appendix D). Eleven studies administered multi-domain training (Bernini et al., 2019, 2021; De Luca et al., 2019; Ferraz et al., 2018; Lawrence et al., 2018; Maggio et al., 2018; NCT01156714; París et al., 2011; van de Weijer et al., 2020; Walton et al., 2018; Zimmermann et al., 2014) and five used single-domain training of working memory (Fellman et al., 2018; Ophey et al., 2020), attention (Cerasa et al., 2014; Vlagsma et al., 2020) or speed of processing (Edwards et al., 2013). All training programs were adaptive. Eight studies compared CCT to active control interventions, three included sham control and three had a passive control group (Table 1). One study had an active intervention and a sham control group (Bernini et al., 2021) and one had an active intervention and a passive control group (Lawrence et al., 2018). Two studies used CCT as a control group (Ferraz et al., 2018; Vlagsma et al., 2020).

3.3. Efficacy of CCT on overall cognition

Across 17 studies encompassing 679 participants and 221 cognitive effect sizes, the overall (composite) cognitive effect of CCT was small and statistically significant ($g = 0.16$, 95% CI = 0.02–0.29, $p = 0.02$), with moderate heterogeneity ($\tau^2 = 0.047$, $I^2 = 31\%$, prediction interval −0.32 to 0.64, Fig. 2a). The funnel plot (Appendix E) and Egger's test ($\beta = 0.65$, $p = 0.41$) did not provide evidence for small-study effect. Sensitivity analysis using hierarchical effects models showed a highly convergent result as the main analysis ($g = 0.19$, 95% CI = 0.07–0.31, $p = 0.01$). There was no evidence for difference in overall cognitive effect size across levels of risk of bias, registration status or type of control (Table 2). Meta-regressions did not confirm between-subgroup differences, although markedly lower effect sizes were noted within studies that targeted people with normal cognition or PD-SCI and those that provided less than the weighted mean dose of 14.3 training hours (Table 2).

3.4. Efficacy of CCT on global cognition

Ten studies encompassing 327 participants and 23 effect sizes reported global cognition outcomes (e.g., the MMSE or MoCA). The pooled effect size was moderate and statistically significant ($g = 0.33$, 95% CI = 0.19–0.48, $p < 0.001$, Fig. 2b). There was no evidence of heterogeneity ($\tau^2 = 0.00$, $I^2 = 0\%$) or funnel plot asymmetry ($\beta = -0.56$, $p = 0.71$, Appendix F). Nine of the ten studies were in PD-MCI; removal of the single study in normal cognition (Walton et al., 2018) did not change the results ($g = 0.35$, 95% CI = 0.18–0.51, $p = 0.002$).

3.5. Efficacy of CCT on individual cognitive domains

Fig. 3 summarizes meta-analyses of individual cognitive domains classified according to the CHC-M framework. Detailed analyses at the outcome measure level are provided in Appendix G to L. Although most analyses were small (median 8 studies per domain), moderate effect

Table 1
Characteristics of included studies.

Study	n (% female)[a]	Mean age	Mean MMSE (or equivalent)	Cognitive status	H&Y range	Mean years since diagnosis	Delivery	Interventions	CCT type	Dose	Attrition[b]	Country	Risk of bias
Bernini et al. (2019)	35 (51)	70.23	25.34	Impaired MCI: MDS criteria	≤ 4	9.0	Supervised	CCT: CoRE + Standard physical rehabilitation Active control intervention: Standard physical rehabilitation	Multi-domain	3 × 45 min per week for 4 weeks, 12 sessions in total.	CCT: 26% CG: 0%	Italy	High
Bernini et al. (2021)	48 (35)	71.44	25.31	Impaired MCI: MDS criteria	≤ 3	10.9	Supervised	CCT: CoRE Active control intervention: paper-and-pencil cognitive training Sham control: unstructured activities	Multi-domain	4 × 45 min per week for 3 weeks, 12 sessions in total.	CCT: 14% CG 1: 14% CG 2: 0%	Italy	Some concerns
Cerasa et al. (2014)	15 (40)	59.70[c]	29.05[c]	Impaired Based on cognitive testing	1–3	3.4[c]	Supervised	CCT: RehaComSham control: Simple visuomotor task	Attention	2 × 60 min per week for 6 weeks, 12 sessions in total.	CCT: 20% CG: 30%	Italy	High
De Luca et al. (2019)	60 (48)	62.55	25.2	Impaired Based on MoCA score	< 3	nr	Supervised	CCT: ERICAActive control intervention: Paper and pencil cognitive training	Multi-domain	3 × 60 min per week for 8 weeks, 24 sessions in total.	0%	Italy	Some concerns
Edwards et al. (2013)	73 (31)	68.85[c]	28.07[c]	No cognitive impairment	1–3	6.9[c]	Home-based	CCT: InSightPC: Waitlist	Speed of Processing	1–3 × 60 min per week for 12 weeks, 20 sessions in total.	CCT: 27% CG: 2%	USA	High
Fellman et al. (2018)	52 (65)	65.15	37.2[d]	No cognitive impairment	nr	5.6	Home-based	CCT: In-house developed Sham control: Online quizzes	Working memory	3 × 30 min per week for 5 weeks, 15 sessions in total.	CCT: 0% CG: 7%	Finland	Low
Ferraz et al. (2018)	42 (38)	69[e]	27[e]	No cognitive impairment	2–3	4[e]	Supervised	CCT: Kinect Adventure games Active control intervention: Functional training	Multi-domain	3 × 30 min per week for 8 weeks, 24 sessions in total.	CCT: 9% CG: 12%	Brazil	Some concerns
Lawrence et al. (2018)	21 (52)	68.65	25.61	ImpairedMCI: MDS criteria	nr	5.5	Home-based	CCT Group 1: Smartbrain Pro Standard CCT Group 2: Smartbrain Pro TailoredPC: No treatment	Multi-domain	3 × 45 min per week for 4 weeks, 12 sessions in total.	0%	Australia	Some concerns
Lawrence et al. (2018) tDCS	21 (71)	67.67	25.9	ImpairedMCI: MDS criteria	nr	5.6	Home-based	CCT Group 1: Smartbrain Pro Standard + tDCS CCT Group 2: Smartbrain Pro Tailored + tDCS Active control intervention: tDCS	Multi-domain	3 × 45 min per week for 4 weeks, 12 sessions in total.	0%	Australia	Some concerns
Maggio et al. (2018)	20 (50)	69.4	23.05	Impaired Based on MMSE score	1–3	9.4	Supervised	CCT: BTS Nirvana Active control intervention: Paper-and-pencil cognitive training	Multi-domain	3 × 60 min per week for 8 weeks, 24 sessions in total.	0%	Italy	Low
NCT01156714	28 (25[c])	63.88[c]	nr	nrNo dementia	1–3	nr	Supervised	CCT: InSight + treadmill training Active control intervention: Treadmill training	Multi-domain	3 × 40 min per week for 12 weeks, 36 sessions in total.	CCT: 15% CG: 45%	USA	High
Ophey et al. (2020)	75 (47)	63.98	27.51[e,f]	No cognitive impairment	2–3	4.9[e]	Home-based	CCT: NeuroNationPC: Waitlist	Working memory	5 × 30 min per week for 5 weeks, 25 sessions in total.	CCT: 0% CG: 3%	Germany	Low
París et al. (2011)	28 (50)	65.04	27.89	Impaired50% with MCI, Petersen criteria	1–3	7.5	Supervised	CCT: SmartBrain Active control intervention: Speech therapy	Multi-domain	3 × 45 min per week for 4 weeks, 12 sessions in total.	CCT: 11% CG: 20%	Spain	High

(*continued on next page*)

Table 1 (*continued*)

Study	n (% female)[a]	Mean age	Mean MMSE (or equivalent)	Cognitive status	H&Y range	Mean years since diagnosis	Delivery	Interventions	CCT type	Dose	Attrition[b]	Country	Risk of bias
Walton et al. (2018)	38 (34)	69.66	27.92	No cognitive impairment	1–4	10.9	Supervised	CCT: Designated "brain training" programs Sham control: Non-specific computerized tasks	Multi-domain	2 × 60 min per week for 7 weeks, 14 sessions in total.	CCT: 0% CG: 29%	Australia	High
van de Weijer et al. (2020)	41 (nr)	64.35	24.70[f]	Impaired MCI, MDS criteria	1–3	7.2	Home-based	CCT: AquaSnap PC: Waitlist	Multi-domain	3 × 30 min per week for 12 weeks, 36 sessions in total.	CCT: 14% CG: 10%	Netherlands	Some concerns
Vlagsma et al. (2020)	43 (37)	61.25	28.48[g]	Impaired Executive dysfunction	1–3	6.3	Supervised	CCT: CogniPlusActive control intervention: ReSET Strategic Executive Treatment	Attention	1–2 × 60 min per week, 14 sessions in total.	CCT: 10% CG: 14%	Netherlands	Some concerns
Zimmermann et al. (2014)	39 (36)	68.05	29[e]	No cognitive impairment	2[e]	5.15[h]	Supervised	CCT: CogniPlusActive control intervention: Nintendo Wii	Multi-domain	3 × 40 min per week for 4 weeks, 12 sessions in total.	CCT: 5% CG: 0%	Switzerland	Some concerns

Abbreviations: CCT = computerized cognitive training. CG = control group. H&Y = Hoehn and Yahr. MCI = mild cognitive impairment. MDS = Movement Disorder Society. MMSE = Mini-Mental State Examination. MoCA = Montreal Cognitive Assessment. nr = not reported. PC = passive control. tDCS = transcranial direct current stimulation.

[a] Included in the analysis

[b] From baseline to post-intervention assessment

[c] Baseline sample

[d] Telephone Interview for Cognitive Status – Modified (0–50)

[e] Average of median scores

[f] Montreal Cognitive Assessment (1–30)

[g] Scales for Outcomes in Parkinson's Disease – Cognition (0–43)

[h] Based on subtracting mean age at diagnosis from mean age at baseline

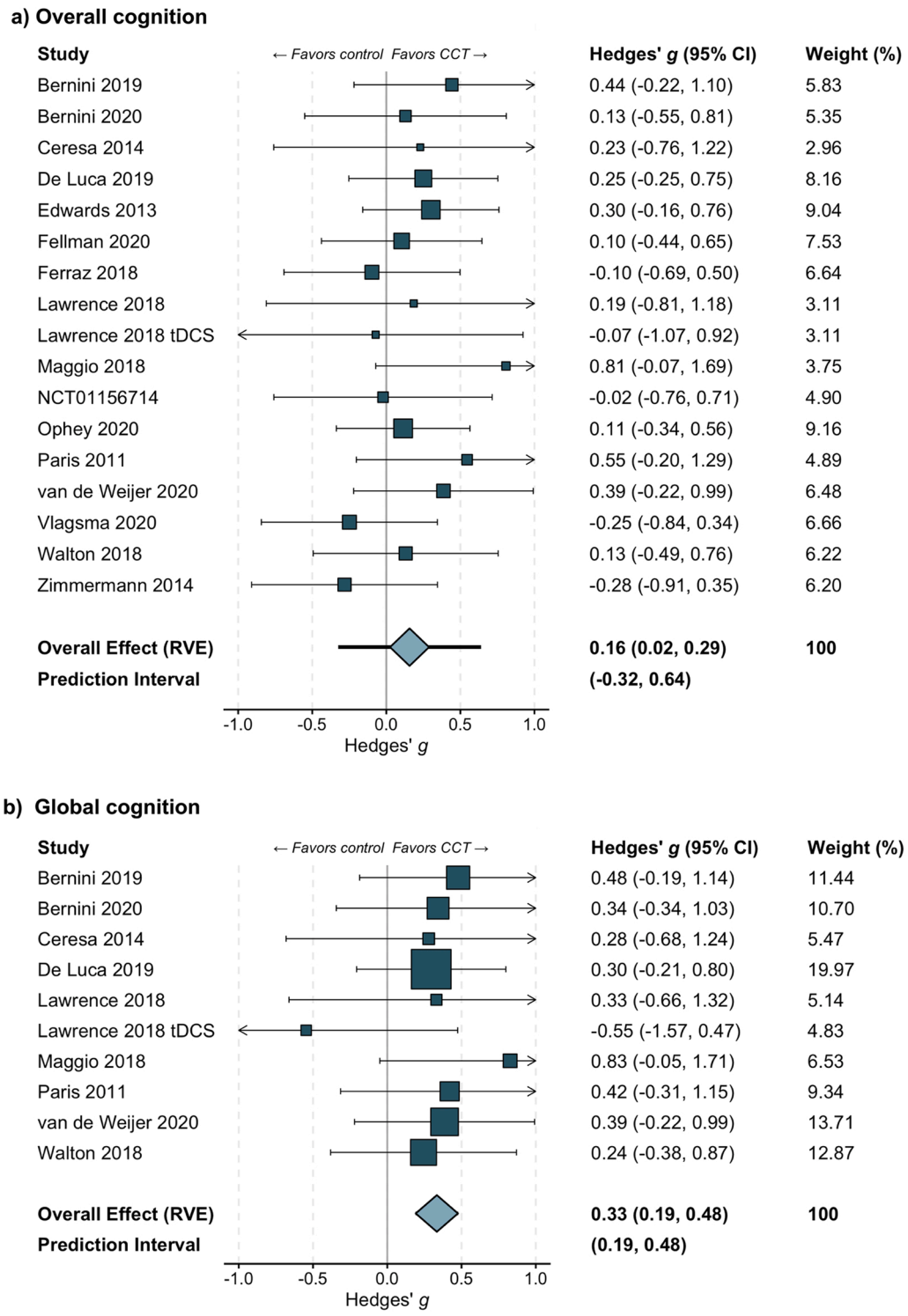

Fig. 2. Efficacy of CCT on (a) overall cognitive outcomes and (b) global cognition.

sizes favoring CCT were found for fluid reasoning, abstract reasoning and short-term memory, as well as a small effect size for retrieval fluency.

3.6. Efficacy of CCT on other outcomes

The pooled analyses revealed small and statistically non-significant effects for executive functions screening outcomes ($k = 6$ RCTs, $g = 0.18$, 95% CI $= -0.30$ to 0.66, $p = 0.37$, $\tau^2 = 0.1$, $I^2 = 49\%$, Appendix M), psychosocial outcomes ($k = 13$, $g = 0.01$, 95% CI $= -0.13$ to 0.14, $p = 0.94$, $\tau^2 = 0.00$, $I^2 = 0\%$, Appendix N), functional abilities ($k = 5$, $g = -0.01$, 95% CI $= -0.37$ to 0.36, $p = 0.95$, $\tau^2 = 0.00$, $I^2 = 0\%$, Appendix O) and subjective cognition ($k = 5$, $g = 0.03$, 95% CI $= -0.11$ to 0.17, $p = 0.54$, $\tau^2 = 0.00$, $I^2 = 0\%$, Appendix P). Only four trials (Bernini et al., 2019; Lawrence et al., 2018; Ophey et al., 2020; Vlagsma et al., 2020) reported long-term outcomes, with follow-up ranging between 7 weeks and 6 months post-training. Pooling of the 95 cognitive outcomes from these follow-ups revealed a small, imprecise and heterogeneous

Table 2
Moderator analyses of CCT efficacy on overall cognition.

Moderator	No. of studies (effect sizes)	Summary effect				Test of moderation		
		Hedges' *g* (95% CI)	t	df	*p*	F	df	*p*
Risk of bias								
Low	3 (42)	0.24 (−0.52 to 1.00)	1.6	1.8	0.28	0.38	1,2.74	0.58
High	14 (179)	0.14 (−0.02 to 0.29)	1.9	11.9	0.08			
Trial registration						0.25	1,13	0.62
Registered	7 (79)	0.12 (−0.07 to 0.32)	1.6	5.70	0.17			
Unregistered	10 (142)	0.19 (−0.04 to 0.42)	1.9	7.97	0.09			
Control						0.81	2,5.1	0.49
Active intervention	10 (114)	0.12 (−0.14 to 0.37)	1.0	8.2	0.33			
Sham control	4 (59)	0.15 (0.05–0.25)	5.3	2.5	0.02			
Passive	4 (48)	0.25 (0.01–0.48)	3.6	2.6	0.05			
Source						0.81	1,4.3	0.85
Leung 2015	4 (45)	0.19 (−0.44 to 0.81)	1.0	2.6	0.37			
Newer RCTs	13 (176)	0.15 (0.05–0.29)	2.3	11.0	0.04			
Cognitive status						2.68	1,13.3	0.13
Normal/PD-SCI	7 (56)	0.06 (−0.12 to 0.24)	0.8	5.7	0.46			
PD-MCI	10 (165)	0.26 (0.03–0.48)	2.6	8.0	0.03			
CCT Type						0.48	1,7.7	0.51
Single domain	5 (54)	0.10 (−0.18 to 0.38)	1.1	3.6	0.36			
Multi-domain	12 (167)	0.19 (0.01–0.37)	2.3	10.2	0.05			
Delivery						0.26	1,9.4	0.62
Supervised	11 (138)	0.14 (−0.08 to 0.35)	1.4	9.4	0.18			
Home-based	6 (83)	0.19 (0.03–0.35)	3.3	4.3	0.03			
Dose (total hours)						4.4	1,7.2	0.07
14 h or less	12 (199)	0.08 (−0.08 to 0.24)	1.1	9.8	0.28			
More than 14 h	5 (22)	0.31 (0.07–0.56)	3.7	3.6	0.02			

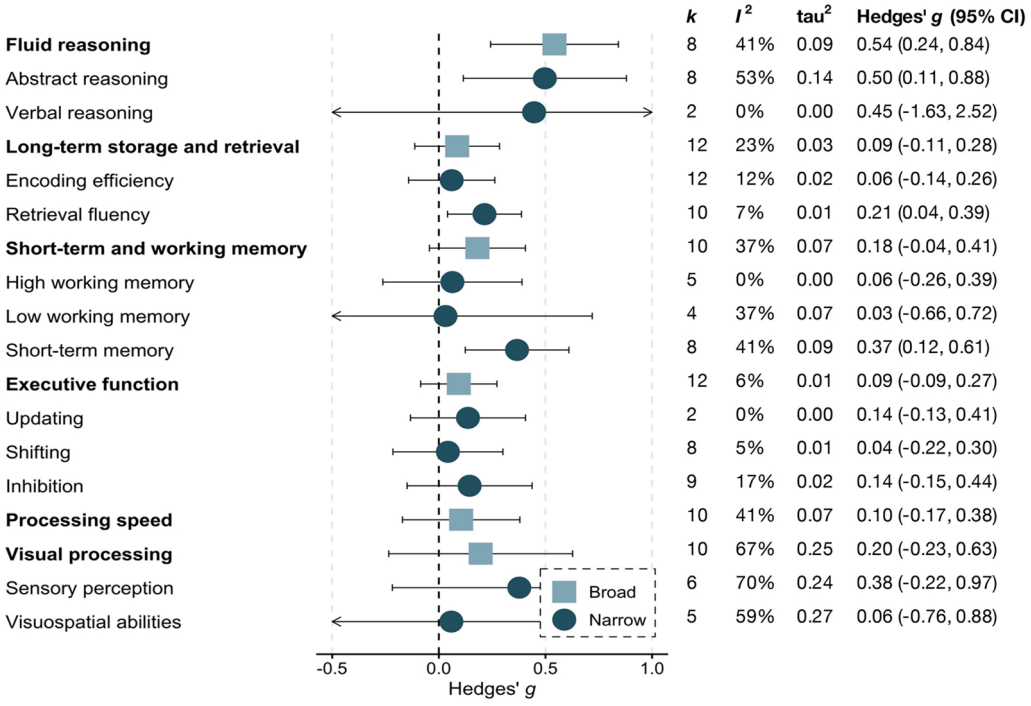

Fig. 3. Efficacy of CCT on individual CHC-M broad (square) and narrow (circle) cognitive domains.

overall effect size ($g = 0.14$, 95% CI = −0.24 to 0.51, $p = 0.36$, $\tau^2 = 0.16$, $I^2 = 55\%$).

4. Discussion

With over three times as many RCTs compared to previous meta-analyses (Lawrence et al., 2017; Leung et al., 2015; Orgeta et al., 2020), we report that CCT is associated with cognitive benefit in people with PD. Critically, we report that CCT is associated with a moderate effect size for clinical measures of global cognition, especially in PD-MCI, with no evidence of heterogeneity or bias across studies. This result updates negative findings from previous meta-analyses (Leung et al., 2015; Orgeta et al., 2020) and confirms that CCT is feasible and efficacious for overall and global cognition in PD-MCI, consistent with the efficacy of CCT in MCI without PD (Hill et al., 2017). Analyses of individual cognitive domains were based on relatively smaller numbers of studies but did suggest moderate effect sizes for abstract reasoning, retrieval fluency and short-term memory, which are common areas of

impairment in PD (Muslimovic et al., 2005; Williams-Gray et al., 2007). Larger RCTs are still needed to investigate whether long-term CCT can indeed attenuate cognitive decline and prevent dementia in this population.

Beyond mere efficacy, the practical questions regarding CCT are what methods should be used, in whom and what outcomes should be anticipated (Goldman et al., 2018; Kalbe et al., 2018). These questions could not be addressed in previous meta-analyses as they were based on significantly fewer studies and used univariate methods, which often underestimate between-study heterogeneity, especially when studies are small (Cheung, 2019). To address this problem, we used multivariate methods and were able to detect considerable heterogeneity and draw several practical conclusions for CCT design, albeit on a preliminary basis due to imprecision within individual studies and subgroups.

First, home-based delivery of CCT seems to be feasible and efficacious, suggesting that this might be the main mode of delivery given the need to provide treatments at scale, perhaps as part of a larger telemedicine package (Kalbe et al., 2018). Second, consistent with the evidence for CCT in older adults without PD (Lampit et al., 2014b, 2020), multi-domain CCT is more likely to be efficacious for overall or global cognitive outcomes compared to programs targeting a single cognitive domain, whose effects tend to be most pronounced in the specific domains they target (Lampit et al., 2014b, 2020). Given the heterogeneity of cognitive impairment in PD (Goldman et al., 2018), multi-domain programs do not only provide practice on multiple areas of impairment, but could be personalized to individual needs, e.g., by focusing on individual areas of weakness and modify the composition of targeted domains over time. Third, CCT effects appear to build up over time (although not necessarily linearly) and wane to some extent without further training, emphasizing the importance of setting dosing guidelines (potentially based on individual performance) as well as booster sessions to maintain benefits and prevent decline in the long-term (Walton et al., 2017).

The 16 RCTs in this review reported data for 20 eligible comparisons, half of which compared CCT head-to-head against active interventions rather than sham or passive control. As expected, these comparisons resulted in smaller, less precise and more heterogeneous effect size, especially within the two trials that compared CCT to other cognitive interventions (Vlagsma et al., 2020; Zimmermann et al., 2014). Other combinations included physical exercise (Bernini et al., 2019; NCT01156714) and tDCS (Lawrence et al., 2018), both considered potentially effective cognitive treatments in PD (Aarsland et al., 2021). Whether combination of CCT with other interventions may results in larger benefit to cognition or psychosocial functioning is a key area for further research in the field (Goldman et al., 2018; Kalbe et al., 2018). It is also very likely that the form of combination will affect the results. For examples, a recent network meta-analysis (Gavelin et al., 2021) found that simultaneous cognitive and physical exercise resulted in the best cognitive and physical outcomes in older adults over and above sequential training.

We found no evidence for benefit in subjective cognition, functional abilities or psychosocial functioning. These findings are consistent with those of previous meta-analyses of cognitive training in PD (Leung et al., 2015; Orgeta et al., 2020), although CCT was previously found efficacious for psychosocial functioning (including subjective cognition and mood) in MCI without PD (Hill et al., 2017). Of note, outcomes within these domains were inconsistently reported in primary trials and a wide array of different measures were employed. Given the observed benefits of CCT on cognition, increased harmonization of clinically relevant functional outcomes across trials is needed to better establish whether these domains are responsive to the intervention or additional components are required (Kalbe et al., 2018). Moreover, few studies investigated long-term effects on cognition and the pooled effect size was small and imprecise. Of note, a recently published RCT in a large sample of patients with PD showed no long-term benefits from CCT on cognition nor any effects on subjective cognitive complaints (van Balkom et al., 2022). Thus, while the findings from the current review support the feasibility and immediate efficacy of CCT on cognition, further delineating how intervention regimens may be designed to enhance clinical value in the long-term remains an essential area for future work.

While the state of the evidence is encouraging, several limitations remain to be addressed. First and foremost, RCTs in the field are relatively small (median sample size 42) and report results from short training duration. Like most interventions targeting cognitive decline, the benefits of CCT wain gradually over time (Lampit et al., 2014a) and periodical booster training will be required to attenuate cognitive decline in the long-term (Edwards et al., 2017). Similarly, small study sizes meant that none of the preplanned meta-regressions found statistically significant effects. Second, we do not know how individual factors interact with CCT adherence and outcomes (Kalbe et al., 2018). We believe that our findings warrant such investigations, in particular individual participant data meta-analysis taking prognostic factors into account. Third, we still do not know whether CCT effects are related to changes in the neuronal mechanisms underpinning cognitive decline in PD important information for initiating and planning individual CCT (Aarsland et al., 2021). Although a few of the included trials reported neuroimaging outcomes (e.g., Cerasa et al., 2014; Giehl et al., 2020a), more studies and greater consistency of methods is needed before a meaningful synthesis will be possible.

4.1. Conclusions

The body of RCTs provides a strong rationale for large, well-powered long-term trials, akin to those conducted in other older adult populations and neurodegenerative disorders. Such RCTs should aim to establish the clinical effectiveness of CCT versus or in combination with alternative treatments, ensuring a sufficient dose of training, and include booster schedules to maintain gains beyond the initial training period. The evidence supports the use of remote delivery at home, as well as increase use of automated personalization and support (Kalbe et al., 2018). Adherence to clinical trial guidelines, most notably blinding of assessors, intention-to-treat analyses and detailed description of treatment protocols is paramount to ensure clinical uptake. Current gaps and challenges notwithstanding, these results should encourage further work aiming to develop guidelines and new technologies to effectively manage cognitive impairment in PD.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101671.

References

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K.R., Ffytche, D.H., Weintraub, D., Ballard, C., 2017. Cognitive decline in Parkinson disease. Nat. Rev. Neurol. 13, 217–231.

Aarsland, D., Batzu, L., Halliday, G.M., Geurtsen, G.J., Ballard, C., Ray Chaudhuri, K., Weintraub, D., 2021. Parkinson disease-associated cognitive impairment. Nat. Rev. Dis. Prim. 7, 47.
Bernini, S., Alloni, A., Panzarasa, S., Picascia, M., Quaglini, S., Tassorelli, C., Sinforiani, E., 2019. A computer-based cognitive training in Mild Cognitive Impairment in Parkinson's Disease. NeuroRehabilitation 44, 555–567.
Bernini, S., Panzarasa, S., Barbieri, M., Sinforiani, E., Quaglini, S., Tassorelli, C., Bottiroli, S., 2021. A double-blind randomized controlled trial of the efficacy of cognitive training delivered using two different methods in mild cognitive impairment in Parkinson's disease: preliminary report of benefits associated with the use of a computerized tool. Aging Clin. Exp. Res. 33, 1567–1575.
Borenstein, M., Higgins, J.P., Hedges, L.V., Rothstein, H.R., 2017. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. Res Synth. Methods 8, 5–18.
Cerasa, A., Gioia, M.C., Salsone, M., Donzuso, G., Chiriaco, C., Realmuto, S., Nicoletti, A., Bellavia, G., Banco, A., D'amelio, M., Zappia, M., Quattrone, A., 2014. Neurofunctional correlates of attention rehabilitation in Parkinson's disease: an explorative study. Neurol. Sci. 35, 1173–1180.
Cheung, M.W., 2019. A guide to conducting a meta-analysis with non-independent effect sizes. Neuropsychol. Rev. 29, 387–396.
Couture, M., Giguère-Rancourt, A., Simard, M., 2019. The impact of cognitive interventions on cognitive symptoms in idiopathic Parkinson's disease: a systematic review. Aging, Neuropsychol., Cogn. 26, 637–659.
De Luca, R., Latella, D., Maggio, M.G., Di Lorenzo, G., Maresca, G., Sciarrone, F., Militi, D., Bramanti, P., Calabrò, R.S., 2019. Computer assisted cognitive rehabilitation improves visuospatial and executive functions in Parkinson's disease: Preliminary results. NeuroRehabilitation 45, 285–290.
Edwards, J.D., Hauser, R.A., O'Connor, M.L., Valdés, E.G., Zesiewicz, T.A., Uc, E.Y., 2013. Randomized trial of cognitive speed of processing training in Parkinson disease. Neurology 81, 1284–1290.
Edwards, J.D., Xu, H., Clark, D.O., Guey, L.T., Ross, L.A., Unverzagt, F.W., 2017. Speed of processing training results in lower risk of dementia. Alzheimers Dement (N. Y) 3, 603–611.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
Fellman, D., Salmi, J., Ritakallio, L., Ellfolk, U., Rinne, J.O., Laine, M., 2018. Training working memory updating in Parkinson's disease: a randomised controlled trial. Neuropsychol. Rehabil. 30, 673–708.
Ferraz, D.D., Trippo, K.V., Duarte, G.P., Neto, M.G., Santos, K.O.B., Oliveira Filho, J., 2018. The effects of functional training, bicycle exercise, and exergaming on walking capacity of elderly patients with Parkinson disease: a pilot randomized controlled single-blinded trial. Arch. Phys. Med. Rehabil. 99, 826–833.
Fisher, Z., Tipton, E., Zhipeng, H., 2017. robumeta: robust variance meta-regression. R. Package Version 2, 0.
Gavelin, H.M., Domellof, M., Leung, I., Neely, A.S., Finke, C., Lampit, A., 2020. Computerised cognitive training in Parkinson's disease: a protocol for a systematic review and updated meta-analysis. BMJ Open 10, e040656.
Gavelin, H.M., Dong, C., Minkov, R., Bahar-Fuchs, A., Ellis, K.A., Lautenschlager, N.T., Mellow, M.L., Wade, A.T., Smith, A.E., Finke, C., Krohn, S., Lampit, A., 2021. Combined physical and cognitive training for older adults with and without cognitive impairment: a systematic review and network meta-analysis of randomized controlled trials. Ageing Res Rev. 66, 101232.
Giehl, K., Ophey, A., Hammes, J., Rehberg, S., Lichtenstein, T., Reker, P., Eggers, C., Kalbe, E., van Eimeren, T., 2020a. Working memory training increases neural efficiency in Parkinson's disease: a randomized controlled trial. Brain Commun. 2, fcaa115.
Giehl, K., Ophey, A., Reker, P., Rehberg, S., Hammes, J., Barbe, M.T., Zokaei, N., Eggers, C., Husain, M., Kalbe, E., 2020b. Effects of home-based working memory training on visuo-spatial working memory in Parkinson's disease: a randomized controlled trial. J. Cent. Nerv. Syst. Dis. 12, 1–9.
Goldman, J.G., Vernaleo, B.A., Camicioli, R., Dahodwala, N., Dobkin, R.D., Ellis, T., Galvin, J.E., Marras, C., Edwards, J., Fields, J., Golden, R., Karlawish, J., Levin, B., Shulman, L., Smith, G., Tangney, C., Thomas, C.A., Troster, A.I., Uc, E.Y., Coyan, N., Ellman, C., Ellman, M., Hoffman, C., Hoffman, S., Simmonds, D., 2018. Cognitive impairment in Parkinson's disease: a report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health. NPJ Park. Dis. 4, 19.
Hedges, L.V., Tipton, E., Johnson, M.C., 2010. Robust variance estimation in meta-regression with dependent effect size estimates. Res Synth. Methods 1, 39–65.
Hill, N.T., Mowszowski, L., Naismith, S.L., Chadwick, V.L., Valenzuela, M., Lampit, A., 2017. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. Am. J. Psychiatry 174, 329–340.
Kalbe, E., Aarsland, D., Folkerts, A.K., 2018. Cognitive interventions in Parkinson's disease: where we want to go within 20 years. J. Park. Dis. 8, S107–S113.
Lampit, A., Hallock, H., Moss, R., Kwok, S., Rosser, M., Lukjanenko, M., Kohn, A., Naismith, S., Brodaty, H., Valenzuela, M., 2014a. The timecourse of global cognitive gains from supervised computer-assisted cognitive training: A randomised, active-controlled trial in elderly with multiple dementia risk factors. J. Prev. Alz Dis. 1, 33–39.
Lampit, A., Hallock, H., Valenzuela, M., 2014b. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. PLoS Med 11, e1001756.
Lampit, A., Gavelin, Malmberg, Sabates, H., Launder, J., Hallock, N.H., Finke, H., Krohn, C., Peeters, G, S., 2020. Computerized cognitive training in cognitively healthy older adults: a systematic review and network meta-analysis. medRxiv 2020, 2010.2007.20208306.
Lawrence, B.J., Gasson, N., Bucks, R.S., Troeung, L., Loftus, A.M., 2017. Cognitive training and noninvasive brain stimulation for cognition in Parkinson's disease: a meta-analysis. Neurorehabil. Neural Repair 31, 597–608.
Lawrence, B.J., Gasson, N., Johnson, A.R., Booth, L., Loftus, A.M., 2018. Cognitive training and transcranial direct current stimulation for mild cognitive impairment in Parkinson's disease: a randomized controlled trial. Parkinson's Dis. 2018, 4318475.
Leung, I.H., Walton, C.C., Hallock, H., Lewis, S.J., Valenzuela, M., Lampit, A., 2015. Cognitive training in Parkinson disease: a systematic review and meta-analysis. Neurology 85, 1843–1851.
Maggio, M.G., De Cola, M.C., Latella, D., Maresca, G., Finocchiaro, C., La Rosa, G., Cimino, V., Sorbera, C., Bramanti, P., De Luca, R., Calabro, R.S., 2018. What about the role of virtual reality in Parkinson disease's cognitive rehabilitation? Preliminary findings from a randomized clinical trial. J. Geriatr. Psychiatry Neurol. 31, 312–318.
Müller, S.V., Klein, T., Benke, T., Bohlhalter, S., Hildebrandt, H., Meiling, C., Hucke, B., Münte, T., Penner, I.-K., Schwerdtfeger, K., Thöne-Otto, A., Wallesch, C.-W., 2020. Kurzfassung der S2e-Leitlinie „Diagnostik und Therapie von exekutiven Dysfunktionen bei neurologischen Erkrankungen" (AWMF-030/125). Z. für Neuropsychol. 31, 135–147.
Muslimovic, D., Post, B., Speelman, J.D., Schmand, B., 2005. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65, 1239–1245.
NCT01156714, Exercise and Cognitive Training in Parkinson's Disease.
Nousia, A., Martzoukou, M., Tsouris, Z., Siokas, V., Aloizou, A.-M., Liampas, I., Nasios, G., Dardiotis, E., 2020. The beneficial effects of computer-based cognitive training in Parkinson's Disease: A systematic review. Arch. Clin. Neuropsychol. 35, 434–447.
Ophey, A., Giehl, K., Rehberg, S., Eggers, C., Reker, P., van Eimeren, T., Kalbe, E., 2020. Effects of working memory training in patients with Parkinson's disease without cognitive impairment: A randomized controlled trial. Park. Relat. Disord. 72, 13–22.
Orgeta, V., McDonald, K.R., Poliakoff, E., Hindle, J.V., Clare, L., Leroi, I., 2020. Cognitive training interventions for dementia and mild cognitive impairment in Parkinson's disease. Cochrane Database Syst. Rev. 2, CD011961.
Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hrobjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., McKenzie, J.E., 2021. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 372, n160.
París, A.P., Saleta, H.G., de la Cruz Crespo Maraver, M., Silvestre, E., Freixa, M.G., Torrellas, C.P., Pont, S.A., Nadal, M.F., Garcia, S.A., Bartolomé, M.V.P., Fernández, V.L., Rusiñol, À.B., 2011. Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. Mov. Disord. 26, 1251–1258.
Pena, J., Ibarretxe-Bilbao, N., Garcia-Gorostiaga, I., Gomez-Beldarrain, M.A., Diez-Cirarda, M., Ojeda, N., 2014. Improving functional disability and cognition in Parkinson disease: randomized controlled trial. Neurology 83, 2167–2174.
Petrelli, A., Kaesberg, S., Barbe, M.T., Timmermann, L., Fink, G.R., Kessler, J., Kalbe, E., 2014. Effects of cognitive training in Parkinson's disease: a randomized controlled trial. Park. Relat. Disord. 20, 1196–1202.
Pompeu, J.E., Mendes, F.A., Silva, K.G., Lobo, A.M., Oliveira Tde, P., Zomignani, A.P., Piemonte, M.E., 2012. Effect of Nintendo Wii-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial. Physiotherapy 98, 196–204.
Pustejovsky, J., 2020. clubSandwich: Cluster-robust (sandwich) variance estimators with small-sample corrections. R package version 0.4.2.
Riley, R.D., Higgins, J.P., Deeks, J.J., 2011. Interpretation of random effects meta-analyses. BMJ 342, d549.
Sterne, J.A., Sutton, A.J., Ioannidis, J.P., Terrin, N., Jones, D.R., Lau, J., Carpenter, J., Rucker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343, d4002.
Sterne, J.A., Savovic, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C.J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernan, M.A., Hopewell, S., Hrobjartsson, A., Junqueira, D.R., Juni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898.
Svaerke, K., Niemeijer, M., Løkkegaard, A., 2020. The effects of computer-based cognitive rehabilitation on working memory in patients with Parkinson's Disease: a systematic review. J. Park. Dis. 10, 47–57.
Svenningsson, P., Westman, E., Ballard, C., Aarsland, D., 2012. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 11, 697–707.
van Balkom, T.D., Berendse, H.W., van der Werf, Y.D., Twisk, J.W.R., Peeters, C.F.W., Hoogendoorn, A.W., Hagen, R.H., Berk, T., van den Heuvel, O.A., Vriend, C., 2022. Effect of eight-week online cognitive training in Parkinson's disease: A double-blind, randomized, controlled trial. Park. Relat. Disord. 96, 80–87.
van de Weijer, S.C., Duits, A.A., Bloem, B.R., de Vries, N.M., Kessels, R.P., Köhler, S., Tissingh, G., Kuijf, M.L., 2020. Feasibility of a cognitive training game in Parkinson's Disease: the randomized Parkin'Play study. Eur. Neurol. 83, 1–7.
Vlagsma, T.T., Duits, A.A., Dijkstra, H.T., van Laar, T., Spikman, J.M., 2020. Effectiveness of ReSET; a strategic executive treatment for executive dysfunctioning in patients with Parkinson's disease. Neuropsychol. Rehabil. 30, 67–84.
Walton, C.C., Naismith, S.L., Lampit, A., Mowszowski, L., Lewis, S.J., 2017. Cognitive training in Parkinson's disease. Neurorehabil. Neural Repair 31, 207–216.
Walton, C.C., Mowszowski, L., Gilat, M., Hall, J.M., O'Callaghan, C., Muller, A.J., Georgiades, M., Szeto, J.Y., Martens, K.A.E., Shine, J.M., Naismith, S.L., Lewis, S.J.

G., 2018. Cognitive training for freezing of gait in Parkinson's disease: a randomized controlled trial. npj Park. 'S. Dis. 4, 15.
Webb, S.L., Loh, V., Lampit, A., Bateman, J.E., Birney, D.P., 2018. Meta-analysis of the effects of computerized cognitive training on executive functions: a cross-disciplinary taxonomy for classifying outcome cognitive factors. Neuropsychol. Rev. 28, 232–250.
Williams-Gray, C.H., Foltynie, T., Brayne, C.E., Robbins, T.W., Barker, R.A., 2007. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130, 1787–1798.
Zimmermann, R., Gschwandtner, U., Benz, N., Hatz, F., Schindler, C., Taub, E., Fuhr, P., 2014. Cognitive training in Parkinson disease: cognition-specific vs nonspecific computer training. Neurology 82, 1219–1226.