Parkinsonism and Related Disorders 60 (2019) 32–42

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Review article

Cognitive profile of non-demented Parkinson's disease: Meta-analysis of domain and sex-specific deficits

Ashley F. Curtis[a,b], Mario Masellis[a,c], Richard Camicioli[d], Heather Davidson[b], Mary C. Tierney[a,b,e,*]

[a] Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, 2075 Bayview Ave, Toronto, ON, M4N 3M5, Canada
[b] Primary Care Research Unit, Department of Family and Community Medicine, Sunnybrook Health Sciences Center, 2075 Bayview Ave, Toronto, ON, M4N 3M5, Canada
[c] Cognitive and Movement Disorders Clinic, Sunnybrook Health Sciences Center, 2075 Bayview Ave, Toronto, ON, M4N 3M5, Canada
[d] Division of Neurology, Department of Medicine, University of Alberta, 116 St & 85 Ave, Edmonton, AB, T6G 2R3, Canada
[e] Department of Family and Community Medicine, University of Toronto, 500 University Ave, Toronto, ON M5G 1V7, Canada

ARTICLE INFO

Keywords:
Parkinson's disease
Executive functions
Verbal memory
Visuospatial abilities
Sex differences

ABSTRACT

Introduction: Better awareness of the cognitive domains affected in non-demented Parkinson's Disease (PD) should improve understanding of cognitive disease mechanisms. A complete understanding of the cognitive areas impaired in non-demented PD is hindered because most studies use small clinical samples without comparison to healthy controls. This meta-analysis examined cumulative evidence across studies to determine if there were impairments in non-demented PD in the three cognitive domains thought to be most widely affected in PD: frontal executive, visuospatial, and verbal memory. Because there are well-documented sex differences in PD, a second objective was to explore sex differences in these findings.

Methods: MEDLINE, EMBASE and PsycINFO databases were searched (1988–March 2017). Random effects models were used to compute and compare effect sizes of differences between PD patients and controls within cognitive domains. Sex differences in effect sizes were also examined in these comparisons. Moderating factors including age, disease duration, motor symptom severity, levodopa dosage, and depression were examined through meta-regression.

Results: PD patients showed deficits of moderate effect sizes in all three cognitive domains relative to controls. Significant sex differences were observed only for frontal executive abilities, with male PD patients showing greater deficits than female PD patients relative to controls. No moderators of effect sizes were identified in the domain specific overall or sex-segregated meta-analyses.

Conclusions: Results indicate that non-demented PD patients have deficits of moderate magnitude in frontal executive, verbal memory, and visuospatial abilities. Our findings of greater frontal executive deficits in males warrant further confirmation.

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting 0.3% of the general population and 3% of individuals over the age of 65 [1,2]. It is well known that motor impairment in PD is due to loss of nigrostriatal dopaminergic neurons associated with intraneuronal Lewy body formation [3], and that extranigral Lewy body formation is associated with non-motor symptoms [4].

There are three cognitive domains thought to be most widely affected in PD: frontal executive, verbal memory, and visuospatial [5]. Attention and working memory abilities are typically included under frontal executive function [6]. While a previous meta-analysis reported frontal executive impairment in non-demented patients with PD relative to healthy controls [7], there remains considerable inconsistencies in findings regarding deficits in non-demented PD relative to controls in visuospatial abilities and verbal memory. For instance, some studies report impairment in visuospatial functioning [8,9], while others do not [10,11]. Similarly, verbal memory has been shown to be impaired [12,13], as well as preserved [14,15], in non-demented PD. While a previous meta-analysis of longitudinal studies reported cognitive decline of small magnitude in non-demented PD patients in the

* Corresponding author. Department of Family & Community Medicine, Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Suite E349, Toronto, ON, M4N 3M5, Canada.
E-mail address: mary.tierney@sunnybrook.ca (M.C. Tierney).

https://doi.org/10.1016/j.parkreldis.2018.10.014
Received 2 March 2018; Received in revised form 24 September 2018; Accepted 12 October 2018

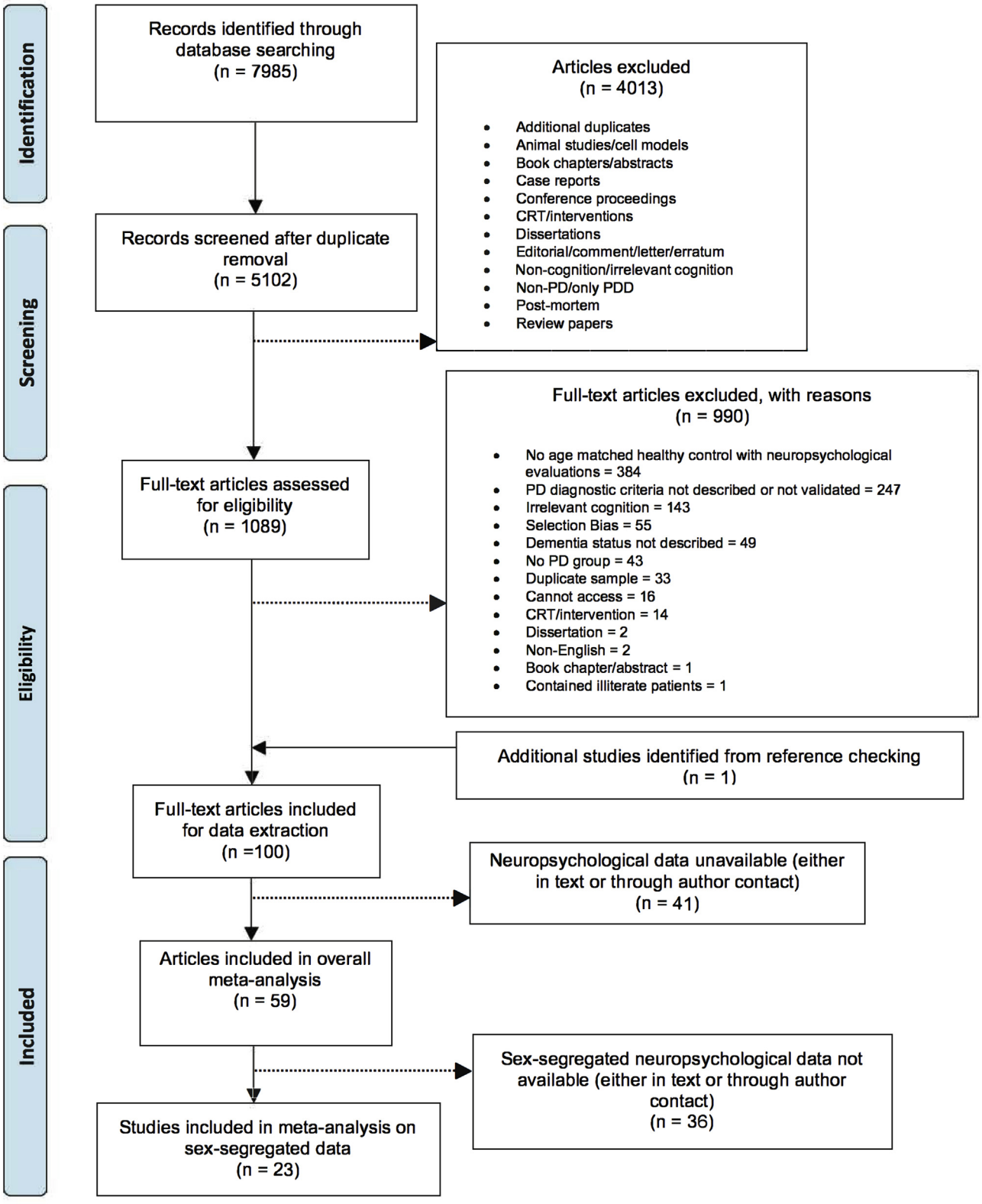

Fig. 1. Flowchart of included articles.

three domains of interest [16], itD did not examine cognitive deficits relative to healthy controls of similar age. It is critically important to demonstrate that any changes in non-demented PD patients are due to PD mechanisms and not normal aging. Therefore, the main goal of the present meta-analysis was to examine differences in cognitive performance in PD patients without dementia across these three domains relative to healthy age-matched controls. Unlike previous meta-analyses in the field, we also examined the role of potential moderating factors, including age, disease duration, motor symptom severity, levodopa dose, and depression, on differences in cognitive performance between PD patients without dementia and controls.

The second goal of this meta-analysis was to examine sex differences

Table 1
Effect sizes and heterogeneity of full meta-analysis and sensitivity analysis of studies of cognitive performance of patients with Parkinson's disease relative to healthy controls across three cognitive domains.

Domain	*N* (PD/HC)	Effect size (*g*)	95% CI	*p*	I^2(%)
Frontal Executive					
Full Meta-Analysis (*k* = 55)	3067/2648	−0.479	−0.547 to −0.410	< 0.001	68.9
Sensitivity Analysis of studies that only included standardized diagnostic criteria to rule out dementia (*k* = 24)	1646/1521	−0.419	−0.483 to −0.356	< 0.001	33.5
Verbal Memory					
Full Meta-Analysis (*k* = 27)	1768/1452	−0.517	−0.583 to −0.451	< 0.001	24.2
Sensitivity Analysis of studies that only included standardized diagnostic criteria to rule out dementia (*k* = 15)	1143/909	−0.462	−0.530 to −0.394	< 0.001	0
Visuospatial					
Full Meta-Analysis (*k* = 21)	1644/1387	−0.555	−0.680 to −0.431	< 0.001	50.8
Sensitivity Analysis of studies that only included standardized diagnostic criteria to rule out dementia (*k* = 14)	1124/1028	−0.509	−0.626 to −0.391	< 0.001	12.8

k = number of studies, *N* = total sample size across studies PD = Parkinson's disease patients HC= Healthy controls.
Note. Negative values of effect sizes indicate worse performance in PD patients relative to controls.

in the cognitive profile of non-demented PD. There is a well-established higher prevalence and incidence of men with PD [17,18], and evidence of a more benign motor phenotype in women with PD [19]. However, findings regarding sex differences in PD cognition are also inconsistent [20]. For instance, one systematic review suggests a more benign cognitive phenotype in women relative to men [20], while some studies show more impairment in visuospatial abilities in women relative to men [21,22], and others show no sex differences in visuospatial abilities [23]. Therefore, we also conducted a separate series of meta-analyses to examine sex differences in the level of cognitive deficits relative to controls across frontal executive, verbal memory, and visuospatial domains. Findings from the present study will improve understanding of the disease specific cognitive profile of non-demented PD, important information for clinical and therapeutic intervention.

2. Methods

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [24] recommendations were followed.

2.1. Study selection and screening

EMBASE, PsycINFO and MEDLINE databases were searched on March 30th, 2017. We restricted the search to articles published after 1988 since this is when the standardized Gibb and Lees PD criteria [25] were established. A full search strategy is provided in Appendix e-1. Reference lists of relevant reviews were searched for additional articles.

Following duplicate removal, abstracts were screened independently by two raters [AFC, Trained Research Assistant 1 (RA1)]. Full text review of included articles was conducted independently by the two raters. If articles contained duplicate samples with the same neuropsychological test measures, the article with the larger sample size was selected. Discrepancies were resolved through discussion with MCT. Articles were included if they met all of the following criteria:

1) PD diagnosed according to the most widely accepted standardized criteria, which rule out other neurological conditions as part of the diagnosis [25–27].
2) Included PD patients who were non-demented (directly stated).
3) Included an age-matched healthy control group with no neurological or psychiatric conditions (directly stated).
4) Assessed performance on at least one valid and reliable neuropsychological test, which measured visuospatial, verbal memory, or frontal executive ability.
5) Provided raw means, standard deviations (SD), and sample sizes for neuropsychological test performance for patients with PD and healthy controls. If articles did not report these data, corresponding authors of included articles were contacted via email and asked to provide them.

Articles were excluded if they met any of the following criteria:

- The study focus was not on neuropsychological assessment and thus a selection bias may have occurred related to disease severity or sex differences in participation because the study excluded PD patients who did not complete the intervention or measurement of interest to the study or did not agree to a subsequent longitudinal follow-up. For example, the focus was on the effect of a medical treatment, MRI or cerebrospinal fluid testing. Because disease severity and sex differences affect driving cessation [28], and driving ability in PD has been associated with cognitive performance [29], studies that focused on driving ability in participants with current drivers' licenses were also excluded.
- Included patients or controls who were illiterate (directly stated) because this would invalidate the neuropsychological test results.

2.2. Data extraction

Data were independently extracted by four raters (AFC, HD, RA1, RA2). For each article, we recorded raw mean scores and SDs for PD patients and controls for every standardized neuropsychological test within the three cognitive domains (visuospatial, verbal memory, and frontal executive). Identified neuropsychological tests were classified into one of the three domains (see Table e-1). We also recorded available data for both PD patients and controls, including mean age, education, sample size, and number of men and women. To further characterize patient samples, we also recorded the average scores of scales assessing PD symptom severity [(Hoehn & Yahr (H&Y) scale, Unified Parkinson's Disease Rating Scale-III (UPDRS-III motor scale)] [30,31], duration of symptoms (in months), PD dopaminergic medication dosage (i.e., levodopa equivalent daily dose, LEDD). Additionally, we recorded available information regarding the depression status of patients (e.g., whether studies excluded depressed patients or provided information regarding diagnosis of depression or symptom severity as measured by a depression rating scale). Because many comorbid medications currently prescribed to treat non-motor symptoms in PD are known to affect the central nervous system (CNS) and can be associated with cognitive disturbances [32], we also recorded available details regarding any comorbid medications currently taken by the PD patients. Finally, we recorded how the dementia status of PD patients was classified (e.g., diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders [33] or Movement Disorders Society Task force criteria [34], cutoffs based on dementia rating scales such as the Mini-Mental State Examination [35], Clinical Dementia Rating Scale

Study Name	PD *N*	Control *N*	Hedges' *g* (95% CI)	*p*	Weight(%)
Aarsland, 2009	187	166	-0.34 (-0.49 to -0.19)	0.000	2.80
Alonso-Recio, 2014	53	53	-0.09 (-0.33 to 0.15)	0.453	2.30
Assogna, 2010	70	70	-0.54 (-0.69 to -0.39)	0.000	2.79
Balas, 2010	12	10	-0.50 (-0.91 to -0.08)	0.018	1.48
Bezdicek, 2016	106	120	-0.67 (-0.88 to -0.47)	0.000	2.48
Bogdanova, 2012	22	22	-0.61 (-0.95 to -0.27)	0.001	1.77
Bouquet, 2003	20	20	-0.70 (-1.06 to -0.34)	0.000	1.68
Bronnick, 2011	133	133	-0.30 (-0.47 to -0.13)	0.001	2.68
Bugalho, 2011	75	45	-0.19 (-0.55 to 0.18)	0.320	1.66
Colman, 2009	27	28	-0.28 (-0.54 to -0.02)	0.036	2.19
Cools, 2001	43	27	-0.24 (-1.12 to 0.63)	0.585	0.51
Crescentini, 2012	16	14	-0.67 (-0.94 to -0.39)	0.000	2.13
Crucian, 2010	40	24	-0.27 (-0.57 to 0.03)	0.073	1.99
Damholdt, 2012	71	30	-0.68 (-0.87 to -0.48)	0.000	2.56
Dujardin, 2004	18	18	-0.84 (-1.14 to -0.54)	0.000	1.99
Dujardin, 2007	27	15	-0.38 (-0.82 to 0.07)	0.095	1.37
Elgh, 2009	88	30	-0.43 (-0.56 to -0.31)	0.000	2.91
Ellfolk, 2012	29	29	-0.51 (-0.88 to -0.15)	0.006	1.67
Eygelshoven, 2017	46	94	-0.03 (-0.35 to 0.29)	0.861	1.87
Farina, 2000	20	18	-0.85 (-1.23 to -0.47)	0.000	1.62
Galtier, 2014	43	20	-0.49 (-0.86 to -0.12)	0.010	1.65
Gunn, 2014	95	48	-0.11 (-0.35 to 0.14)	0.386	2.28
Hanoglu, 2014	28	19	-0.15 (-0.72 to 0.43)	0.619	0.98
Hausdorff, 2006	30	25	-0.69 (-1.23 to -0.15)	0.012	1.07
Johnson, 2011	47	191	-0.10 (-0.47 to 0.26)	0.572	1.68
Kensinger, 2003	20	112	-0.73 (-1.41 to -0.05)	0.036	0.76
Koerts, 2013	88	65	-0.45 (-0.61 to -0.29)	0.000	2.73
Lord, 2014	121	184	-0.48 (-0.64 to -0.31)	0.000	2.72
MacDonald, 2013	29	27	-1.87 (-2.81 to -0.93)	0.000	0.45
McKinlay, 2009	38	39	-0.44 (-0.71 to -0.17)	0.001	2.14
Miller, 2013	42	28	-0.86 (-1.31 to -0.42)	0.000	1.36
Monetta, 2007	17	17	-0.87 (-1.56 to -0.18)	0.013	0.75
Monza, 1998	14	18	-0.52 (-2.19 to 1.15)	0.544	0.16
Muslimovic, 2007	95	44	-0.53 (-0.65 to -0.41)	0.000	2.93
Obeso, 2012	300	50	-1.08 (-1.30 to -0.86)	0.000	2.42
O'Callaghan, 2013	50	27	-0.32 (-0.87 to 0.24)	0.268	1.02
Pell, 2005	21	21	-0.35 (-0.69 to 0.00)	0.048	1.76
Pellicano, 2015	84	84	-0.43 (-0.55 to -0.30)	0.000	2.91
Pirogovsky-Turk, 2017	68	30	-0.28 (-0.52 to -0.03)	0.028	2.26
Ramirez-Ruiz, 2006	21	21	-0.67 (-1.10 to -0.24)	0.002	1.40
Roca, 2012	32	22	-0.72 (-1.11 to -0.33)	0.000	1.56
Rodrigues, 2015	37	63	-0.11 (-0.39 to 0.18)	0.465	2.06
Rodrigues-Ferreiro, 2010	50	42	-0.28 (-0.99 to 0.43)	0.443	0.71
Rosen, 2015	20	23	-0.85 (-1.15 to -0.54)	0.000	1.94
Scholtissen, 2006	25	15	-0.20 (-0.56 to 0.16)	0.281	1.68
Souza, 2016	59	88	0.12 (-0.11 to 0.35)	0.302	2.34
Stefanova, 2001	39	30	-0.71 (-0.92 to -0.50)	0.000	2.47
Stefanova, 2006	54	37	-0.48 (-1.12 to 0.15)	0.136	0.85
Tremblay, 2012	12	13	-0.55 (-0.94 to -0.16)	0.006	1.57
Vanhoutte, 2012	10	10	-0.26 (-1.10 to 0.59)	0.553	0.54
Volpato, 2009	25	20	-0.85 (-1.20 to -0.50)	0.000	1.74
Wang, 2015	224	163	-0.36 (-0.52 to -0.20)	0.000	2.73
Witt, 2006	22	22	-0.79 (-1.12 to -0.46)	0.000	1.81
Yogev, 2005	30	28	-0.65 (-1.02 to -0.28)	0.001	1.65
Zhang, 2016	74	36	-0.44 (-0.66 to -0.23)	0.000	2.45
Overall	3067	2648	-0.48 (-0.55 to -0.41)	0.000	

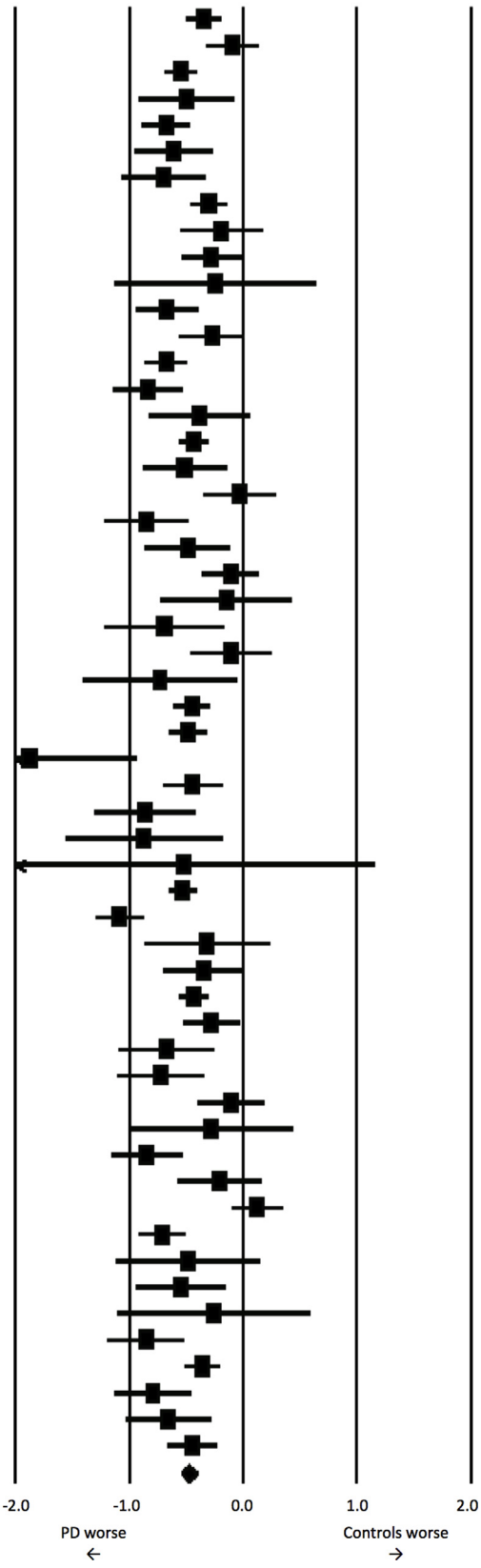

Fig. 2. Forest plot of performance on tests of frontal executive function in patients with non-demented PD relative to controls.

[36], etc.)

To achieve our second aim of examining sex differences in cognitive profiles, we recorded available raw mean age and neuropsychological test scores and SDs separately for male and female PD patients and controls. If articles did not report these sex-segregated data, corresponding authors of included articles were asked to provide these

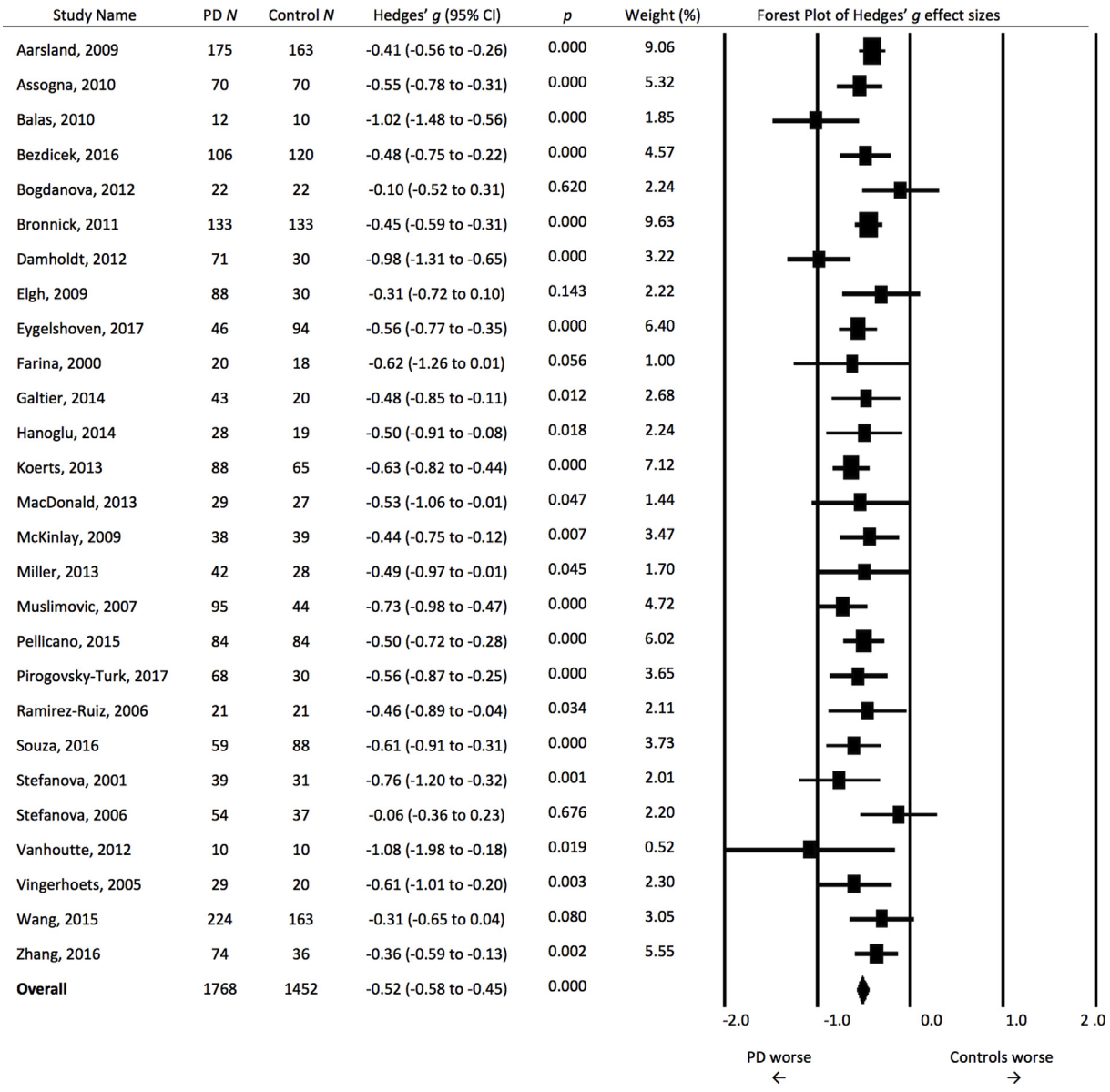

Fig. 3. Forest plot of performance on tests of verbal memory function in patients with non-demented PD relative to controls.

additional data. If no response was received from contacted authors after two weeks, an additional follow-up email was sent. Data received from authors were entered independently by two raters (AFC, RA2).

2.3. Statistical analysis

Inter-rater agreement of included articles was assessed using the Kappa (κ) statistic. Inter-rater agreement of data extraction was computed as percentage of agreement. Hedges' g (g) was computed as our measure of effect size, defined as the difference in cognitive performance between patients with PD and healthy controls, divided by the pooled SD. Values were coded so that effect sizes greater than 0.00 represent worse performance in controls, whereas values less than 0.00 represent worse performance in patients with PD. For each individual study, effect size estimates were calculated for each cognitive domain (frontal executive, visuospatial, and verbal memory). If studies included more than one neuropsychological test per cognitive domain, effect sizes for all tests within that cognitive domain were averaged. Thus, each study contributed only one effect size for each cognitive domain. Separate meta-analyses of Hedges' g values were then conducted for each domain, using random effects models to compute the pooled effect size across all studies. Statistically significant differences were determined by assessing the corresponding Hedges' g 95% confidence intervals (CI). Effect sizes were considered statistically significant if the 95% CI did not include the neutral value of 0.0.

For the meta-analyses examining magnitude of cognitive deficits in PD in each domain, effect sizes comparing entire patient and control samples were computed. In addition to examining differences between patients and controls on these domains, we examined several moderating variables, through meta-regression and subgroup analyses [using the Q-between (Q_b) statistic], that could potentially influence the magnitude of the observed group differences. These variables included age at testing, education, disease duration, H&Y score, UPDRS-III score, LEDD, continent where study took place and depression rating score of PD patients.

To examine sex differences, effect sizes were computed separately for men and women with PD (relative to their same-sex controls) for each cognitive domain. Subgroup analyses were conducted to determine whether effect size estimates differed between men and women (using Q_b). Available sex-segregated patient characteristics were

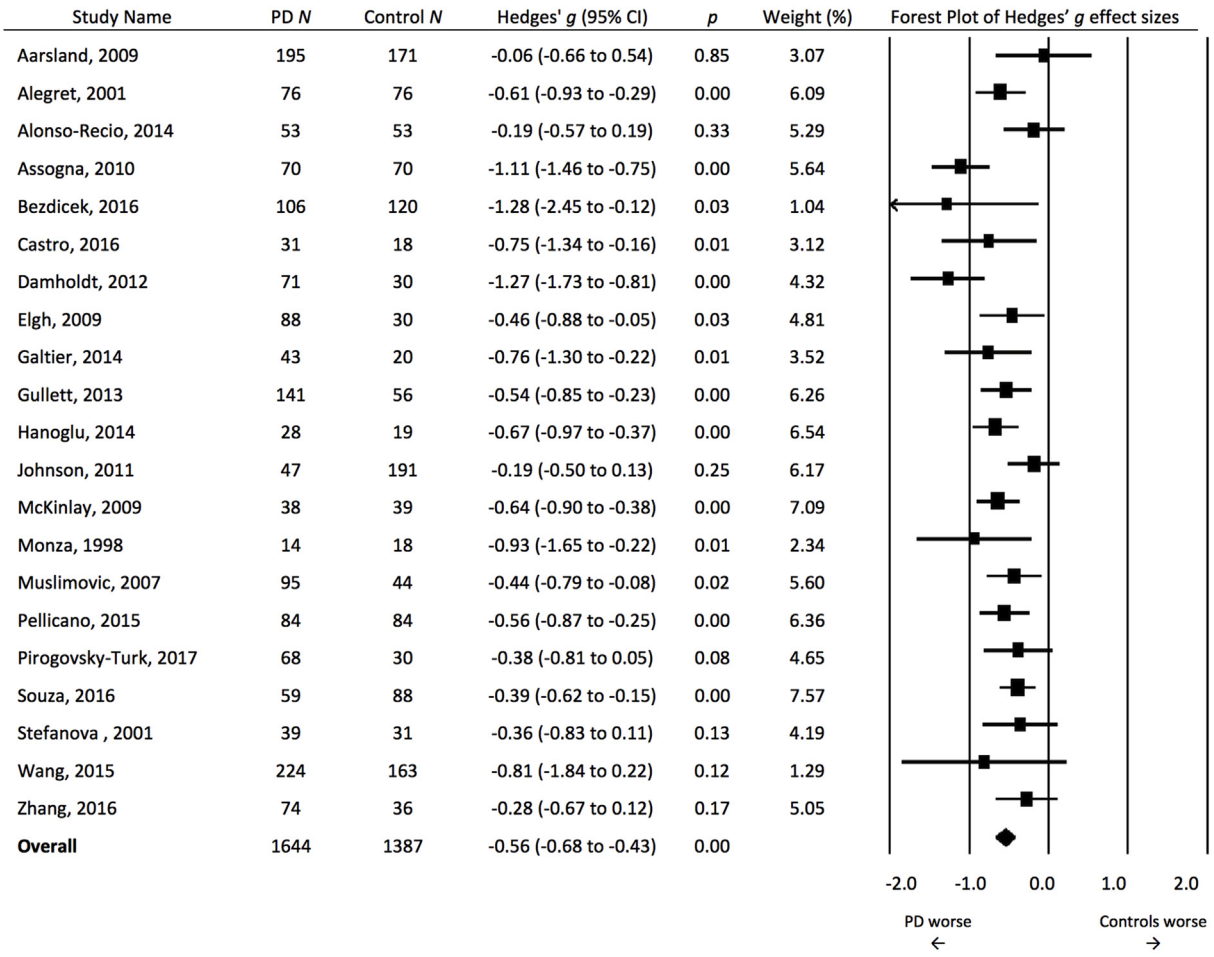

Fig. 4. Forest plot of performance on tests of visuospatial function in patients with non-demented PD relative to controls.

examined as potential moderators through meta-regression.

P-values less than 0.05 were considered statistically significant. Publication bias was assessed using Egger's test. Between-study heterogeneity and publication bias were assessed using I^2, and I^2 values of 30% or higher were investigated further for sources of heterogeneity [37]. Comprehensive Meta-Analysis (CMA) version 3 was used to conduct statistical analyses.

3. Results

3.1. Literature search and screening

As shown in Fig. 1, 7895 articles were identified in the initial search, 1089 articles underwent full text review, and 100 were included in data extraction. There was good inter-rater agreement for articles included for data extraction ($\kappa = 0.67$). Neuropsychological test data measuring one or more of the three cognitive domains for PD patients and controls were available for 50 articles and authors from nine additional studies also provided these data, resulting in a total of 59 articles [8,10,11,13–15], [38–50], [51-65], [66-89] included in the main meta-analysis. Sex-segregated neuropsychological test information was available in only one of these articles [38] and authors from 23 of the included articles (see Table e-2) provided the requested sex-segregated data, a response rate of 40%. Inter-rater agreement for data entry of extracted data was 98%, with the majority of items having 100% agreement, and the worst agreement was 92% for PD male and female sample size and H&Y scale score. All discrepancies were discussed until 100% agreement was achieved. Inter-rater agreement for data entry of sex-segregated neuropsychological information provided by authors was 100%.

3.2. Study characteristics

Descriptive information for each article included in the meta-analysis for the comparisons of PD patients in each cognitive domain is provided in Table e-2. For the cognitive domain meta-analyses, 55 articles provided relevant neuropsychological test data for the frontal executive domain, 27 articles for the verbal memory domain, and 21 articles for the visuospatial domain. Average age of onset for PD patients across all articles was 57.1. Within included articles, PD patients (64.1 years) and healthy controls (63.7 years) were of similar age at testing.

For the sex-segregated meta-analysis, data were obtained from 22 articles for the frontal executive domain, 9 for the verbal memory domain, and 10 for the visuospatial domain. Women with PD (63.9 years) were of similar age at testing as female controls (63.9 years). Similarly, men with PD (64.0 years) were of similar age at testing as same sex controls (64.5 years).

3.3. Meta-analysis of domain specific overall cognitive deficits in PD

As shown in Table 1 and Figs. 2–4, we observed worse performance in PD patients relative to healthy controls across all three cognitive domains, with effect sizes that could be classified as medium in magnitude and which represent milder deficits of approximately 0.50 SD below the healthy control values [90]. Egger's test revealed no evidence of publication bias in the frontal executive ($p = 0.43$), verbal memory ($p = 0.33$), or visuospatial ($p = 0.33$) domains. Between-study

Table 2
Summary of study sample characteristics, and meta-regression results examining the effects of several moderators on cognitive performance of patients with Parkinson's disease relative to healthy controls across three cognitive domains.

				Regression Results		
Cognitive domain/Moderator	*M*	*SD*	*k*	Co-efficient	*p*	R^2
Frontal Executive Domain						
Age at testing (years; PD)	64.3	4.7	55	0.011	0.13	0.04
Education (years; PD)	11.9	3.0	47	−0.022	0.09	0.05
Education (years; HC)	12.3	2.9	46	−0.026	0.06	0.08
PD duration (months)	69.2	35.1	50	0.001	0.28	0.00
H&Y symptom score	2.0	0.40	40	−0.116	0.37	0.00
UPDRS-III motor symptom score	20.9	5.5	35	−0.004	0.62	0.00
LEDD	449.0	261.0	28	−0.000	0.89	0.00
Verbal Memory Domain						
Age at testing (years; PD)	62.9	4.8	27	−0.000	0.95	0.00
Education (years; PD)	11.8	3.1	22	0.004	0.71	0.00
Education (years; HC)	12.0	2.9	21	0.007	0.56	0.00
PD duration (months)	67.4	34.6	27	−0.001	0.49	0.00
H&Y symptom score	2.0	0.40	22	−0.007	0.96	0.00
UPDRS-III motor symptom score	20.5	5.6	20	0.011	0.12	0.00
LEDD	453.0	216.4	17	−0.000	0.25	0.03
Visuospatial Domain						
Age at testing (years; PD)	63.6	4.9	21	0.003	0.82	0.00
Education (years; PD)	11.1	2.9	18	0.011	0.62	0.00
Education (years; HC)	11.7	2.7	17	0.013	0.60	0.00
PD duration (months)	76.7	41.4	20	−0.002	0.18	0.00
H&Y symptom score	2.1	0.47	17	−0.106	0.45	0.00
UPDRS-III motor symptom score	21.7	6.2	15	−0.003	0.73	0.00
LEDD	430.8	283.0	10	−0.000	0.44	0.00

k = number of studies included in analysis, PD = Parkinson's disease patients; HC = healthy controls, H&Y= Hoehn and Yahr; UPDRS-III = Unified Parkinson's Disease Rating Scale part 3, LEDD = Levodopa Equivalent Daily Dosage.

heterogeneity is considered [91] moderate to high for the frontal executive domain, small for the verbal memory domain, and moderate for the visuospatial domain (see Table 1). Because studies varied in the diagnostic criteria used to exclude patients with dementia (see Table e-2), we conducted sensitivity analyses which excluded those studies not using standardized diagnostic criteria. As shown in Table 1, effect sizes did not change in the sensitivity analysis for any cognitive domain, although the heterogeneity was substantially reduced. Because effect size results were replicated in the sensitivity analysis, all subsequent moderator analyses were conducted using the full dataset.

Meta-regression results for each cognitive domain are presented in Table 2. Age at testing, education, PD duration, H&Y score, UPDRS-III score, and LEDD were not significantly associated with effect sizes in any domain (all $p > 0.05$). Similarly, sub-group analyses revealed that effect sizes did not differ by continent for any domain (all $p > 0.25$, see Table e-3). Depression level was examined as a potential moderator of effect sizes, as 48 studies (81%) provided depression information for PD patients (see Table e-2). Raw mean scores on depression rating scales were categorized into normal, mild, moderate or severe groups according to guidelines of their respective scale [92–96]. Patients in studies that excluded patients with depression were categorized as normal. According to these criteria, all 48 studies included patients with mean depression ratings that were in the normal or mild category. Subgroup analyses revealed that depression level did not significantly moderate effect sizes for any domain ($p > 0.05$; see Table e-3). Only 27 studies (46%) provided data on comorbid medications that could affect the CNS and therefore this variable could not be examined further due to insufficient data.

3.4. Meta-analysis of sex-segregated data

Because sex-segregated data were only available from 23 of 59 studies, we first determined whether these 23 studies could be considered representative of the larger dataset. We compared the pooled effect sizes of deficits relative to controls across domains in the subset of 23 studies to those in the full dataset and found that these were all of similar moderate magnitude (Table 3). We thus conducted separate meta-analyses for the sex-segregated data. Men and women differed in their level of deficit relative to their same-sex controls in the frontal executive domain ($Q_b = 4.21$, $p = 0.04$), with men showing a greater deficit than women. The magnitude of deficits for men with PD relative to controls can be characterized as moderate, i.e., approximately 0.60 SD below controls. Whereas, the magnitude of deficits in women with PD relative to controls was mild to moderate, i.e., approximately 0.40 SD below controls. Sex differences were not found in the level of deficits relative to controls in the verbal memory ($Q_b = 1.65$, $p = 0.20$) or visuospatial ($Q_b = 1.51$, $p = 0.22$) domains.

Given the observed sex differences in the frontal executive domain, we perfomed meta-regressions examining the effect of age at testing for men and women with PD on this domain. Age at testing was not associated with effect sizes for men ($p = 0.81$) or women ($p = 0.70$). Sex-segregated data for other potential moderators were not available and thus their effects on this sex difference could not be examined.

4. Discussion

The findings of our meta-analyses demonstrated that non-demented PD patients showed deficits of moderate effect sizes in frontal

Table 3
Pooled effect size, effect size differences between men and women and sex-segregated effect sizes for studies containing sex-specific performance of patients with Parkinson's disease relative to healthy controls across three cognitive domains.

			Pooled effect size		Effect size differences between men and women		Sex-segregated effect size*	
Domain	*k*	*N* (PD/HC)	*g* (95% CI)	I^2(%)	Q_b	*p* (Q_b)	*g* (95% CI)	I^2(%)
Frontal Executive								
women	22	513/544	−0.478 (−0.667 to −0.289)	65.3	4.21	0.04	−0.382 (−0.511 to −0.254)	60.1
men	22	854/587					−0.575 (−0.708 to −0.443)	63.8
Verbal Memory								
women	9	236/322	−0.509 (−0.667 to −0.352)	45.0	1.65	0.199	–	–
men	9	377/403						
Visuospatial								
women	10	270/340	−0.686 (−0.902 to −0.471)	64.9	1.43	0.23	–	–
men	10	484/441						

PD = Parkinson's disease patients; HC = healthy controls.
Note. Negative effect sizes indicate worse performance in PD patients relative to controls.
*Effect sizes not examined by sex when Q_b was non-significant.

executive, verbal memory, and visuospatial abilities compared to age-matched controls. Our finding of frontal executive deficts in non-demented PD relative to healthy controls is consistent with a previous meta-analysis [7]. While a previous meta-analysis found longitudinal decline of small magnitude in verbal memory and visuospatial abilities in non-demented PD [16], our meta-analysis of cross-sectional non-demented PD data adds a unique aspect to the understanding of deficts in these domains. We examined deficits in non-demented PD patients relative to healthy controls of similar age in verbal memory and visuospatial abilities, and found deficts of moderate magnitude in these two domains as well. Furthermore, the finding that age at testing, disease duration, motor symptom severity, LEDD and depression did not moderate effect sizes in any domain suggests that the deficits reported here are independent of these variables in PD patients who had not progressed to dementia.

Given that PD is a progressive neurodegenerative disease, our findings that disease duration did not moderate performance in the three cognitive domains in non-demented PD patients is somewhat suprising, as it suggests that cognitive impairment is seemingly stable in these non-demented patients. A previous meta-analysis reported a constant rate of cognitive decline in non-demented PD patients which was independent of disease duration across the same three cognitive domains that were examined in our study [16]. This meta-analysis, however, did not compare PD patients with a healthy control group. Given that our effect sizes and moderators were based on cross-sectional data, it is possible that a selection bias contributed to the absence of a moderating effect of disease duration on cognitive deficits in the present analysis. That is, with increasing disease duration, it is likely that fewer patients volunteer for cognitive studies, and the ones who do are more likely to be relatively high functioning. Clearly more longitudinal studies of non-demented PD patient cohorts relative to controls are required to examine the effects of disease duration on cognitive decline.

Whereas we found no association between education and cognitive deficits in non-demented PD relative to healthy controls, two previous meta-analyses found that more education was associated with better frontal executive, verbal memory, and visuospatial abilities in non-demented PD [97], as well as less decline over time in verbal memory and frontal executive functioning [16], and visuospatial functioning [97]. However, our meta-analysis differed from these prior reviews in two important ways. First, our analyses included more studies with a greater number of patients and therefore had higher statistical power. Second, we examined the effect of moderating variables on effect sizes of cognitive performance of non-demented PD patients relative to healthy controls of similar ages. This allows us to more accurately attribute the associations (or lack thereof) between patient characteristics and cognitive deficits to disease specific mechanisms. Therefore the findings of our meta-analysis, even though based on cross-sectional studies, are more likely to reflect disease specific cognitive performance and their moderating influences. According to our results, cognitive impairment in all three domains appears to be an important characteristic of PD patients without dementia, and this impairment does not appear to be related to the potential moderators herein examined.

Another unique aspect of this meta-analysis is that we examined whether sex differences in PD patients relative to their age-matched healthy controls existed in frontal executive, visuospatial, and verbal memory domains. Previous work only qualitatively described sex differences in PD cognition, and did not compare performance of patients to healthy controls [20]. Importantly, we directly examined sex-specific cognitive deficits relative to healthy controls of similar age, which allowed us to investigate how sex-related factors might interact with PD mechanisms rather than age-related mechanims. Taken together, our results do not support the conclusion of a previous systematic review of a more benign generalized cognitive phenotype in women [20], and instead suggest that sex differences in cognitive deficits in non-demented PD are restricted to a certain cognitive domain. That is, relative to controls, men showed greater deficits than women in frontal executive functions, but both men and women were similarly impaired relative to controls in verbal memory and visuospatial abilities.

We propose several possibile explanations for these findings. Regarding the sex differences in frontal executive deficits, estrogen neuroprotection or neuromodulation that contributes to dopaminergic neuron survival may play a critical role [98,99]. One of the earliest neural mechanisms mediating motor impairment in PD is the loss of dopaminergic neuronal terminals in the striatum [3], and the frontal executive network is thought to be mediated by the frontal striatal pathway [100]. Thus, it is possible that women with PD show less deficit in frontal executive function because they have more dopaminergic neurons relative to men in the earlier stages of the disease, which may protect women from more severe frontal executive impairment. We encourage future studies to investigate how sex-related factors might selectively interact with disease mechanisms, particularly in early disease stages, in order to provide insight into possible targets for intervention aimed at improving cognitive or other disease symptoms. LEDD is a potential area of interest, given its varying effects on executive function [101], and reports of higher doses in men relative to women with PD [102]. However, LEDD did not moderate performance in any domain in the overall meta-analysis. Thus, it is unlikely that higher doses in men with PD account for our observed sex differences in frontal executive function.

It is well established that there are sex differences in the prevalence, incidence and motor phenotype of PD, and our findings further support the notion that sex-related factors play an important role in PD expression as they suggest that sex might also be associated with cognitive phenotype expression.

4.1. Strengths & limitations

One limitation of studies included in the cognitive domain specific overall meta-analyses was a lack of reporting of patient characteristics. We were unable to examine several important potential moderators of the cognitive deficits observed (e.g., comorbid medications known to affect the CNS). Further, while we found no association between cognitive deficits and motor symptom severity, as measured by the UPDRS-III score, a prior study [103] has shown that cognitive performance of patients with PD correlates with axial aspects of motor dysfunction, as measured by the postural instability gait difficulty (PIGD) score. Thus, it is possible that PIGD may be associated with level of cognitive deficits in PD. Unfortunately, only 4 (7%) included studies provided either PIGD scores or the UPDRS-III subscores which could be used to calculate the PIGD. Therefore, there were too few included studies to examine whether this aspect of motor dysfunction moderated the findings. We encourage future studies to provide PIGD information in order to examine its potential influence on cognition in PD. Given that we observed low to moderate levels of between-study heterogeneity across domains and found no evidence that any of the examined patient characterics accounted for any of this between-study variability, it is likely that our results reflect cognitive characteristics of non-demented PD. Our focus on studies examining neuropsychological deficits in non-demented PD patients likely resulted in the inclusion of a majority of patients with mild to moderate motor symptoms, as they would have been more likely to complete the cognitive testing. Therefore, the cognitive deficits reported here are likely characteristic of early stage PD patients with mild to moderate motor deficits.

Another limitation of the studies included in this meta-analysis is the lack of information regarding patients' independence or quality of life. We were unable to examine whether the cognitive deficits found in the study were associated with functional problems because only 5 (8%) included studies provided information on measures of independence or quality of life. In order to better understand how the moderate deficits reported here impact activities of daily living, it will be important for future studies to measure and report these outcomes,

so that future quantitative syntheses may examine the association between these values and cognition in non-demented PD.

While a main strength of our study is that it is the first to quantitatively pool results of cognitive deficits separately for men and women, we note that this was challenging due to the lack of sex-segregated reporting in the included articles. Because we were unable to obtain sex-segregated data for all of the included studies in the domain specific meta-analyses, a potential limitation of the current study is the possibility of insufficient power in our sex-segregated meta-analyses to detect sex differences in cognitive deficits in two of the three cognitive domains. For instance, only nine studies could be included for the verbal memory domain and only 12 studies for the visuospatial domain, whereas 23 studies were included for the frontal executive domain where sex differences were observed. Empirical guidelines exist for the minimum number of studies required for adequately powered meta-analyses (i.e., a minimum of 5 studies are required to obtain higher power than the primary studies contained within the meta-analysis) [104]. However, it is nevertheless important to be cautious when interpreting results with a relatively low number of studies and more than 30% heterogeneity. Despite this potential limitation, however, the pooled effect sizes observed in the sex-segregated meta-analyses (see Table 3) are similar to the domain specific overall meta-analyses (see Table 1), thus supporting the generalizability of the sex-segregated results found in the smaller meta-analyses to the broader patient group.

Although we observed moderate between-study heterogeneity in the sex-segregated analyses, we were unable to examine effects of potential moderators beyond age at testing due to lack of sex-segregated reporting of other patient characteristics. Therefore, we encourage authors to report all measured variables separately by sex, so that future work can examine the replicability of our findings in a larger set of studies and investigate potential sex-specific moderators of cognitive deficits. Finally, it will be important for future studies to analyze sex-segregated longitudinal data to examine the association between sex-related factors and cognitive function in patients with PD, relative to healthy controls.

5. Conclusions

Our findings of deficits of moderate magnitude in frontal executive, verbal memory, and visuospatial domains, which were not moderated by any examined variables, suggest that wide-spread cognitive impairment is an important feature of nondemented PD profile. Sex differences were observed in the frontal executive domain, suggesting that in addition to the benefits of reduced motor symptom severity reported in other studies [19], sex-related factors (e.g., neuroprotective effects of estrogen against dopaminergic loss) may also protect women against more severe frontal executive decline in non-demented PD. Our results contribute to a growing literature on sex differences in PD [105], which ultimately, could facilitate sex-specific clinical treatment of PD.

Funding

A.F.C. was funded through a Postdoctoral Fellowship award by the Women, Gender, Sex and Dementia Program of the Canadian Consortium on Neurodegeneration in Aging (CCNA). The CCNA is supported by a grant from the Canadian Institutes of Health Research (CIHR; CAN 137794) with funding from several partners. M.C.T. was supported by a Clinical Scientist Award from the Department of Family and Community Medicine, University of Toronto. M.M. is supported by an Early Researcher Award from the Ministry of Research, Innovation, and Science (MRIS; Ontario). Indirect funding related to the current work included the CIHR CCNA grant (CAN 137794) to M.C.T, M.M., and R.C.

Author disclosure

M. M. serves as an advisor to Bioscape Medical Imaging CRO, Novartis, and UCB; received honoraria from Novartis; received royalties from Henry Stewart Talks; received an investigator-initiated research grant from Teva; and received contract research support from Novartis and Axovant. R.C. has served on the following editorial boards: Dementia and Geriatric Cognitive Disorders, Frontiers in Aging Neuroscience, Parkinsonism and Related Disorders.

Acknowledgements

Kathy Zhang (RA1) and Gabriella Boccone (RA2) (Sunnybrook Research Institute, Primary Care Research Unit, Sunnybrook Health Sciences Centre) assisted with screening, data extraction and preparation of manuscript figures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.014.

References

[1] G.E. Gillies, I.S. Pienaar, S. Vohra, Z. Qamhawi, Sex differences in Parkinson's disease, Front. Neuroendocrinol. 35 (3) (2014) 370–384.
[2] A. Lee, R.M. Gilbert, Epidemiology of Parkinson disease, Neurol. Clin. 34 (4) (2016) 955–965.
[3] C.W. Olanow, P. Brundin, Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Mov. Disord. 28 (1) (2013) 31–40.
[4] H. Braak, U. Rüb, E.J. Steur, K. Del Tredici, R. De Vos, Cognitive status correlates with neuropathologic stage in Parkinson disease, Neurology 64 (8) (2005) 1404–1410.
[5] A.A. Kehagia, R.A. Barker, T.W. Robbins, Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis, Neurodegener. Dis. 11 (2) (2012) 79–92.
[6] A. Diamond, Executive functions, Annu. Rev. Psychol. 64 (2013) 135–168.
[7] A. Kudlicka, L. Clare, J.V. Hindle, Executive functions in Parkinson's disease: systematic review and meta-analysis, Mov. Disord. 26 (13) (2011) 2305–2315.
[8] M. Alegret, P. Vendrell, C. Junque, F. Valldeoriola, E. Tolosa, Visuospatial deficits in Parkinson's disease assessed by Judgment of Line Orientation test: error analyses and practice effects, J. Clin. Exp. Neuropsychol. 23 (5) (2001) 592–598.
[9] J.M. Gullett, C.C. Price, P. Nguyen, M.S. Okun, R.M. Bauer, D. Bowers, Reliability of three Benton Judgment of Line Orientation short forms in idiopathic Parkinson's disease, Clin. Neuropsychol. 27 (7) (2013) 1167–1178.
[10] D.K. Johnson, J.E. Galvin, Longitudinal changes in cognition in Parkinson's disease with and without dementia, Dement. Geriatr. Cognit. Disord. 31 (2) (2011) 98–108.
[11] J.R. Zhang, J. Chen, Z.J. Yang, H.J. Zhang, Y.T. Fu, Y. Shen, P.C. He, C.J. Mao, C.F. Liu, Rapid eye movement sleep behavior disorder symptoms correlate with domains of cognitive impairment in Parkinson's disease, Chin. Med. J. 129 (4) (2016) 379–385.
[12] F. Assogna, F.E. Pontieri, L. Cravello, A. Peppe, M. Pierantozzi, A. Stefani, P. STANZIONE, C. Pellicano, C. Caltagirone, G. Spalletta, Intensity-dependent facial emotion recognition and cognitive functions in Parkinson's disease, J. Int. Neuropsychol. Soc. 16 (5) (2010) 867–876.
[13] I. Galtier, A. Niet, J.N. Lorenzo, J. Barroso, Cognitive impairment in Parkinson's disease: more than a frontostriatal dysfunction, Spanish J. Psychol. 17 (2014) (2014) ArtID E68 17.
[14] Y. Bogdanova, A. Cronin-Golomb, Neurocognitive correlates of apathy and anxiety in Parkinson's disease, Parkinsons Dis. (793076) (2012) no pagination).
[15] E. Stefanova, A. Potrebic, L. Ziropadja, J. Maric, I. Ribaric, V.S. Kostic, Depression predicts the pattern of cognitive impairment in early Parkinson's disease, J. Neurol. Sci. 248 (1–2) (2006) 131–137.
[16] D. Muslimović, B. Schmand, J.D. Speelman, R.J. De Haan, Course of cognitive decline in Parkinson's disease: a meta-analysis, J. Int. Neuropsychol. Soc. 13 (6) (2007) 920–932.
[17] T. Pringsheim, N. Jette, A. Frolkis, T.D. Steeves, The prevalence of Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 29 (13) (2014) 1583–1590.
[18] L. Hirsch, N. Jette, A. Frolkis, T. Steeves, T. Pringsheim, The incidence of Parkinson's disease: a systematic review and meta-analysis, Neuroepidemiology 46 (4) (2016) 292–300.
[19] C.A. Haaxma, B.R. Bloem, G.F. Borm, W.J. Oyen, K.L. Leenders, S. Eshuis, J. Booij, D.E. Dluzen, M.W. Horstink, Gender differences in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 78 (8) (2007) 819–824.
[20] J. Heller, I. Dogan, J.B. Schulz, K. Reetz, Evidence for gender differences in cognition, emotion and quality of life in Parkinson's disease? Aging Dis. 5 (1) (2014) 63.

[21] J.J. Locascio, S. Corkin, J.H. Growdon, Relation between clinical characteristics of Parkinson's disease and cognitive decline, J. Clin. Exp. Neuropsychol. 25 (1) (2003) 94–109.

[22] O. Riedel, J. Klotsche, A. Spottke, G. Deuschl, H. Förstl, F. Henn, I. Heuser, W. Oertel, H. Reichmann, P. Riederer, Cognitive impairment in 873 patients with idiopathic Parkinson's disease, J. Neurol. 255 (2) (2008) 255–264.

[23] M.M. Amick, H.E. Schendan, G. Ganis, A. Cronin-Golomb, Frontostriatal circuits are necessary for visuomotor transformation: mental rotation in Parkinson's disease, Neuropsychologia 44 (3) (2006) 339–349.

[24] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269.

[25] W. Gibb, A. Lees, The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 51 (6) (1988) 745–752.

[26] D.J. Gelb, E. Oliver, S. Gilman, Diagnostic criteria for Parkinson disease, Arch. Neurol. 56 (1) (1999) 33–39.

[27] D. Calne, B. Snow, C. Lee, Criteria for diagnosing Parkinson's disease, Ann. Neurol. 32 (S1) (1992) S125–S127.

[28] N. Baines, B. Au, M.J. Rapoport, G. Naglie, M.C. Tierney, Meta-analysis of driving cessation and dementia: does sex matter? J. Gerontol. B Psychol. Sci. Soc. Sci. 73 (7) (2016) 1185–1189.

[29] E.I. Klimkeit, J.L. Bradshaw, J. Charlton, R. Stolwyk, N. Georgiou-Karistianis, Driving ability in Parkinson's disease: current status of research, Neurosci. Biobehav. Rev. 33 (3) (2009) 223–231.

[30] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology 57 (10,Suppl3) (2001) S11–S26.

[31] C. Goetz, B. Tilley, S. Shaftman, G. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M. Stern, R. Dodel, Movement disorder society URTF (2008) movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23(15) 2129-2170.

[32] T. Müller, Drug therapy in patients with Parkinson's disease, Transl. Neurodegener. 1 (1) (2012) 10.

[33] A. Frances, H.A. Pincus, M.B. First, Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, American Psychiatric Association, 1994.

[34] B. Dubois, D. Burn, C. Goetz, D. Aarsland, R.G. Brown, G.A. Broe, D. Dickson, C. Duyckaerts, J. Cummings, S. Gauthier, Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force, Mov. Disord. 22 (16) (2007) 2314–2324.

[35] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (3) (1975) 189–198.

[36] C.P. Hughes, L. Berg, W.L. Danziger, L.A. Coben, R. Martin, A new clinical scale for the staging of dementia, Br. J. PsychiatryPsychiat. 140 (6) (1982) 566–572.

[37] J. Higgins, S. Green, 9.5. 2 Identifying and Measuring Heterogeneity, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0 1, (2008).

[38] D. Aarsland, K. Bronnick, J. Larsen, O. Tysnes, G. Alves, Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study, Neurology 72 (13) (2009) 1121–1126.

[39] L. Alonso-Recio, P. Martin, S. Rubio, J.M. Serrano, Discrimination and categorization of emotional facial expressions and faces in Parkinson's disease, J. Neuropsychol. 8 (2) (2014) 269–288.

[40] F. Assogna, F.E. Pontieri, L. Cravello, A. Peppe, M. Pierantozzi, A. Stefani, P. Stanzione, C. Pellicano, C. Caltagirone, G. Spalletta, Intensity-dependent facial emotion recognition and cognitive functions in Parkinsons disease, J. Int. Neuropsychol. Soc. 16 (5) (2010) 867–876.

[41] M. Balas, Y. Balash, N. Giladi, T. Gurevich, Cognition in multiple system atrophy: neuropsychological profile and interaction with mood, J. Neural. Transm. 117 (3) (2010) 369–375.

[42] O. Bezdicek, T. Nikolai, J. Michalec, F. Ruzicka, P. Havrankova, J. Roth, R. Jech, E. Ruzicka, The Diagnostic Accuracy of Parkinson's Disease Mild Cognitive Impairment Battery Using the Movement Disorder Society Task Force Criteria, Movement Disorders Clinical Practice, (2016).

[43] C.A. Bouquet, V. Bonnaud, R. Gil, Investigation of supervisory attentional system functions in patients with Parkinson's disease using the hayling task, J. Clin. Exp. Neuropsychol. 25 (6) (2003) 751–760.

[44] K. Bronnick, G. Alves, D. Aarsland, O.B. Tysnes, J.P. Larsen, Verbal memory in drug-naive, newly diagnosed Parkinson's disease. The retrieval deficit hypothesis revisited, Neuropsychology 25 (1) (2011) 114–124.

[45] P. Bugalho, J. Vale, Brief cognitive assessment in the early stages of Parkinson disease, Cognit. Behav. Neurol. 24 (4) (2011) 169–173.

[46] P.C.F. Castro, C.C. Aquino, A.C. Felicio, F. Dona, L.M.I. Medeiros, S.M.C.A. Silva, H.B. Ferraz, P.H.F. Bertolucci, V. Borges, Presence or absence of cognitive complaints in Parkinson's disease: mood disorder or anosognosia? Arq. Neuropsiquiatr. 74 (6) (2016) 439–444.

[47] K.S.F. Colman, J. Koerts, M. van Beilen, K.L. Leenders, W.J. Post, R. Bastiaanse, The impact of executive functions on verb production in patients with Parkinson's disease, Cortex 45 (8) (2009) 930–942.

[48] R. Cools, R.A. Barker, B.J. Sahakian, T.W. Robbins, Mechanisms of cognitive set flexibility in Parkinson's disease, Brain 124 (12) (2001) 2503–2512.

[49] C. Crescentini, F. Mondolo, E. Biasutti, T. Shallice, Preserved and impaired task-switching abilities in non-demented patients with Parkinson's disease, J. Neuropsychol. 6 (1) (2012) 94–118.

[50] G.P. Crucian, S. Armaghani, A. Armaghani, P.S. Foster, D.W. Burks, B. Skoblar, V. Drago, K.M. Heilman, Visual-spatial disembedding in Parkinson's disease, J. Clin. Exp. Neuropsychol. 32 (2) (2010) 190–200.

[51] M. Damholdt, M. Shevlin, P. Borghammer, L. Larsen, K. Ostergaard, Clinical heterogeneity in Parkinson's disease revisited: a latent profile analysis, Acta Neurol. Scand. 125 (5) (2012) 311–318.

[52] K. Dujardin, S. Blairy, L. Defebvre, S. Duhem, Y. Noel, U. Hess, A. Destee, Deficits in decoding emotional facial expressions in Parkinson's disease, Neuropsychologia 42 (2) (2004) 239–250.

[53] K. Dujardin, C. Deneve, M. Ronval, P. Krystkowiak, C. Humez, A. Destee, L. Defebvre, Is the paced auditory serial addition test (PASAT) a valid means of assessing executive function in Parkinson's disease? Cortex 43 (5) (2007) 601–606.

[54] E. Elgh, M. Domellof, J. Linder, M. Edstrom, H. Stenlund, L. Forsgren, Cognitive function in early Parkinson's disease: a population-based study, Eur. J. Neurol. 16 (12) (2009) 1278–1284.

[55] U. Ellfolk, S. Huurinainen, J. Joutsa, M. Karrasch, The effect of encoding condition on free recall in Parkinson's disease: incidental and intentional memory are equally affected, Clin. Neuropsychol. 26 (6) (2012) 909–925.

[56] S. Eygelshoven, A. van den Hout, L. Tucha, A.B.M. Fuermaier, D.F. Bangma, J. Thome, J. Lobbestael, O. Tucha, J. Koerts, Are non-demented patients with Parkinson's disease able to decide about their own treatment? Park. Relat. Disord. 11 (2017).

[57] E. Farina, G. Gattellaro, S. Pomati, E. Magni, A. Perretti, A.P. Cannata, P. Nichelli, C. Mariani, Researching a differential impairment of frontal functions and explicit memory in early Parkinson's disease, Eur. J. Neurol. 7 (3) (2000) 259–267.

[58] J.M. Gullett, C.C. Price, P. Nguyen, M.S. Okun, R.M. Bauer, D. Bowers, Reliability of three Benton Judgment of Line Orientation short forms in idiopathic Parkinson's disease, Clin. Neuropsychol. 27 (7) (2013) 1167–1178.

[59] D.G. Gunn, S.L. Naismith, S.J. Bolitho, S.J. Lewis, Actigraphically-defined sleep disturbance in Parkinson's disease is associated with differential aspects of cognitive functioning, J. Clin. Neurosci. 21 (7) (2014) 1112–1115.

[60] L. Hanoglu, H.A. Hakyemez, F. Ozer, S. Ozben, S. Demirci, E.O. Akarsu, Relation between olfactory dysfunction and episodic verbal memory in early Parkinson's disease, Noropsikiyatri Arsivi 51 (4) (2014) 389–394.

[61] J.M. Hausdorff, G.M. Doniger, S. Springer, G. Yogev, N. Giladi, E.S. Simon, A common cognitive profile in elderly fallers and in patients with Parkinson's disease: the prominence of impaired executive function and attention, Exp. Aging Res. 32 (4) (2006) 411–429.

[62] E.A. Kensinger, D.K. Shearer, J.J. Locascio, J.H. Growdon, S. Corkin, Working memory in mild Alzheimer's disease and early Parkinson's disease, Neuropsychology 17 (2) (2003) 230–239.

[63] J. Koerts, H.A. Meijer, K.S. Colman, L. Tucha, K.W. Lange, O. Tucha, What is measured with verbal fluency tests in Parkinson's disease patients at different stages of the disease? J. Neural. Transm. 120 (3) (2013) 403–411.

[64] S. Lord, B. Galna, S. Coleman, A. Yarnall, D. Burn, I. Rochester, Cognition and gait show a selective pattern of association dominated by phenotype in incident Parkinson's disease, Front. Aging Neurosci. 6 (OCT) (2014) 249 no pagination.

[65] A.A. MacDonald, K.N. Seergobin, A.M. Owen, R. Tamjeedi, O. Monchi, H. Ganjavi, P.A. MacDonald, Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval, PLoS ONE [Electronic Resource] 8 (9) (2013) e74044.

[66] A. McKinlay, R.C. Grace, J.C. Dalrymple-Alford, D. Roger, Cognitive characteristics associated with mild cognitive impairment in Parkinson's disease, Dement. Geriatr. Cognit. Disord. 28 (2) (2009) 121–129.

[67] I.N. Miller, S. Neargarder, M.M. Risi, A. Cronin-Golomb, Frontal and posterior subtypes of neuropsychological deficit in Parkinson's disease, Behav. Neurosci. 127 (2) (2013) 175–183.

[68] L. Monetta, M.D. Pell, Effects of verbal working memory deficits on metaphor comprehension in patients with Parkinson's disease, Brain Lang. 101 (1) (2007) 80–89.

[69] D. Monza, P. Soliveri, D. Radice, V. Fetoni, D. Testa, P. Caffarra, T. Caraceni, F. Girotti, Cognitive dysfunction and impaired organization of complex motility in degenerative parkinsonian syndromes, Arch. Neurol. 55 (3) (1998) 372–378.

[70] I. Obeso, E. Casabona, M.L. Bringas, L. Alvarez, M. Jahanshahi, Semantic and phonemic verbal fluency in Parkinson's disease: influence of clinical and demographic variables, Behav. Neurol. 25 (2) (2012) 111–118.

[71] C. O'Callaghan, S. Naismith, J. Shine, M. Bertoux, S. Lewis, M. Hornberger, A novel bedside task to tap inhibitory dysfunction and fronto-striatal atrophy in Parkinson's disease, Park. Relat. Disord. 19 (9) (2013) 827–830.

[72] M.D. Pell, C.L. Leonard, Facial expression decoding in early Parkinson's disease, Cognit. Brain Res. 23 (2–3) (2005) 327–340.

[73] C. Pellicano, F. Assogna, L. Cravello, R. Langella, C. Caltagirone, G. Spalletta, F.E. Pontieri, Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients, Park. Relat. Disord. 21 (9) (2015) 1096–1100.

[74] E. Pirogovsky-Turk, R.C. Moore, J. Filoteo, I. Litvan, D.D. Song, S.L. Lessig, D.M. Schiehser, Neuropsychiatric predictors of cognitive decline in Parkinson disease: a longitudinal study, Am. J. Geriatr. Psychiatry 25 (3) (2017) 279–289.

[75] B. Ramirez-Ruiz, C. Junque, M.J. Marti, F. Valldeoriola, E. Tolosa, Neuropsychological deficits in Parkinson's disease patients with visual hallucinations, Mov. Disord. 21 (9) (2006) 1483–1487.

[76] M. Roca, F. Manes, A. Chade, E. Gleichgerrcht, O. Gershanik, G.G. Arevalo, T. Torralva, J. Duncan, The relationship between executive functions and fluid intelligence in Parkinson's disease, Psychol. Med. 42 (11) (2012) 2445–2452.

[77] I.T. Rodrigues, J.J. Ferreira, M. Coelho, M.M. Rosa, A. Castro-Caldas, Action verbal fluency in Parkinson's patients, Arq. Neuro. Psiquiatr. 73 (6) (2015) 520–525.

[78] J. Rodriguez-Ferreiro, F. Cuetos, E. Herrera, M. Menendez, R. Ribacoba, Cognitive impairment in Parkinson's disease without dementia, Mov. Disord. 25 (13) (2010) 2136–2141.

[79] J.B. Rosen, E. Rott, G. Ebersbach, E. Kalbe, Altered moral decision-making in patients with idiopathic Parkinson's disease, Park. Relat. Disord. 21 (10) (2015) 1191–1199.
[80] B. Scholtissen, J. Dijkstra, J. Reithler, A.F.G. Leentjens, Verbal fluency in Parkinson's disease: results of a 2-min fluency test, Acta Neuropsychiatr. 18 (1) (2006) 38–41.
[81] C.P. Souza, G.N. Oliveira, M.P. Foss, V. Tumas, The interlocking finger test in patients with Parkinson's disease and healthy subjects, J. Clin. Neurosci. 29 (2016) 145–148.
[82] E. Stefanova, V.S. Kostic, L. Ziropadja, G. Ocic, M. Markovic, Declarative memory in early Parkinson's disease: serial position learning effects, J. Clin. Exp. Neuropsychol. 23 (5) (2001) 581–591.
[83] C. Tremblay, O. Monchi, C. Hudon, J. MacOir, L. Monetta, Are verbal fluency and nonliteral language comprehension deficits related to depressive symptoms in Parkinson's disease? Parkinsons Dis. 308501 (2012) no pagination.
[84] S. Vanhoutte, M. De Letter, P. Corthals, J. Van Borsel, P. Santens, Quantitative analysis of language production in Parkinson's disease using a cued sentence generation task, Clin. Linguist. Phon. 26 (10) (2012) 863–881.
[85] G. Vingerhoets, E. Vermeule, P. Santens, Impaired intentional content learning but spared incidental retention of contextual information in non-demented patients with Parkinson's disease, Neuropsychologia 43 (5) (2005) 675–681.
[86] C. Volpato, M. Signorini, F. Meneghello, C. Semenza, Cognitive and personality features in Parkinson disease: 2 sides of the same coin? Cognit. Behav. Neurol. 22 (4) (2009) 258–263.
[87] Y.Q. Wang, B.S. Tang, X.X. Yan, Z.H. Chen, Q. Xu, Z.H. Liu, K. Li, K. Wang, J.F. Guo, A neurophysiological profile in Parkinson's disease with mild cognitive impairment and dementia in China, J. Clin. Neurosci. 22 (6) (2015) 981–985.
[88] K. Witt, C. Daniels, V. Daniel, J. Schmitt-Eliassen, J. Volkmann, G. Deuschl, Patients with Parkinson's disease learn to control complex systems-an indication for intact implicit cognitive skill learning, Neuropsychologia 44 (12) (2006) 2445–2451.
[89] G. Yogev, N. Giladi, C. Peretz, S. Springer, E.S. Simon, J.M. Hausdorff, Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? Eur. J. Neurosci. 22 (5) (2005) 1248–1256.
[90] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, revised ed., Academic Press, New York, 1977.
[91] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ Br. Med. J. (Clin. Res. Ed.) 327 (7414) (2003) 557.
[92] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. ERBAUGH, An inventory for measuring depression, Arch. Gen. Psychiatr. 4 (6) (1961) 561–571.
[93] A.T. Beck, R.A. Steer, R. Ball, W.F. Ranieri, Comparison of beck depression inventories-IA and-II in psychiatric outpatients, J. Pers. Assess. 67 (3) (1996) 588–597.
[94] M. Hamilton, Rating depressive patients, J. Clin. Psychiatr. (1980).
[95] S.A. Montgomery, M. Asberg, A new depression scale designed to be sensitive to change, Br. J. Psychiatry 134 (4) (1979) 382–389.
[96] J.A. Yesavage, T.L. Brink, T.L. Rose, O. Lum, V. Huang, M. Adey, V.O. Leirer, Development and validation of a geriatric depression screening scale: a preliminary report, J. Psychiatr. Res. 17 (1) (1982) 37–49.
[97] J.V. Hindle, A. Martyr, L. Clare, Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis, Park. Relat. Disord. 20 (1) (2014) 1–7.
[98] I.N. Miller, A. Cronin-Golomb, Gender differences in Parkinson's disease: clinical characteristics and cognition, Mov. Disord. 25 (16) (2010) 2695–2703.
[99] M.C. Morale, P.A. Serra, F. L'Episcopo, C. Tirolo, S. Caniglia, N. Testa, F. Gennuso, G. Giaquinta, G. Rocchitta, M.S. Desole, Estrogen, neuroinflammation and neuroprotection in Parkinson's disease: glia dictates resistance versus vulnerability to neurodegeneration, Neuroscience 138 (3) (2006) 869–878.
[100] B.B. Averbeck, J. Lehman, M. Jacobson, S.N. Haber, Estimates of projection overlap and zones of convergence within frontal-striatal circuits, J. Neurosci. 34 (29) (2014) 9497–9505.
[101] G. Dirnberger, M. Jahanshahi, Executive dysfunction in Parkinson's disease: a review, J. Neuropsychol. 7 (2) (2013) 193–224.
[102] M. Lubomski, R.L. Rushworth, W. Lee, K.L. Bertram, D.R. Williams, Sex differences in Parkinson's disease, J. Clin. Neurosci. 21 (9) (2014) 1503–1506.
[103] T. Herman, A. Weiss, M. Brozgol, N. Giladi, J.M. Hausdorff, Identifying axial and cognitive correlates in patients with Parkinson's disease motor subtype using the instrumented Timed up and Go, Exp. Brain Res. 232 (2) (2014) 713–721.
[104] D. Jackson, R. Turner, Power Analysis for Random-effects Meta-analysis, Research Synthesis Methods, 2017.
[105] D. Georgiev, K. Hamberg, M. Hariz, L. Forsgren, G.M. Hariz, Gender differences in Parkinson's disease: a clinical perspective, Acta Neurol. Scand. 136 (6) (2017) 570–584.