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# Cognitive And Visual Processing Performance In Parkinson's Disease Patients With vs Without Visual Hallucinations: A Meta-Analysis

**Word count:** (not including abstract, tables, figures, acknowledgments, references, onlineonly material) = 4,103 words Abstract = 300 words

### Abstract

Importance. Cognitive and visual impairments in Parkinson's Disease Psychosis (PDP) raise the question of whether a specific profile of impaired cognition and visual function is linked to vulnerability to visual hallucinations (VHs). Previous studies have limited sample sizes and only included a sub-sample of tests. This is the first meta-analysis quantifying visuo-cognitive impairments in PDP patients across a spectrum of tests and taking into account potential confounding factors such as levodopa medication, illness duration and general cognitive ability. **Objective**. Compare visual processing and cognitive performance between PD patients with and without VHs (PDVH and PDnoVH). Methods. Four databases (PubMed, PsychINFO, Scopus, WebOfScience) were searched for studies on visual and/or cognitive performance of PDnoVH and PDVH published up to 02/2020. For each task, means and SDs were extracted and standardized-mean-differences (SMDs) between-groups calculated. Effectsizes (Hedges' g) were calculated for all comparisons and synthesized in random-effects metaanalyses with robust-variance-estimation (accounting for multiple correlated measures within each study per cognitive/visual domain). Publication bias was assessed with funnel plots and Egger intercept. **Results**. N=99 studies including 2508 PDVH patients (mean age 68.4 years) and 5318 PDnoVH (mean age 66.4 years) were included in the seven meta-analyses. PDVH patients performed worse than PDnoVH across all measures of cognition and visual processing, with the greatest between-group effect-sizes in executive functions, attention, episodic memory and visual processing. Study characteristics were not significantly associated with betweengroup differences in the domains investigated. Age-differences were significantly associated with performance differences in general cognition, working memory and executive functions. Conclusion. Models of PDVH need to incorporate a wider range of cognitive and processing domains than currently included. There is a need for studies disentangling the temporal

relationship between cognitive/visual deficits and VHs as early identification of risk before the onset of VHs could mitigate later outcomes such as progression to dementia.

# Key Words

Parkinson's psychosis; Hallucinations; Visual processing; Vision; Cognition; Cognitive deficits; Cognitive profile; Parkinson's disease; Psychosis; Perception, Meta-analysis, Meta-regression.

### 1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder affecting around 2-3% of the population above the age of 65<sup>1</sup>, an estimate that is likely to rise with increased longevity in the world population <sup>2,3</sup>. Despite motor symptoms being characteristic features of this disorder, non-motor symptoms are also recognised<sup>4</sup>. These include sleep behaviour disorders<sup>5</sup>, dementia<sup>4</sup> and PD psychosis<sup>6</sup>. These non-motor symptoms adversely and substantially impact patients' and carers' quality of life<sup>7</sup>.

PD psychosis (PDP)<sup>8</sup> refers to a spectrum of symptoms that can affect around half of patients with PD<sup>9</sup> and that includes hallucinations and delusions (i.e. percepts without corresponding external stimuli and abnormal beliefs, respectively) and illusions (incorrect percepts of external stimuli).

In PDP hallucinations are more prevalent in the visual (VH) rather than auditory modality (although see the following paper<sup>10</sup> for rates of multimodal hallucinations). For an overview of their clinical presentation and progression see work by ffytche and colleagues<sup>6</sup>. The presence of hallucinations in PD has been identified as a significant predictor of dementia and has been associated with steeper cognitive decline<sup>11</sup>, especially in those with pre-existent dementia<sup>12</sup>. However, the relationship between cognitive dysfunction and PD psychosis remains unclear. In PD patients at an earlier stage of disease progression before the onset of PD dementia, VHs are associated with cognitive dysfunction across several domains compared to those without VHs. For example, patients with VHs have deficits in executive function<sup>13</sup>, sustained attention<sup>14</sup> and visuo-perceptual functions<sup>15,16</sup>. However, the studies from which such evidence is derived typically have small samples, assess the same functions using a range of different tests and control for different factors. It is therefore difficult to determine which deficits form the core visuo-cognitive perceptual profile of patients with PDP and which deficits are less

consistent across patients. For example, memory deficits are not often discussed in relation to PDVH (e.g. Katzen eand colleagues<sup>17</sup>), although there are some studies suggesting that they are present (see <sup>18</sup> and <sup>19</sup>). To date, memory deficits are not incorporated in models of VH in PD (such as the PAD model<sup>20</sup> or the attentional networks dysfunction model<sup>21</sup>). For a more detailed summary of visual hallucination models in PD see Supplementary section 1.7. Furthermore, it is unclear the extent to which medication, age, illness duration and general cognitive impairment (e.g. measured by MMSE) have influenced group differences identified in previous studies. A general deficit in cognition or a later disease stage would be expected to result in non-specific performance deficits across all tests. In studies that have not controlled for such factors, deficits of specific cognitive/visual perceptual domains are difficult to interpret and may not indicate a specific role in the mechanism of VHs.

A meta-analytic approach can be used to better understand these issues and to account for the relatively small numbers of participants in individual studies, alongside investigating potentially confounding factors such as medication dose, illness duration and general cognition. Furthermore, while most studies include tests of general cognition, a meta-analysis is required to understand the effects across multiple cognitive and visual processing domains and to see whether they relate to a general cognitive deficit. The search terms for this review were developed to be inclusive so that the maximum number of eligible studies could be evaluated.

### 2. Methods

We registered our systematic review protocol with the International Prospective Register of Systematic reviews (PROSPERO) prior to data collection and analysis. The protocol can be accessed online (<u>https://osf.io/zu7kp/</u>) and we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for reporting.

### 2.1. Search strategy and study selection

A comprehensive online literature search was conducted on PubMed, Scopus, PsychINFO and WebOfScience. The full search strategy can be accessed online (https://osf.io/2tgyw/). Key terms for a first search on cognition in PDP included: *Parkinson, visual hallucinations, psychosis, psychotic, hallucinat\*, cognitive, cognition, cognit\*, psych\**. A second search was done focusing on visual aspects of PDP and key terms were: *Parkinson, visual hallucinations, psychosis, psychotic, hallucinat\*, vis\*, visual, vision, visual percept*. No limits were applied to date of publication. Non-English papers were excluded.

Eligible studies had to be case-control studies including both patients diagnosed with PD and experiencing hallucinations (PDP or PDVH) as well as PD patients without VHs (PDnoVH). We excluded studies primarily focussing on participants with major cognitive impairments such as dementia, and other neurological/psychiatric impairments. We excluded studies that only looked at PDVH patients predominantly experiencing delusions. For longitudinal studies of cognition with an intervention the baseline assessments were used.

#### 2.2. Quality assessment and data extraction

We used the Covidence platform for importing and collating citations from the different databases. M.Mon. did the screening of title and abstracts and both M.Mon and M.Mehta completed full-text assessments. Discrepancies were resolved by consensus with all coauthors. The information collected during data extraction included authors, cognitive and visual tasks used, and for both PDVH and PDnoVH groups: mean score and standard deviation (SD) for the tasks, sample size, mean age, gender ratio, daily levodopa mean and SD, mean duration of illness and SD, mean Hoehn&Yahr stage/or UPDRS-III score and SD. Authors of selected studies that had missing data were contacted. All scores were coded so that high scores indicated better performance. The following cognitive domains were chosen and data assigned to each: general cognition, attention, language, executive functions, working memory, episodic memory and visual processing. The visual processing domain was further divided into subdomains based on putative associations with the dorsal stream, ventral stream and lateral occipital cortex and imagery networks by DF with acuity and contrast sensitivity classified separately. See *Supplementary* for details on this subdivision and work by ffytche et al,<sup>22</sup> for an overview of the visual neuroanatomical classificatory scheme.

M.Mon. and M.Mehta independently evaluated risk of bias for each study using criteria adapted from the GRADE Handbook<sup>23</sup> and the quality of the studies was assessed across the domains (see *Supplementary*). No studies were removed after this analysis.

#### 2.3. Meta-analyses

For each task, the standardised-mean-difference (SMD) was calculated between the PDVH and PDnoVH groups. Many studies provided multiple effect sizes as the participants were tested with battery of tests. In such cases, all of the relevant effect sizes were extracted and included in the analysis.

Traditional meta-analytic methodologies assume that effect sizes are independent of one another but having multiple effect sizes drawn from the same participants violates this assumption of independence<sup>24</sup>. For domains with studies mostly providing one effect size each, a traditional meta-analytic approach was used. For domains in which multiple effect sizes were derived from each study, as the covariance matrices for all measures in these studies were not available, a random-effect multilevel modelling approach was used to account for the dependency in effect sizes. We used the *metaphor* package in R<sup>25</sup> and then applied robustvariance-estimation. This allowed us to minimise information-loss by including all of the relevant effect sizes whilst a) calculating an estimation of study weights that takes into account the nested structure of the data, and b) accounting for the violation of independence as residual errors might not be orthogonal within clusters at the different levels<sup>26</sup>. Participants are described at the first level, within-study variance at the second, and between-study variance at the third<sup>27</sup>.

Heterogeneity was assessed using both the  $\tau^2$  test and the Higgins and Thompson I<sup>2</sup> statistic. Publication bias was checked via funnel plots and Egger's tests. We ran random-effects metaanalytic models with DerSimonian-Laird estimator for  $\tau^2$  and standardised-mean-difference (SMD) as an outcome for each task and Hedges' g as a summary measure (similar to Cohen's d but accounting for bias in small studies<sup>28</sup>).

For the visual processing domain, a subgroup analysis with visual subdomain as a moderator was run. For all domains, robust meta-regressions were run to test for the effect of the following *differences* between PDVH and PDnoVH on performance differences: age, daily levodopa medication, illness duration, illness severity (both in terms of H&Y and MDS UPDRS-III z-score<sup>\*</sup>), general cognition (MMSE) and gender. Reports of these analyses included standardised regression coefficients (Beta), 95% CIs and p-values. Permutations tests (1000 permutations) were done to assess the robustness of our meta-regression models<sup>29</sup>.

<sup>\*</sup> Both the H&Y and the MDS UPDRS-III subscale tap on motor symptoms. We included the motor subscale of the UPDRS as opposed to the total MDS UPDRS score to allow for a more uniform comparison across the two measures of illness severity available across the studies.

# 3. Results

### 3.1. Search Results and Sample Characteristics

The electronic database search identified 2505 articles, and 2 added through snowballing. After duplicates removal, title and abstract screening, 267 articles were retained for full-text assessment. Overall, 99 fulfilled our review criteria and were included in our meta-analyses (*Figure 1*). See *Table 1* for summary demographics.



Figure 1- PRISMA flowchart of study selection

Table 1- Summary demographic information for the two groups of PD patients.

Variable	PD noVH (overall N= 5318)		PD V (overall N	VH N= 2508)	Statistics
	Mean	SD	Mean	SD	Value (df), Significance p<0.05
Age (years)	66.46	8.18	68.39	7.52	T-test = 2.993 (190.48), p = 0.003**
Gender (male to female in percentage)	176	7	169	.60	T-test = 0.355 (153.93), p = 0.722

Daily levodopa (mg)	548.98	306.4	638.5	327.2	T-test = 2.618 (165.95), p = 0.009**
Illness duration (years)	6.98	4.47	8.77	4.96	T-test = 4.513 (180.97), p < 0.001***
Illness severity					
H&Y ( $n=27$ studies)	2.40	0.69	2.42	0.73	T-test = 0.084 (23.55), p = 0.933
UPDRS-III (n=9 studies)	20.80	9.32	30.75	12.05	T-test = 1.857 (6.54), p = 0.108
General cognition					
MMSE (n= 72 studies)	27.46	2.64	26.01	3.06	T-test = 4.398 (100.56), p = <.0001***
Moca $(n = 16)$	25.90	2.62	24.63	2.80	T-test = 1.489 (25.42), p = 0.148

SD, standard deviation; df= degrees of freedom.

\* significant differences at p<0.05; \*\* significant differences at p<0.01; \*\*\* significant differences at p<0.001

### 3.2. Overall effects – Visual and cognitive domains in PDVH and PDnoVH

From comparing effect sizes across the different domains of interest, results show that PDVH patients were overall worse than PDnoVH patients in all of the domains investigated. Looking at the overall observed effect size (see *Table 2*), the difference between the groups is greatest for executive functions, followed by attention, episodic memory and visual processing, general cognition and working memory. The smallest is for the language domain.

See Figure 2 (a,b,c) and Figure 3 (d,e,f,g) of the forest plots of each of the domains of interest.

	g (95%Cl), p-value	I <sup>2</sup> (95 %)	N studies (Sample size PDVH, PDnoVH)	Туре
Executive functions	-0.67 [-0.90, -0.44], p < 0.0001	Overall: 87.7% BS: 65.25% WS: 22.45% SEV: 12.3%	40 (929, 1844)	Multilevel meta with RVE correction
Attention	-0.59 [-0.92; -0.27], p = 0.0017	71% [51%; 83%]	12 (299, 467)	Traditional meta-analysis
Episodic memory	-0.57 [-0.79, -0.36], p < 0.0001	Overall: 84.86% BS: 48.37% WS: 36.49% SEV: 15.14%	32 (755, 1301)	Multilevel meta with RVE correction
Visual processing	-0.57 [-0.80; -0.34], p < 0.0001	Overall: 87.3% BS: 28.35% WS: 58.95% SEV: 12.7%	37 (812, 1377)	Multilevel meta with RVE correction
General cognition	-0.56 [-0.66; -0.46], p < 0.0001	72% [66%; 77%]	99 (2508, 5318)	Traditional meta-analysis
Working memory	-0.47 [-0.71, -0.24], p = 0.0005	Overall: 72.89% BS: 69.34% WS: 3.54% SEV: 27.11%	19 (426, 714)	Multilevel meta with RVE correction
Language	-0.27 [-0.40; -0.14], p = 0.0002	50% [27%; 66%]	24 (523, 850)	Traditional meta-analysis

*Table 2-* Comparison of effect sizes (negative means favouring PDnoVH, positive favours PDVH) ordered from greatest to smallest.

g = Hedges' g;  $I^2 =$  Heterogeneity measure; BS = Between-studies; WC= Within-studies; SEV= Sampling error variance

*Figure 1* – Results from using traditional meta-analytic approaches are shown in the forest plot for the domains of a) general cognition, b) attention and c) Language. Each forest plot shows the standardized mean difference estimate across measures in each sample (grey square) and its 95% CI (black horizontal li ne). The size of the grey square is proportional to the weight of each sample in the meta-analysis. The vertical dashed line and the blue diamond show the weighted standardized mean difference in overall performance and its 95% CI, estimated in random-effects meta-analysis. Values < 0 and on the left side of the dotted vertical line reflect worse performance in PDP patients compared to PDnoVH.

#### a) General cognition

Author	N	PD With VH Mean SD N	PD Mear	No VH SD	Favours PI no Vi	D Favours PD H with VH	g	95% CI	weight
1 Aarsland 1999 MMSE	23	18.10 8.50 138	26.00	5.50			-1.31	[-1.77; -0.84]	1.1%
2 Ballanger 2010 Moca 4 Barnes 2001 MMSE	7 21	27.00 1.01 7 26.70 1.40 23	28.00	) 1.01	-	-	-0.93 -0.71	[-2.05; 0.20] [-1.32; -0.09]	0.5% 0.9%
14 Barnes 2003 MMSE	17	26.70 1.14 20	27.50	1.39		- -	-0.61	[-1.27; 0.05]	0.9%
38 Barnes 2008 MMSE 38 Barnes 2010 MMSE	17	26.43 1.09 20 27.32 1.89 20	27.20	1.23	1	삪	-0.64	[-0.77; 0.49]	0.9%
64 Barrett 2017 Moca 70 Beir-kasem 2018 PD-CRS Total score	33	24.80 2.60 68	24.70	2.30		È.	0.04	[-0.37; 0.46]	1.2%
73 Boecker 2007 MMSE	8	25.75 1.67 13	26.82	1.54	-	÷.	-0.65	[-1.55; 0.26]	0.7%
81 Boubert 2015 MMSE 89 Chang 2016 MMSE	35 12	26.95 1.54 20 27 73 2.20 23	27.56	i 1.94		1	-0.35	[-0.91; 0.20] [-0.61: 0.79]	1.0% 0.8%
110 Cho 2017 Moca	11	26.00 1.80 8	26.90	1.90		<u>-</u>	-0.47	[-1.39; 0.46]	0.6%
118 Chung 2015 MMSE 119 Chung 2015 Moca	26 26	24.20 2.80 32 20.00 4.60 32	26.20	) 2.30 ) 4.30		+	-0.78 -0.73	[-1.32; -0.24] [-1.27; -0.20]	1.0% 1.0%
120 Clegg 2018 MMSE 121 Clegg 2018 Mose	34	28.20 1.40 120	28.80	1.30			-0.45	[-0.84; -0.07]	1.2%
130 Creese 2018 BTACT Total (Brief Assessment of Adult Cognition by Telephone)	24	-0.01 0.78 45	-0.01	0.54			0.00	[-0.50; 0.50]	1.1%
132 Dauwan 2019 MMSE 134 de Mandreiville 2004 MMP (Mini-Mental Parkinson)	20 19	25.17 4.79 20 26.20 6.60 55	28.17	1.60	+	÷	-0.82	[-1.47; -0.18] [-1.00: 0.06]	0.9%
137 Diederich 1998 MMSE	14	27.86 1.70 21	28.95	0.86	+	Ð.	-0.85	[-1.55; -0.14]	0.8%
14/ Factor 2014 MMSE 149 Factor 2017 Moca	25 48	-0.30 1.00 96 23.90 3.60 96	24.60	3 1.00 3.50			-0.33	[-0.77; 0.11] [-0.54; 0.15]	1.1% 1.2%
150 Fenelon 2000 MMP (Mini-Mental Parkinson)	48	19.30 6.20 130	26.90	4.50			-1.51	[-1.88; -1.14]	1.2%
154 ffytche 2017 Moca	115	27.16 2.30 286	27.10	2.30		j.	0.03	[-0.19; 0.24]	1.4%
159 Firbank 2018 CAMCOG (Cambridge Cognitive Examination revised test battery) 160 Firbank 2018 MMSE	17 17	74.60 15.30 19 23.10 4.90 19	84.50 25.60	21.70	+	벽	-0.72	[-1.40; -0.05] [-0.81: 0.50]	0.9%
163 Forsaa 2010 MMSE	70	20.40 7.20 160	26.50	4.50			-1.11	[-1.41; -0.81]	1.3%
177 Gallagher 2011 SCOPA-COG Total	30	24.30 2.20 15 21.82 2.23 64	24.70	2.54		Ī	-1.98	[-0.91; 0.52] [-2.50; -1.46]	1.0%
179 Gama 2014 MMSE 180 Gootz 2006 MMSE	11	19.30 3.70 28	25.60	4.30	+		-1.49	[-2.27; -0.71]	0.8%
181 Goldman 2014 MMSE	25	23.90 5.40 25	25.10	4.40		11 11	-0.24	[-0.80; 0.32]	1.0%
182 Gordon 2016 Addenbrooke's Cognitive examination – ACE 195 Grossi 2005 MMSE	16 14	45.00 15.10 52 26.56 2.15 34	71.70 27.00	2.13	-	1	-1.46 -0.20	[-2.07; -0.84] [-0.83; 0.42]	0.9%
204 Grossi 2011 MMSE	19	22.83 3.54 19	24.61	4.27		<u>1</u>	-0.44	[-1.09; 0.20]	0.9%
220 Hall 2016 MMSE	25	28.72 1.72 28	29.00	1.47	1	힌 문	0.09	[-0.45; 0.63]	1.0%
224 Hepp 2013 MMSE 236 Hepp 2017 CAMCOG (Cambridge Cognitive Examination revised test battery)	31 15	27.00 2.00 31	28.00	2.00			-0.49	[-1.00; 0.01]	1.1%
243 Hepp 2017 MMSE	15	26.00 4.00 40	28.00	1.00		•	-0.89	[-1.50; -0.27]	0.9%
249 Holroyd 2001 TICS- M (Modified Telephone Interview for Cognitive Status) 254 Ibarrexte-Bilbao 2008 MMSE	26 16	29.90 5.80 72 26.00 2.10 19	33.00	) 3.50 ) 1.70		-	-0.73	[-1.19; -0.27] [-1.86; -0.41]	1.1%
257 Ibarrexte-Bilbao 2010 MMSE	12	26.90 1.90 14	29.30	1.60	-		-1.33	[-2.20; -0.47]	0.7%
272 Imamura 2008 MMSE	11	26.50 2.70 23	28.10	2.00	+	i i i i i i i i i i i i i i i i i i i	-0.35	[-1.13; 0.42]	0.8%
278 Janzen 2011 MMSE 290 Katzen 2010 MMSE	13 47	28.00 1.70 16 26.50 3.10 105	28.90	1.60	-	<del>4</del>	-0.53	[-1.28; 0.21] [-0.60: 0.09]	0.8%
298 Kiferle 2007 MMSE	60	28.18 2.13 62	28.09	2.24		1. 1.	0.04	[-0.31; 0.40]	1.2%
299 Kiferle 2014 MMSE 301 Koerts 2010 MMSE	18 14	24.90 3.10 18 26.20 1.30 14	25.40 26.40	) 2.60 ) 1.60		÷.	-0.17 -0.13	[-0.83; 0.48] [-0.87; 0.61]	0.9% 0.8%
311 Kopal 2015 Moca	18	17.39 6.58 34	21.35	3.27			-0.84	[-1.43; -0.24]	1.0%
313 Lee 2012 MMSE 314 Lee 2013 MMSE	20	25.00 2.67 20	29.30	4.28		¥	-0.25	[-0.35; 0.90]	0.9%
316 Lee 2016a MMSE 317 Lee 2016b MMSE	10	27.70 1.60 14	28.40	1.40	-	불	-0.46	[-1.28; 0.37] [-1.14: 0.38]	0.7%
326 Lefebvre 2016 MMSE	18	28.00 1.24 16	28.88	1.20	÷	<u>i</u>	-0.70	[-1.40; -0.01]	0.8%
338 Lenka 2018 Moca 347 Leu-semenescu 2011 MMSE	42 26	25.80 2.70 51 27.60 2.10 74	25.40	1.80			-0.42	[-0.26; 0.56] [-0.87; 0.03]	1.2%
353 Llebaria 2010 MDRS - Total score	21	125.02 13.46 28	130.10	9.30			-0.44	[-1.02; 0.13]	1.0%
364 Mack 2012 MMSE	65	28.30 0.20 40	28.60	0.30	5		-1.23	[-1.66; -0.80]	1.1%
369 Marsh 2004 MMSE 373 Matsui 2005 MMSE	11 10	26.20 2.90 25 24.90 4.70 9	28.20	) 2.10 ) 3.00	+	<u>+</u>	-0.83 -0.41	[-1.56; -0.09] [-1.32; 0.51]	0.8%
376 Matsui 2006 MMSE	31	25.70 3.20 39	26.40	2.80			-0.23	[-0.71; 0.24]	1.1%
378 Meppelink 2009 MMSE 383 Meral 2007 Short Test of Mental Status	17	25.30 1.60 26	27.40	1.60		<u>क</u>	-0.48	[-0.80; 0.42]	0.7%
392 Morgante 2012 MMSE 393 Moustata 2014 MMSE	37 21	27.80 2.20 443 23.80 2.50 23	28.00	2.20		휘	-0.09	[-0.43; 0.24] [-1.48; -0.24]	1.2% 0.9%
398 Muller 2017 MMSE	15	28.00 7.00 18	29.50	4.00			-0.26	[-0.95; 0.43]	0.9%
401 Nagano-saito 2004 MMSE 404 Nishio 2018 MMSE	8 19	28.30 1.80 11 26.60 2.90 53	28.50	) 1.70 ) 1.70			-0.11 -0.86	[-1.02; 0.80] [-1.40; -0.31]	0.6%
408 O'Callaghan 2017 MMSE	20	28.79 1.72 25	28.39	1.47		圭	0.25	[-0.34; 0.84]	1.0%
409 O Galaghan 2017 Moda 410 Oishi 2005 MMSE	24	25.10 3.70 41	26.50	3.10			-0.42	[-0.92; 0.09]	1.0%
411 Oka 2007 MMSE 414 Ozer 2007 Short Test of Mental Status	31 33	25.00 2.80 37 25.00 6.63 30	27.80	2.00			-1.15 -0.70	[-1.67; -0.64] [-1.21; -0.19]	1.0% 1.0%
423 Papapetropoulos 2005 MMSE	19	23.68 4.90 104	27.72	1.80			-1.60	[-2.13; -1.07]	1.0%
424 Papapetropoulos 2006 MMSE 425 Park 2013 MMSE	7	26.10 1.70 13	26.90	1.40	-		-0.25	[-1.44; 0.43]	0.6%
426 Park 2013 Moca 434 Porter 2009 MMSE	23	21.10 2.30 13	25.60	2.40			-1.82	[-2.93; -0.71] [-0.68: 0.23]	0.5%
437 Ramirez-Ruiz 2006 MMSE	24	26.70 2.10 21	29.20	1.40	-	I	-1.36	[-2.01; -0.70]	0.9%
445 Hamirez–Ruiz 2006 WAIS–III Information 451 Ramirez–Ruiz 2007 MMSE	24 20	11.50 6.90 21 25.70 2.30 20	12.40 28.10	) 6.10 ) 1.80		i i	-0.14	[-0.72; 0.45] [-1.81; -0.47]	1.0% 0.9%
461 Ramirez-Ruiz 2008 MMSE	10	25.80 0.60 10	29.40	0.40	<sub>E</sub>		-6.76	[-9.26; -4.26]	0.1%
466 Santangelo 2007 MMSE	9	24.27 5.30 15	26.20	2.40			-0.48	[-1.32; 0.36]	0.7%
472 Sawada 2013 MMSE 473 Sawczak 2019 Moca	52 30	21.80 5.10 140 25.70 2.50 30	25.60	) 4.20 ) 2.30	1		-0.85	[-1.18; -0.52] [-0.84: 0.18]	1.3%
474 Schumacher-Schuh 2013 MMSE	54	23.74 4.99 151	25.25	3.36			-0.39	[-0.70; -0.08]	1.3%
482 Shin 2012 MMSE	50 46	25.20 3.00 64	25.20	2.90		<b>4</b>	-0.36	[-0.66; -0.04] [-0.55; 0.21]	1.3%
496 Shine 2013 Moca 498 Shine 2014 Moca	9 10	26.70 2.10 13 26.00 3.00 9	27.10	2.10	-	*	-0.18 -0.59	[-1.04; 0.67] [-1.52: 0.33]	0.7% 0.6%
502 Shine 2015a Moca	21	27.20 2.00 14	28.60	2.00	+	-	-0.68	[-1.38; 0.01]	0.8%
500 Shine 20150 MMSE 507 Stebbins 2004 MMSE	86 14	27.20 3.70 111 26.17 2.25 14	28.20	2.50	+	<b>1</b>	-0.32 -0.80	[-0.61; -0.04] [-1.57; -0.03]	1.3% 0.8%
508 Straughan 2015 MMSE 514 Thota 2017 MMSE	16 34	27.19 1.60 20 28.20 1.90 35	28.50	1.53	+		-0.82	[-1.51; -0.13] [-0.79: 0.16]	0.9%
519 Uchiyama 2015 MMSE	11	27.60 0.60 42	28.20	0.30	-	L	-1.56	[-2.30; -0.83]	0.8%
529 weintraub 2006 MMSE 530 Yao 2016 MMSE	21 12	28.40 1.80 62 27.42 4.82 15	28.30 29.00	1.50 1.64			0.06 -0.45	[-0.43; 0.56] [-1.22; 0.32]	1.1% 0.8%
534 Zhu 2013 SCOPA-COG Total	81	20.90 7.83 305	26.79	5.74	1		-0.94	[-1.20; -0.69]	1.3%
333 2111 2017 MIOCA	12	24.12 2.34 299	25.60	2.74			-0.56	[-0.83; -0.30]	1.3%
Overall effect Prediction interval	•					4	-0.56	[-0.66; -0.46] [-1.39: 0.271	100.0%
Heterogeneity: J <sup>2</sup> = 72% [66%; 77%], p < 0.01					-			,,	
					-0	0 D			

### b) Attention

Author	N	PD V Mean	Vith VH SD	N	PD Mean	No VH SD	Favours PD no VH	Favours PD with VH	g	95% CI	weight
66 Barrett 2017 Trails B-A raw score (time in s)	32	-56.50	41.20	67	-50.10	36.90	- •	_	-0.17	[-0.59; 0.26]	8.8%
100 Cho 2017 Brief test of attention	11	0.13	0.28	8	0.13	0.54		<u> </u>	0.00	[-0.91; 0.91]	5.2%
113 Cho 2017 Trails B-A raw score	11	-2.59	3.73	8	-0.31	1.55		_	-0.72	[-1.67; 0.23]	5.0%
133 Dauwan 2019 Trails B-A raw score (time in s)	16	-101.69	112.96	18	-74.13	58.16		_	-0.31	[-0.98; 0.37]	6.8%
174 Gallagher 2011 SCOPA-COG attention	30	3.75	0.14	64	4.00	0.20			-1.35	[-1.83; -0.88]	8.3%
207 Grossi 2011 RCPM (Raven Attention Matrices)	19	15.39	7.03	19	21.56	7.11			-0.85	[-1.52; -0.19]	6.9%
233 Hepp 2013 Trails B-A raw score (time in s)	31	-110.00	96.00	31	-72.00	665.00		<u> </u>	-0.08	[-0.58; 0.42]	8.2%
238 Hepp 2017 CAMCOG Attention	15	7.70	1.80	40	8.50	0.80			-0.68	[-1.29; -0.08]	7.3%
330 Lefebvre 2016 Trails B-A raw score (time in s)	18	-3.58	1.14	16	-2.48	0.64			-1.14	[-1.88; -0.41]	6.4%
348 Llebaria 2010 MDRS – Attention	21	35.06	1.50	28	34.50	2.00	_		0.31	[-0.26; 0.87]	7.6%
361 Llebaria 2010 PD-CRS - Sustained attention	21	6.19	3.40	28	7.50	2.30		-	-0.46	[-1.03; 0.12]	7.6%
365 Marsh 2004 MDRS – Attention	9	35.60	0.50	23	35.70	0.30			-0.27	[-1.04; 0.51]	6.1%
505 Shine 2015b Attention dysfunction score (PsycH–Q)	86	-6.80	4.40	111	-3.30	3.80			-0.86	[-1.15; -0.56]	9.7%
521 Uchiyama 2015 Trails B-A raw score (time in s)	11	-126.60	42.00	42	-88.00	13.00			-1.73	[-2.48; -0.99]	6.3%
Overall effect							<b>~</b>		-0.59	[-0.92; -0.27]	100.0%
Prediction interval								_		[-1.63; 0.45]	
Heterogeneity: $I^2 = 71\%$ [51%; 83%], $p < 0.01$										- · · -	
							-2 -1 0	) 1 2			

### c) Language

Author	N	PD Wi Mean	th VH SD	N	PD Mean	No VH SD	Favours PD no VH	Favours PD with VH	g	95% CI	weight
15 Barnes 2003 NART (National Adult Reading Test)	17	113.53	9.65	20	111.90	8.14	<del></del>		0.18	[-0.47; 0.83]	2.4%
34 Barnes 2008 Reading span	17	2.04	0.48	20	2.19	0.31		_	-0.37	[-1.02; 0.28]	2.3%
39 Barnes 2010 NART (National Adult Reading Test)	19	112.92	9.54	20	111.03	7.82			0.21	[-0.42; 0.84]	2.4%
58 Barrett 2017 COWA (Controlled Oral Word Association)	32	46.10	12.40	66	48.20	11.00		_	-0.18	[-0.60; 0.24]	3.6%
68 Barrett 2017 WTAR	33	110.40	10.60	68	111.10	9.70		<u> </u>	-0.07	[-0.49; 0.35]	3.6%
82 Boubert 2015 NART (National Adult Reading Test)	35	112.03	9.90	20	113.13	8.31			-0.12	[-0.67; 0.43]	2.8%
83 Boubert 2015 Reading span	35	2.16	0.63	20	2.98	0.51			-1.37	[–1.98; –0.76]	2.5%
99 Cho 2017 Boston Naming Test	11	0.42	0.83	8	0.66	0.67			-0.30	[-1.22; 0.62]	1.5%
117 Cho 2017 WTAR	11	113.30	9.15	8	116.25	8.28			-0.32	[-1.24; 0.60]	1.5%
145 Factor 2014 Boston Naming Test & Timed phonemic fluency	25	-0.10	0.97	96	0.02	0.82			-0.14	[-0.58; 0.30]	3.5%
184 Graham 1997 –early VH NART (National Adult Reading Test)– IQ	13	108.60	7.50	54	111.70	8.80		_	-0.36	[-0.97; 0.25]	2.5%
190 Graham 1997 – late VH NART (National Adult Reading Test) – IQ	11	108.30	6.10	42	110.90	8.70			-0.31	[-0.98; 0.36]	2.3%
216 Haeske-Dewick 1995 NART (National Adult Heading Test)	16	106.00	15.56	20	108.00	16.67		-	-0.12	[-0.78; 0.54]	2.3%
221 Hepp 2013 Boston Naming Test	31	121.00	46.00	31	111.00	42.00			0.22	[-0.28; 0.72]	3.1%
239 Hepp 2017 CAMCOG Language	15	26.30	2.60	40	27.80	2.30			-0.62	[-1.23; -0.02]	2.5%
255 Ibarrexte-Bilbao 2010 Boston Naming Test	12	48.80	6.40	14	52.50	5.00		-	-0.63	[-1.42; 0.16]	1.8%
263 Ibarrexte-Bilbao 2010 Token test	12	29.40	3.40	14	30.30	2.90			-0.28	[-1.05; 0.50]	1.9%
200 Kalzen 2010 Doston Naming Test	47	49.60	7.60	105	15.00	0.30		-	-0.06	[-0.41; 0.26]	4.1%
261 Katzen 2010 COWA (Controlled Oral Word Association)	47	14.20	0.40	105	105.00	4.90			-0.29	[-0.64; 0.05]	4.1%
231 Ratzen 2016 Rooton Naming Test	47	109.90	9.50	100	100.20	1.50			0.00	[ 1 00: 0 26]	4.1%
310 Lefebyre 2016 Boston Naming Test	10	20.22	3.77	16	20.88	1.57			-0.32	[-0.83: 0.52]	2.2%
360 Lebaria 2010 PD_CRS - Naming	21	18.00	1 68	28	18 20	1 70			-0.15	[-0.63: 0.52]	2.2/0
370 Marsh 2004 NABT (National Adult Beading Test)	11	109.30	10 10	25	111 10	11.30			-0.16	[-0.87: 0.55]	2.1%
394 Moustafa 2014 NART (National Adult Reading Test)	21	32.60	11.30	23	33.20	12 40			-0.05	[-0.64: 0.54]	2.6%
397 Muller 2017 COWA (Controlled Oral Word Association) – animals (z–score)	15	0.18	1.15	18	0.95	1.25		-	-0.62	[-1.33: 0.08]	2.1%
400 Muller 2017 COWA (Controlled Oral Word Association) – letters (z–score)	15	0.22	3.89	18	-0.01	3.37		·	0.06	[-0.62: 0.75]	2.2%
435 Ramirez-Ruiz 2006 Boston Naming Test	24	47.30	7.00	21	51.80	4.30			-0.75	[-1.36: -0.14]	2.5%
443 Ramirez-Ruiz 2006 Token test	24	27.80	4.40	21	30.60	2.80			-0.74	[-1.34: -0.13]	2.5%
449 Ramirez-Ruiz 2007 Boston Naming Test	20	46.80	7.20	20	51.70	4.30			-0.81	[-1.46; -0.16]	2.4%
456 Ramirez-Ruiz 2007 Token test	20	28.10	3.80	20	30.80	2.60			-0.81	[-1.46; -0.17]	2.4%
476 Shin 2012 Boston Naming Test	46	40.40	9.90	64	40.30	9.70		-	0.01	[-0.37; 0.39]	3.9%
478 Shin 2012 COWA (Controlled Oral Word Association) – phonemic generative naming	46	16.20	11.10	64	16.70	12.00		-	-0.04	[-0.42; 0.34]	3.9%
479 Shin 2012 COWA (Controlled Oral Word Association) – semantic generative naming	46	25.40	7.30	64	27.30	7.30		-	-0.26	[-0.64; 0.12]	3.9%
513 Thota 2017 Frontal Assessment Battery (FAB) – Lexical fluency	34	2.40	0.60	35	2.70	0.50			-0.54	[-1.02; -0.06]	3.2%
523 Uchiyama 2015 Verbal fluency – syllables	11	23.40	2.60	42	25.40	1.30			-1.20	[–1.91; –0.50]	2.1%
526 Uchiyama 2015 Western Aphasia Battery for language - Object naming	11	59.10	0.40	42	59.30	0.20			-0.78	[-1.46; -0.10]	2.2%
Overall effect							•		-0.27	[-0.40; -0.14]	100.0%
Prediction interval								-		[-0.84; 0.29]	
Heterogeneity: <i>I</i> <sup>2</sup> = 50% [27%; 66%], <i>p</i> < 0.01							-1 (	1			
							-1 (				

*Figure 3* - Results from multi-level meta-analysis with robust variance method correction (RVM) are shown in the forest plot for the domains of d) visual processing (and its subdomains shaded in grey), e) episodic memory, f) working memory and g) executive functions. Each forest plot shows the standardized mean difference estimate across measures in each sample (grey square) and its 95% CI (black horizontal line). The size of the grey square is proportional to the weight of each sample in the meta-analysis. The vertical dashed line and the black diamond show the weighted standardized mean difference in overall performance and its 95% CI, estimated in random-effects meta-analysis after RVE correction. Values < 0 and on the left side of the dotted vertical line reflect worse performance in PDP patients compared to PD noVH.

#### d) Visual processing

		PD noVH N Mean SD	PD VH N Mean SD	Favours PD noVH I Favours PD VH	
Acuity	B. Bejr-kasem 2019. Snellen charl – Log/AAR excity BI. Dederich 1988, Snellen charl – teacion 24. Firbank 2018, Bestein charl – teacion 24. Horizyd 2011. Visual acuity decimal 40. Horizyd 2011. Visual acuity 48. Koorts 2010. Visual acuity (ocn) 60. Matsui 2005. Visual acuity (locn) 60. Matsui 2005. Visual acuity (corrected) 60. Matsui 2005. Visual acuity (cardid) 62. Moppelink 2009. Snellen charl – fraction 79. Ramirez – Ruiz 2000. Visual acuity 90. Ramirez – Ruiz 2000. Visual acuity	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccc} 18 & 0.09 & 0.08 \\ 14 & 0.68 & 0.04 \\ 17 & 0.8 & 0.3 \\ 26 & 44.6 & 36.6 \\ 14 & 0.6 & 0.2 \\ 20 & 0.6 & 0.58 \\ 10 & 0.84 & 0.29 \\ 10 & 0.32 & 0.24 \\ 9 & 0.94 & 0.1 \\ 24 & 0.5 & 0.2 \\ 20 & 0.5 & 0.2 \\ 20 & 0.5 & 0.2 \\ 10 & 0.62 & 0.1 \\ \end{array}$		$\begin{array}{c} 0.87\% & -0.29 \left[ -100 & 0.41 \right] \\ 0.98\% & -0.24 \left[ -0.43 & 0.92 \right] \\ 0.91\% & -0.82 \left[ -1.50 & -0.14 \right] \\ 0.85\% & 0.55 \left[ 0.09 \right] & 1.00 \\ 0.92\% & -0.97 \left[ -1.75 & -0.19 \right] \\ 0.73\% & -0.54 \left[ -1.46 \right] & 0.37 \\ 0.73\% & -0.54 \left[ -1.46 \right] & 0.37 \\ 0.72\% & 0.25 \left[ -1.16 \right] & 0.65 \\ 0.72\% & 0.29 \left[ -0.55 \right] & 1.13 \\ 0.87\% & -0.49 \left[ -1.90 \right] & 0.10 \\ 0.88\% & -0.49 \left[ -1.12 \right] & 0.14 \\ 0.70\% & -0.48 \left[ -1.12 \right] & 0.41 \\ 0.70\% & -0.48 \left[ -1.12 \right] & 0.41 \\ 0.70\% & -0.48 \left[ -1.12 \right] & 0.41 \\ 0.70\% & -0.48 \left[ -1.12 \right] & 0.41 \\ \end{array}$
Dorsal stream	<ul> <li>4. Barnes 2003, VOSP Dot counting</li> <li>4. Barnes 2003, VOSP Number location</li> <li>4. Barnes 2003, VOSP Number location</li> <li>4. Barnes 2003, VOSP Number location</li> <li>6. Barnes 2010, VOSP Cube analysis</li> <li>6. Barnes 2010, VOSP Position discrimination</li> <li>6. Barnes 2010, VOSP Position discrimination</li> <li>7. Barnet 2017, VOSP Number location</li> <li>7. Barnet 2017, VOSP Number location</li> <li>7. Barnet 2016, RCFT (Rey-Osterrieth Complex Figure Test) – immediate copying</li> <li>12. Cho 2017, LOC (Benton Judgment of Line Orientation)</li> <li>12. Cho 2017, RCFT (Rey-Osterrieth Complex Figure Test) – immediate copying</li> <li>13. Chot 2017, LOC (Benton Judgment of Line Orientation)</li> <li>24. Fribank 2018, Motion test</li> <li>27. Gallagher 2011, BORB foreon/enal time of Line Orientation)</li> <li>24. Fribank 2011, BORB foreon/enal time 2011, BORB foreon/enal time of Line Orientation)</li> <li>25. Grossi 2011, Copying peometric dramping Figure Test) – immediate copying</li> <li>26. Grossi 2011, RCFT (Rey-Osterrieth Complex Figure Test) – immediate copying</li> <li>27. Gallagher 2011, BORB foreon/enald</li> <li>27. Gallagher 2011, BORB foreon/enald</li> <li>28. Grossi 2011, Copying peometric drawings</li> <li>29. Grossi 2011, RCFT (Rey-Osterrieth Complex Figure Test) – immediate copying</li> <li>48. Koerts 2010, VOSP Dot counting</li> <li>48. Koerts 2010, VOSP Dot counting</li> <li>49. Koerts 2010, VOSP Position discrimination</li> <li>49. Leftborz (Sci. L.U. (Benton Judgment of Line Orientation)</li> <li>41. Leftborz (Sci. L.U. (Benton Judgment of Line Orientation)</li> <li>42. Leftborz (Sci. L.U. (Benton Judgment of Line Orientation)</li> <li>43. Koerts 2010, VOSP Position discrimination</li> <li>44. Koerts 2010, VOSP Position discrimination</li> <li>45. Leftborz (Sci. L.U. (Benton Judgment of Line Orientation)</li> <li>46. Leftborz (Sci. L.U. (Benton Judgment of Line Orientation)</li> <li>47. Leibaita 2010, PD-CFRS - Clock copying</li> <li>48. Koerts 2010, VOSP Posteriti</li></ul>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Dorsal stream/ Ventral stream	4. Barnes 2003, WCBF Silincuettes 6. Barnes 2010, VCBF Progressive silincuettes 6. Barnes 2010, VCBF Votal 12, Cho 2017, VCBF Total 45, Katzen 2010, Hooper Visual Orientation Test 48, Koerts 2010, VCBF Progressive silincuettes 48, Koerts 2010, VCBF Silincuettes 50, Lichyama 2015, VCBF Silincuettes	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Imagery	4, Barnes 2003, Imagery Snapes 4, Barnes 2003, Imagery Luring non-visual 4, Barnes 2003, Imagery Luring non-visual 4, Barnes 2003, Imagery Non-living non-visual 4, Barnes 2003, Imagery Non-living visual 4, Barnes 2003, WIQ (vividness of Visual Imagery questionnaire) 89, Shine 2014, Imagery strength three	20 9.75 0.44 20 9.76 0.46 20 9.75 0.44 20 9.7 0.47 20 9.63 0.48 20 9.7 0.57 20 -35.25 10.9 9 48.4 5 20 0.57	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		1.03% -0.11[-0.75, 0.54] 1.03% 0.02[-0.62, 0.67] 1.02% 0.32[-0.33, 0.97] 1.03% 0.11[-0.53, 0.76] 1.02% 0.42[-0.23, 1.08] 1.03% -0.09[-0.74, 0.56] 0.02% 0.31[-0.34, 0.96] 0.66% 1.34[0.34, 2.33] 0.66% 1.05[2,72, 1.12]
Low level vision apperception	<ol> <li>Barnes 2010, VCSP Incomplete Network</li> <li>A, Fribank 2011, Parcikolian Inoise task</li> <li>Callagher 2011, BORB length match decision</li> <li>Callagher 2011, BORB inngth match decision</li> <li>Callagher 2011, BORB issue match (Birmingham Object Recognition Battery)</li> <li>Hopp 2013, Visual association test – number of objects</li> <li>Libarceto-Elibaz 2010, Visual Bornd Scientiniation test</li> <li>Kacht 2010, VGSP incomplete letters</li> <li>Nosho 2018, Overlapping figure test</li> <li>Ramirez-Ruiz 2006, Visual form discrimination test</li> <li>Shine 2015, Bistable percept paradigm (error score %)</li> <li>Shine 2015a, Bistable percept paradigm (error score %)</li> </ol>	$\begin{array}{c} \begin{array}{c} 2 \\ 2 \\ 0 \\ 8 \\ 1 \\ 1 \\ 1 \\ 2 \\ 2 \\ 2 \\ 1 \\ 2 \\ 2 \\ 2$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		$\begin{array}{c} -36\% & -127 [-15, -0.16]\\ 0.90\% & -127 [-15, -0.16]\\ 1.09\% & -120 [-1.66, -0.73]\\ 1.09\% & -120 [-1.66, -0.73]\\ 1.01\% & -3.22 [-3.85, -2.59]\\ 0.75\% & -1.83 [-2.33, -1.32]\\ 0.91\% & -0.56 [-1.70, -0.05]\\ 0.73\% & -0.79 [-0.43, 0.25]\\ 0.39\% & -0.56 [-1.31, 0.20]\\ 0.82\% & -0.14 [-1.70, -0.56]\\ 0.85\% & -0.92 [-0.43, 0.25]\\ 0.85\% & -0.92 [-0.43, 0.027]\\ 0.85\% & -0.92 [-0.43, 0.027]\\ 0.85\% & -0.92 [-1.57, -0.27]\\ 0.85\% & -0.22 [-0.88, 0.48]\\ 0.87\% & -0.20 [-0.88, 0.48]\\ 0.87\% & -0.23 [-0.81, -1.51] \end{array}$
Ventral stream	<ol> <li>resp. 2017, LARUCUS Perception</li> <li>A. Barnes 2030, VOSP Object decision</li> <li>B. Barnes 2010, VOSP Object decision</li> <li>B. Bejr-Assem 2018, Farnsworth-Munsal 100 hue test – color discrimination</li> <li>B. Bederich 1998, Lamforny D-15 total</li> <li>B. Dederich 1998, Lamforny D-15 total</li> <li>B. Dederich 1998, Lamforny D-15 total</li> <li>Callagher 2011, BORB association match</li> <li>A. Koerts 2011, VOSP Object decision</li> <li>G. Lohyama 2015, BORB object</li> <li>S. Lohyama 2015, BORB object</li> </ol>	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	┝╶╧╌╡╌╢╘╴╡ ┝╶╧╎╡╵┝╘╸┤ ┝╼╎┦╼╶╢╵┲╶╢	$\begin{array}{c} u.uvv & - u.01 \ [-1.21, - 0.01] \\ 0.83\% & - 2.11 \ [-2.92, - 1.31] \\ 0.84\% & - 2.98 \ [-3.89, -2.07] \\ 0.87\% & - 0.10 \ [-0.80, 0.60] \\ 0.96\% & - 0.85 \ [-1.56, - 0.15] \\ 0.95\% & - 1.14 \ [-1.86, -0.41] \\ 1.04\% & - 2.60 \ [-3.17, -2.03] \\ 0.99\% & - 3.59 \ [-4.26, -2.92] \\ 0.89\% & - 1.40 \ [-2.23, -0.57] \\ 0.93\% & - 0.72 \ [-1.40, -0.04] \\ 0.93\% & 0.00 \ [-0.66, 0.66] \\ \end{array}$
Visual contrast	Bej regi-rasem 2018, Pelli-Robosn test – Log contrast sensitivity     18, Diederich 1998, Pelli-Robosn test – Log contrast sensitivity     18, Diederich 1998, Vis tech (VT) CPD 1.5     18, Diederich 1998, Vis tech (VT) CPD 18     18, Diederich 1998, Vis tech (VT) CPD 18     19, Diederich 1998, Vis tech (VT) CPD 199     19, Diederich 1998, Vis tech (VT) CPD 199     19, Diederich 1998, Vis tech (VT) CPD 199     19, Diederich 1998, Vis tech 1998, Diederich		16         0.2           13         -1.55         0.2           13         5.15         0.6           13         5.15         0.6           13         5.17         1.4           13         2.69         1.7           13         5.62         0.1           13         5.62         0.1           13         4.69         1.1           15         0.39         0.2           18         175.17         124.12		0.87% 0.00 [-0.70, 0.70] 0.96% -0.26 [-0.45, 0.97] 0.95% -0.78 [-1.51, -0.05] 0.96% -0.48 [-1.20, 0.23] 0.94% -1.05 [-1.80, -0.30] 0.45% -0.68 [-1.41, 0.04] 0.75% 0.76 [-0.02, 1.50] 0.88% 0.76 [-0.20, -0.54] 100.00% -0.57 [-0.80, -0.34]

-4

-2 Observed out

### e) Episodic memory

	PD noVH N Mean SD	N	PD VH Mean	SD	Favours PD noVH   Favours PD VH	
3, Barnes 2001, Face Recognition Memory	23 32.2 5.4	21	28.5	4.6		0.85% -0.72 [-1.33, -0.11]
3, Barnes 2001, Words Recognition Memory 4, Barnes 2003, Face Recognition Memory	23 31.5 6.7	21	29.2 28.53	5.5 4.61		0.85% -0.37 [-0.96, 0.23] 0.80% -0.70 [-1.37, -0.04]
4, Barnes 2003, Words Recognition Memory	20 31.45 6.7	4 17	29.24	5.51	I I <u>I</u> → ₹ ₹ 1	0.81% -0.35 [-1.00, 0.30]
6, Barnes 2010, Recognition test – black and white conect 6, Barnes 2010, Recognition test – br-black and white	20 7.89 1.5 20 -0.46 0.1	7 19 5 19	-0.38	0.08	┌╼┐╎┤	1.08% 0.65 [ 0.00, 1.29]
6, Barnes 2010, Hecognition test – br–color 6, Barnes 2010, Recognition test – Color correct	20 -0.5 0.1 20 7.94 1.1	5 19 5 19	-0.48 7.75	0.16 1.68		1.10% 0.13 [-0.50, 0.75] 1.10% -0.13 [-0.76, 0.50]
6, Barnes 2010, Recognition test – false alarm black and white 6, Barnes 2010, Becognition test – false alarms color	20 -1.51 0.6	9 19	-3.22	1.09		0.97% -1.85 [-2.60, -1.10]
6, Barnes 2010, Recognition test – pr-black and white	20 0.45 0.2	1 19	0.3	0.13		1.07% -0.84 [-1.49, -0.18]
6, Barnes 2010, Recognition test – pr-color 6, Barnes 2010, Recognition test – spatial errors black and white	20 0.57 0.1 20 -3.27 0.8	2 19 4 19	0.52 -5.3	0.15		1.09% -0.36 [-0.99, 0.27] 0.92% -2.22 [-3.02, -1.42]
6, Barnes 2010, Recognition test – spatial errors color 7, Barrett 2017, HVIT–B delayed recall	20 -3.28 0.9	9 19	-4.08 40.8	1.38		1.08% -0.66 [-1.30, -0.01] 1.21% -0.07 [-0.49 0.34]
7, Barrett 2017, HVLT–R recognition	68 42 11.	3 33	45	12.6	· \ [==-	1.21% 0.25 [-0.17, 0.66]
7, Barrett 2017, HVLT-R total recall (Hopkins Verbal Learning Test-Revised)	68 42.1 14. 68 43.3 9.8	33	41.7 43.2	14.8		1.21% -0.01 [-0.43, 0.41]
<ol> <li>Chang 2016, RCFT (Rey–Osterrieth Complex Figure Test)– delayed copying</li> <li>Chang 2016, Word list learning recall</li> </ol>	23 11.96 9.1 23 19.19 3.7	9 12 5 12	7.71	6.76 3.66		0.77% -0.49 [-1.20, 0.22] 0.77% -0.52 [-1.23, 0.19]
12, Cho 2017, CALT (Conditional Associative Learning Test) – errors	8 -0.05 0.9	7 11	-0.82	1.94	┝┷╼ <sub>┇</sub> ┟┷┥ <sub>╸</sub> ╶╷	0.76% -0.46 [-1.38, 0.47]
12, Cho 2017, CVLT (total learning slope) – California Verbal Learning	8 -0.19 0.5	3 11	0.32	0.93		0.75% 0.62 [-0.32, 1.55]
12, Cho 2017, CVLI (total learning trials) – California Verbal Learning 12, Cho 2017, Face Recognition Memory	8 -0.08 1.2 8 -0.33 1.1	5 11 3 11	0.29 -0.5	1.1 1.51		0.77% -0.12 [-1.03, 0.79]
12, Cho 2017, FRT (Benton Facial Recognition Test) 12, Cho 2017, Words Recognition Memory	8 0.2 1.0	7 11	0.7	0.93		0.76% 0.48 [-0.44, 1.41] 0.75% 0.75 [-0.19, 1.69]
15, Creese 2018, BTACT Delayed recall	45 3.98 2.1	5 24	3.92	2.87		1.05% -0.02 [-0.52, 0.47]
15, Creese 2018, BTACT episodic memory combined 15, Creese 2018, BTACT Immediate recall	45 0.02 0.8 45 6.44 1.8	2 24 5 24	-0.01 6.38	1.21 2.89		1.05% -0.03 [-0.53, 0.46] 1.05% -0.03 [-0.52, 0.47]
23, ffytche 2017, HVLT (Hopkins Verbal Learning Test) Delayed recall 27, Gallagher 2011, SCOPA-COG memory	286 8.26 2.5	115	8.65	2.4		0.79% 0.16 [-0.06, 0.37] 0.71% -1.34 [-1.82, -0.87]
32, Graham 1997 –early VH, Pattern recognition memory	54 19.6 3.1	13	18.5	3.4		0.85% -0.34 [-0.95, 0.26]
32, Granam 1997 –early VH, Spatial recognition memory 33, Graham 1997 –late VH, Pattern recognition memory	54 14.2 2.6 41 19.6 2.6	13	13.4 17.9	2.5 3.6		0.85% -0.31 [-0.91, 0.30] 0.79% -0.59 [-1.27, 0.08]
33, Graham 1997 -late VH, Spatial recognition memory 34, Grossi 2005, Rev auditory 15-word learning test - Delayed free recall	40 14.4 2.8	11 14	12.9	2.8		0.79% -0.53 [-1.20, 0.15] 0.83% -0.23 [-0.86, 0.39]
34, Grossi 2005, Rey auditory 15-word learning test - Immediate free recall	34 35.51 7.4	5 14	29.93	8.51		0.82% -0.71 [-1.35, -0.07]
35, Grossi 2011, RCFT (Rey–Osterrieth Complex Figure Test)– delayed copying 35, Grossi 2011, Rey auditory 15–word learning test – Delayed free recall	19 4.89 3.7 19 5 3.3	19 3 19	2.69	2.67		0.89% -0.74 [-1.40, -0.09]
35, Grossi 2011, Rey auditory 15-word learning test - Immediate free recall 38, Hepp 2013, RCET (Rev-Osterrieth Complex Figure Test)- delayed conving	19 24.44 8.7	3 19	17.06	4.72	┝┼╼╌┨╵╸	0.88% -1.03 [-1.71, -0.35]
38, Hepp 2013, Rey auditory 15–word learning test – Delayed recall	31 7 3	31	6	3		1.16% -0.33 [-0.83, 0.17]
<ol> <li>Hepp 2013, Hey auditory 15–word learning test – Immediate free recall</li> <li>Hepp 2013, Rey auditory verbal learning test – false recognition words</li> </ol>	31 39 9 31 2 2	31 31	32 3	9 3		1.15% -0.77 [-1.28, -0.25] 1.16% 0.39 [-0.12, 0.89]
38, Hepp 2013, Rey auditory verbal learning test – recognition words 39, Hepp 2017, CAMCOG Memory	31 28 2	31	27	4		1.16% -0.31 [-0.81, 0.19] 0.84% -0.93 [-1.54 -0.31]
39, Hepp 2017, Pattern recognition memory test (correct responses)	40 20.5 2.8	15	20.7	3.2		0.85% 0.07 [-0.53, 0.66]
41, Ibarrexte-Bilbao 2008, Rey auditory 15-word learning test - Delayed free recall 41, Ibarrexte-Bilbao 2008, Rey auditory 15-word learning test - Immediate free recall	19 8.2 2.1 19 39.3 6.5	16	4.9 26.5	1.9 7.4		0.80% -1.60 [-2.37, -0.84] 0.79% -1.81 [-2.59, -1.02]
<ol> <li>Ibarrexte-Bilbao 2008, Rey auditory verbal learning test – recognition words</li> <li>Ibarrexte-Bilbao 2010, FRT (Benton Facial Recognition Test)</li> </ol>	19 12.9 2.2 14 49.42 4.4	16 12	12.4 43.7	1.8 4.6		0.87% -0.24 [-0.91, 0.43] 0.80% -1.23 [-2.07, -0.39]
42, Ibarrexte-Bilbao 2010, Rey auditory 15-word learning test - Delayed free recall	14 9 1.6	12	5	2	╷┝──╇─┼┤╴╹┊	0.70% -2.16 [-3.13, -1.19]
42, Ibarrexte-Bilbao 2010, Rey auditory verbal learning test – inimitate nee recail 42, Ibarrexte-Bilbao 2010, Rey auditory verbal learning test – recognition words	14 41.2 4.9	12	12.7	1.2		0.83% -0.71 [-1.50, 0.09]
<ol> <li>Harrexte-Bilbao 2010, Warrington recognition memory for faces</li> <li>Katzen 2010, CVLT (long-delay free recall) - California Verbal Learning</li> </ol>	14 28.6 3.9 105 7.2 3.5	12 47	30.9 6.6	5.4 3.1		0.84% 0.48 [-0.30, 1.26] 1.20% -0.18 [-0.52, 0.17]
45, Katzen 2010, CVLT (short-delay free recall) – California Verbal Learning	105 6.9 3.4	47	5.9	2.8		1.20% -0.31 [-0.65, 0.04]
54, Lefebvre 2016, HVLT-R recognition	16 11.69 0.4	5 47 3 18	33.6 11.5	0.79		0.88% -0.28 [-0.96, 0.40]
54, Lefebvre 2016, HVLT-R retention (%) 54, Lefebvre 2016, HVLT-R total recall (Hopkins Verbal Learning Test-Revised)	16 92.2 12.2 16 26.63 4 1	7 18	95.91 25.17	11.26 5.08		0.88% 0.31 [-0.37, 0.99] 0.88% -0.30 [-0.98, 0.37]
55, Lenka 2018, RCFT (Rey-Osterrieth Complex Figure Test) - Delayed recall	51 21.3 5.6	42	17.1	5.5	┢┶╾┧	1.29% -0.75 [-1.17, -0.33]
55, Lenka 2018, RCFT (Rey–Osterrieth Complex Figure Test) – Recognition	51 33.7 2	42	30.9	5.6	┟┼┳─┤╽	1.29% -0.69 [-1.11, -0.27]
55, Lenka 2018, Rey auditory 15-word learning test - Learning 55, Lenka 2018, Rey auditory 15-word learning test - Delayed free recall	51 49.3 10. 51 8.5 2.6	5 42 42	44.1 7.1	9 2		1.30% -0.52 [-0.94, -0.11] 1.29% -0.59 [-1.01, -0.17]
55, Lenka 2018, Rey auditory 15-word learning test - Immediate free recall	51 10.9 2.3	42	9.7	2.3	h <b>⊨</b> ∎,↓	1.30% -0.52 [-0.93, -0.10]
57, Llebaria 2010, PD-CRS – Delayed verbal memory	28 4.9 2.6	21	4.19	2.28	<b>⊢</b> ∎∔4	0.98% -0.28 [-0.85, 0.29]
57, Liebaria 2010, PD–CRS – Immediate verbal memory 59, Marsh 2004, MDRS – Memory	28 7.4 1.8 23 23.4 0.6	21	6.98 21.3	1.98 0.9		0.98% -0.22 [-0.79, 0.35] 0.48% -2.95 [-4.01, -1.90]
63, Meral 2007, Face Recognition Memory (Benton) 63, Meral 2007, Wechsler Memory Scale – Delayed recall	26 38.2 2.1	17	39.1	2.3	╵	0.92% 0.41 [-0.21, 1.02]
63, Meral 2007, Wechsler Memory Scale – immediate recall	26 6.25 0.9	17	4.8	0.9		0.86% -1.58 [-2.28, -0.88]
72, Ozer 2007, Face Recognition Memory (Benton)	18 9 8 30 40.43 9.1	15 3 33	10.5 40.03	11 4.61		1.05% -0.06 [-0.55, 0.44]
72, Ozer 2007, Wechsler Memory Scale – Delayed recall 72, Ozer 2007, Wechsler Memory Scale – immediate recall	30 5.68 3.8 30 7.73 3.7	3 33	2.68	2.3		1.03% -0.94 [-1.46, -0.42] 1.03% -0.86 [-1.38, -0.34]
76, Pereira 2013, Face Recognition Memory (Benton)	18 47.9 5.1	18	44.3	4.4		0.93% -0.74 [-1.41, -0.06]
76, Pereira 2013, Rey auditory 15–word learning test – Denyed nee recail 76, Pereira 2013, Rey auditory 15–word learning test – Immediate free recall	18 6.9 2.8 18 35.5 7.1	18	4.7 25.8	7.2		0.89% -1.33 [-2.05, -0.60]
<ol> <li>Pereira 2013, Rey auditory verbal learning test – recognition words</li> <li>Ramirez–Ruiz 2006, Face Recognition Memory (Benton)</li> </ol>	18 12.8 2.4 21 49 4.3	18 24	12.5 43.7	1.7 4.5		0.95% -0.14 [-0.80, 0.51] 1.02% -1.18 [-1.82, -0.55]
78, Ramirez-Ruiz 2006, Rey auditory 15-word learning test - Memory loss %	21 -3.7 4.4	24	-8.4	10.8		1.05% -0.55 [-1.14, 0.05]
78, Ramirez-Ruiz 2006, Rey auditory verbal learning test – laise tecognition words	21 12.8 2.1	24	12.5	2.3		1.06% -0.14 [-0.73, 0.45]
<ol> <li>Hamirez–Huiz 2006, Warrington recognition memory</li> <li>Ramirez–Ruiz 2007, Face Recognition Memory (Benton)</li> </ol>	21 33.5 6.5 20 49 4.2	24 20	31.1 43.3	5.6 4.4		1.06% -0.39 [-0.98, 0.20] 0.93% -1.30 [-1.98, -0.62]
79, Ramirez-Ruiz 2007, Rey auditory 15-word learning test - Memory loss %	20 -3.4 4.6	20	-6.8	9.3		0.98% -0.45 [-1.08, 0.17]
79, Ramirez-Ruiz 2007, Warrington recognition memory	20 33 6.3	20	31	5.6	ı∫ <del>⊢_∎ ∔</del> lı	0.98% -0.33 [-0.95, 0.30]
82, Santangelo 2007, Rey auditory 15-word learning test – Delayed free recall 82, Santangelo 2007, Rey auditory 15-word learning test – Immediate free recall	15 4.7 3.3 15 26.1 7.2	9	3.34 19.84	8.6		0.68% -0.44 [-1.28, 0.39] 0.67% -0.78 [-1.64, 0.07]
<ol> <li>Shin 2012, RCFT (Rey–Osterrieth Complex Figure Test)</li> <li>Shin 2012, RCFT (Rev–Osterrieth Complex Figure Test) – Delayed recall</li> </ol>	64 29.3 8.7 64 10.7 6.6	46	31.7	8.3		1.37% 0.28 [-0.10, 0.66] 1.36% -0.49 [-0.88 -0.11]
87, Shin 2012, RCFT (Rey-Osterrieth Complex Figure Test) - Immediate recall	64 10.1 6.2	46	8.2	5.3		1.37% -0.32 [-0.70, 0.06]
87, Shin 2012, Verbal memory – delayed recall	64 18.2 2.3 64 4.2 2.9	46 46	17.9 3.8	1.9 2.9		1.37% -0.14 [-0.52, 0.24]
<ol> <li>87, Shin 2012, Verbal memory – immediate recall</li> <li>87, Shin 2012, Verbal memory – recognition</li> </ol>	64 16.8 4.9 64 19.3 2.7	46 46	15.3 18.8	5.2 2.6 I		1.37% -0.30 [-0.68, 0.08] 1.37% -0.19 [-0.57, 0.19]
95, Uchiyama 2015, ADAS (Alzheimer's Disease Assessment Scale) – word recall 97, Yao 2016, Paired Associates Learning (PAL) – 1et trial memory score	42 20.8 0.3	11	17.4	1.2		0.41% -5.62 [-6.88, -4.36]
Overall effect (Random effects with RVE calculations)	13 12.0 4.7	12	10.0		'	100.00% =0.57[-0.70 -0.92]
					•	
				_8		
				5	Observed outcome	

### f) Working memory

		PD noVH			PD VH			
	Ν	Mean	SD	N	Mean	SD	Favours PD noVH   Favours PD VH	
5 Barnae 2008 2-back tack (% tales alarme)	20	11.6	0.00	47	10.0/	1 4 10	1 70% _0	37 [_1 02 0 28]
5, Barnes 2008, 2-back task (% hits)	20	79.4	2.20	17	70.07	E 00	172% -0	17[-0.82 0.48]
5. Barnes 2008, 2-back task (corrected hit rate of hits_false alarms)	20	61.8	67	17	50.52	8.2	171% -0	30 [=0.95, 0.35]
5 Barnes 2008, Digit shan	20	6 34	0.50	17	638	0.37	172% 0	08 [=0.57 0.72]
5 Barnes 2008 Word snan	20	4 56	0.33	17	4 4 2	0.07	1 70% -0	36[=1.01 0.29]
10 Boubert 2015, 2-back task (% false alarms)	20	-12.02	3.43	35	-16.35	3 5 95	2 12% -0/	82 [=1 39 =0 25]
10. Boubert 2015, 2 - back task (% hits)	20	7/ 88	7.88	35	65.06	10.18	2.09% -0.0	93 [=1 51 =0 36]
10. Boubert 2015, 2-back task (corrected hit rate of hits-false alarms)	20	62.43	6.23	35	49.63	7 64	180% -1	76 [-2 40, -1, 12]
10. Bouhert 2015. Digit span	20	6.74	0.62	35	5 74	0.74	193% -1/	41 [-2 02 -0 80]
10. Boubert 2015. Word span	20	4 79	0.3	35	4 1 4	0.71	2.05% -10	07 [-1.66, -0.49]
11 Chang 2016 Wechsler – Digit span	23	15.88	2 76	12	15.64	4.24	0.76% -0	07 [-0 77 0 63]
15 Creese 2018 BTACT 30 seconds and counting	45	37.8	9.5	24	38.42	10.4	2.38% 0	06 [-0.43 0.56]
15 Creese 2018 BTACT Digits backward	45	5.02	1.32	24	5.33	1.31	2 37% 0	23 [-0.26 0.73]
15. Creese 2018. BTACT Number series	45	3.33	1.02	24	3.33	1.01	2.38% 0	00 [-0.50, 0.50]
16. Dauwan 2019. Digit span forward	20	8.85	1.66	20	8.2	1.51	0.83% -0.	.40 [-1.03, 0.22]
32 Graham 1997 -early VH Digit ordering	54	61.9	23.6	13	47.4	24.8	0.84% -0	60[-1.22, 0.01]
33 Graham 1997 –late VH. Digit ordering	41	62.6	19.9	11	47 1	25.4	0.78% -0	72 [-1 40 -0.04]
38. Hepp 2013. Digit span forward	31	12	3	31	12	2	1.95% 0.	.00 [-0.50, 0.50]
38. Hepp 2013. Digit span index (DS backward/DS forward)	31	0.7	0.2	31	0.7	0.2	1.95% 0.	.00 [-0.50, 0.50]
39. Hepp 2017. Spatial span test	40	5	1.1	15	3.8	1.1	1.39% -1.0	08 [-1.70, -0.45]
39. Hepp 2017. Spatial working memory (between errors)	40	-35.8	20	15	-51	29.2	1.42% -0.0	66 [-1.26, -0.05]
43. Imamura 2008. Counting backwards	23	-11.7	42	11	-16.6	5.6	1.25% -1.0	02 [-1.78, -0.26]
43 Imamura 2008. Counting letters	23	-9.1	2.3	11	-12.2	3.1	122% -1	17 [-1.95 -0.40]
43. Imamura 2008. Digit span	23	12.3	3.2	11	11.7	1.8	1.34% -0.	.21 [-0.93. 0.51]
43. Imamura 2008. Months forwards	23	-6.7	1.6	11	-72	1.6	1.34% -0.	.31 [-1.03, 0.42]
45. Katzen 2010. Benton Visual Retention Test	105	9.9	2.8	47	8.8	3.2	4.63% -0.5	37 [-0.72, -0.03]
45. Katzen 2010. Digit span	105	15	4.2	47	14.2	5	4.65% -0.	.18 [-0.52. 0.17]
45. Katzen 2010, Paced Auditory Serial Addition Task (PASAT) – 3 s	105	32.9	9.5	47	28.8	13.3	4.63% -0.5	38 [-0.72, -0.03]
45. Katzen 2010. Paced Auditory Serial Addition Task (PASAT) - 5 s	105	36.2	9.5	47	28.1	13.3	4.52% -0.	75 [-1.10, -0.39]
54. Lefebyre 2016. Digit span backward	16	4.31	0.7	18	4 22	0.94	1.41% -0.	.11 [-0.78. 0.57]
54. Lefebvre 2016. Digit span forward	16	6.06	0.99	18	5.67	0.91	1.39% -0.	.40 [-1.08, 0.28]
54, Lefebvre 2016, Symbol Digit Modalities Test	16	48.38	9.74	18	41.39	12.05	1.37% -0.	.62 [-1.31, 0.07]
55. Lenka 2018. Corsi block tapping backward	51	3.9	0.6	42	3.6	0.6	3.50% -0.5	50 [-0.91, -0.08]
55. Lenka 2018. Corsi block tapping forward	51	4.7	0.7	42	4.3	0.2	3.43% -0.	74 [-1.16, -0.32]
55, Lenka 2018, Digit span backward	51	3.9	0.7	42	3.7	0.7	3.54% -0	.28 [-0.69, 0.13]
55, Lenka 2018, Digit span forward	51	5.1	0.9	42	47	1	3.52% -0.4	42 [-0.83, -0.01]
57, Llebaria 2010, PD-CRS - Working memory	28	3.8	2.1	21	3.38	1.5	0.88% -0.	.22 [-0.79, 0.35]
65, Moustafa 2014, Working memory - accuracy long delay	23	66.85	6.37	21	67.98	5.48	1.49% 0.	.19 [-0.41, 0.78]
65, Moustafa 2014, Working memory - accuracy short delay	23	77.24	6.91	21	78.32	7.65	1.49% 0.	.15 [-0.45, 0.74]
68, Nishio 2018, Digit span backward	53	3.9	0.8	19	3.8	1	2.35% -0.	.12 [-0.64, 0.41]
68, Nishio 2018, Digit span forward	53	5.5	1	19	5.4	0.8	2.35% -0.	.10 [-0.63, 0.42]
68, Nishio 2018, Tapping span backward	53	4.8	0.8	19	4.3	1	2.31% -0.5	58 [-1.11, -0.05]
68, Nishio 2018, Tapping span forward	53	5.6	0.9	19	4.8	0.8	2.24% -0.9	90 [-1.45, -0.36]
87, Shin 2012, Digit span backward	64	3.2	1.1	46	3.1	1.1	2.93% -0.	.09 [-0.47, 0.29]
87, Shin 2012, Digit span forward	64	5.5	1.3	46	5.8	1.2	2.93% 0.	.24 [-0.14, 0.62]
95, Uchiyama 2015, Wechsler – Digit span	42	12.4	0.4	11	11.6	1	1.08% -1.5	38 [-2.10, -0.67]
95, Uchiyama 2015, Wechsler - Spatial span	42	15.7	0.4	11	14.5	1	1.01% -2.0	07 [-2.85, -1.30]
97, Yao 2016, Delayed Matching to sample (DMS) - % correct all delay	15	71.1	3.6	12	61	4.9	0.71% -2.5	32 [-3.30, -1.34]
97, Yao 2016, Delayed Matching to sample (DMS) - % correct simultaneous	15	90	14.1	12	80	15.6	0.90% -0.	.66 [-1.44, 0.12]
Overall effect (Random effects with RVE calculations)							100.00% -0.4	47 [-0.71, -0.24]
							-4 -3 -2 -1 0 1	
							Observed outcome	

### g) Executive functions

	PD noVH N Mean SD	PD VH N Mean SD	Favours PD noVH 1 Favours PD VH	
4, Barnes 2003, FAS (Verbal fluency test) 5, Barnes 2008, Category fluency – % responses that were perseverations 5, Barnes 2008, Category fluency – o correct category expensions	20 39.3 9.69 20 -3.49 0.85	17 39.59 10.49 17 -4.55 1.14	<u> </u> ,+ <u>+</u> ++-1	0.43% 0.03 [-0.62, 0.6 0.89% -1.04 [-1.73, -0.3 0.92% 0.67 [-1.73, -0.3
5, Barnes 2008, Category fluency – n correct category exemplars 5, Barnes 2008, Go_NoGo accuracy	20 10.1 2.22 20 77.2 5.54	17 8.74 1.63 17 72.47 5.09	│ │ │ <del>│ ■ ■ ↓ │</del>	0.92% -0.67 [-1.34, -0.0 0.91% -0.87 [-1.54, -0.1
Barnes 2008, Stroop interference score	20 26.65 2.68 20 94.53 4.32	17 19.84 4.77		0.83% -1.15 [-1.85, -0.4
arrett 2017, Semantic fuency (animals) arrett 2017, WAIS–IV Matrix Reasoning	68 49 8.5 66 56.5 15.3	33 47.5 13.8 33 55.3 13.2		0.91% -0.14 [-0.56, 0.2 0.91% -0.08 [-0.50, 0.3
ubert 2015, Category fluency – % responses that were perseverations ubert 2015, Category fluency – n correct category exemplars	20 -4.19 0.8 20 9.13 2.68	35 -6.37 1.86 35 6.71 2.8		0.99% -1.37 [-1.98, -0.7 1.02% -0.87 [-1.44, -0.2
ubert 2015, Go_NoGo accuracy ubert 2015, Stroop colour-word raw – time	20 /9.52 6.14 20 -89.55 14.92	35 63.68 6.5 35 -128.34 17.38		0.88% -2.45 [-3.17, -1.7 0.90% -2.31 [-3.01, -1.6
ng 2016, Five-point test (correct number)	20 -27.74 6.03 23 4.57 2.92	35 -39.41 7.04 12 2.79 2.46	╵┝╼╄┾┲╌┥╷	0.96% -1.72 [-2.35, -1.0 0.90% -0.63 [-1.34, 0.0
3 2016, Stroop (errors)	23 10.12 7.11 23 -7.33 8.45	12 9.29 608 12 -7.92 9.09		0.91% -0.00[-0.70, 0.7 0.91% -0.07[-0.76, 0.6
.g 2016, Wisconsin card sorting test – category (number) 1g 2016, Wisconsin card sorting test – PN/total errors %	23 6 1.7 23 -72.8 31.4	12 5.21 2.12 12 -63 32.91		0.91% -0.42 [-1.12, 0.2 0.91% 0.30 [-0.40, 1.0
ng 2016, Word list generation 2017, D–KEFS Category fluency	23 44.21 11.29 8 -0.21 0.94	12 41 14.81 11 -0.06 1.06		0.91% -0.25 [-0.95, 0.4 0.64% 0.14 [-0.77, 1.0
2017, D-KEFS Letter fluency 2017, Stroop interference score	8 0.22 1.31 8 -0.12 0.44	11 0.28 1.05 11 -0.37 0.64		0.64% 0.05 [-0.86, 0.9 0.64% -0.42 [-1.34, 0.5
2 2017, VVT (Visual Verbal Test) – correct shifts ese 2018, BTACT Category fluency – n correct category exemplars	8 -1.63 1.53 45 22.49 6.44	11 -1.38 2.07 24 21 5.12		0.64% 0.13 [-0.78, 1.0 0.84% -0.24 [-0.74, 0.2
se 2018, BTACT executive function combined or 2014, Combined measures (TrailmakingB, Digit Symbol, Stroop, Wisconsin).	45 -0.03 0.6 96 0.11 0.77	24 -0.01 0.69 25 -0.14 0.64		0.84% 0.03 [-0.46, 0.5 0.47% -0.33 [-0.78, 0.1
e 2017, Letter Number Sequencing e 2017, Semantic fluency (all categories)	286 10.52 2.6 286 48.58 11.6	115 10.68 2.6 115 48.11 11.4		1.08% 0.06 [-0.16, 0.2 1.08% -0.04 [-0.26, 0.2
agher 2011, Frontal Assessment Battery (FAB) lagher 2011, SCOPA-COG executive	64 16.5 0.5 64 9.575 0.8057	30 14 1.17 30 7.12 1.03		0.73% -3.19 [-3.82, -2.5 0.75% -2.76 [-3.35, -2.1
nam 1997 –early VH, Letter fluency nam 1997 –early VH, Set-shifting	54 10.9 4.8 54 14.2 2.6	13 9.4 5 13 65 32		0.70% -0.31 [-0.91, 0.3 0.65% -2.80 [-3.57, -2.0
ham 1997 –late VH, Letter fluency ham 1997 –late VH, Set-shifting	42 12.2 3.9 41 7.6 2.6	11 8.7 2.7		0.68% -0.93 [-1.62, -0.2 0.69% -0.50 [-1.17 0.1
2005, Phonological fluency 2005, BCPM (Bayen Coloured Progressive Matrices)	34 31.57 7.49	14 23.81 8.31		0.83% -0.99 [-1.64, -0.3 0.84% -0.47 [-1.10 0.1
si 2005, Semantic fluency si 2011 Frontal Assessment Battery (FAB)	34 14.9 3.69	14 10.37 3.61		0.82% -1.21 [-1.88, -0.5 0.89% -1.24 [-1.93 -0.5
ssi 2011, Phonemic fluency	19 19.44 9.87	19 9.17 4.95	<u>⊮_</u> ∎_]	0.89% -1.29 -1.99, -0.5
ssi 2011, Semantic fluency (all categories) ssi 2011, Stroop colour-word raw – items	19 13.37 3.74	19 8.66 3.04	, <u>  + + + - 1</u> ]	0.88% -1.35 [-2.06, -0.6
sske-Dewick 1995, FAS (Verbal fluency test) 2016 Attentional Network Test (ANT) – Alerting Reaction Time	20 48 10	16 24.5 16.3		0.41% -1.75 [-2.52, -0.9
I 2016, Attentional Network Test (ANT) – Crienting Reduction Time	28 -1.3 60.82 28 -151.44 80.77	25 -0.86 60.82 25 -158.15 115.04	╵╵┟┼ <u></u> ┹┨╿	0.95% -0.07 [-0.61, 0.4
2010, Recentional receiver less (AIVI) - Orienting Reaction Time op 2013, Category fluency (animals) 2010, Semantic fluency (all categories)	28 -28.96 63.29 31 22 7	25 -38.74 61.8 31 21 7	Ĩ <mark>−</mark> ∎−Ĩ	1.00% -0.14 [-0.64, 0.3
p 2013, Stroop interference score (score part 3/score part 2) p 2013, Stroop interference score (score part 3/score part 2) p 2017, CAMCOG Abstract thisking	31 35 10 31 -1.9 0.6	31 33 11 31 -1.8 0.5	. I <sup>™</sup> <mark>┣</mark> ┋╋┥	1.00% 0.18 [-0.32, 0.6
pp 2017, CAMCOG Abstract trinking pp 2017, IED (intraextra dimensional set shift test)	40 6.6 1.4 40 7.5 2.5	15 6.2 1.4 15 6.2 3.4	╷╵┞╤╋╤╢╵╷	0.96% -0.28[-0.88, 0.3 0.96% -0.46[-1.06, 0.1
2017, Semantic fluency 2017, Vienna Perseveration Test (redundancy)	40 21.3 5.9 40 23.3 10.9	15 14.8 6.3 15 30 12.7		0.93% -1.07 [-1.69, -0.44 0.95% 0.58 [-0.02, 1.17
axte-Bilbao 2010, Phonetic fluency exte-Bilbao 2010, Semantic fluency	14 10 3.5 14 14.4 3.9	12 8.5 5.6 12 11.7 4.6		0.71% -0.32 [-1.09, 0.46 0.70% -0.62 [-1.41, 0.1
exte-Bilbao 2010, WAIS-III Similarities nura 2008, Category fluency – n correct category exemplars	14 13.4 6.9 23 18.6 5.6	12 13 4.7 11 12.5 4.1	┝─╼┼┫╹╴┤	0.71% -0.06 [-0.84, 0.7 0.81% -1.15 [-1.92, -0.3
nura 2008, Stroop (errors) nura 2008, Stroop colour raw – items	23 -0.1 0.4 23 60.1 12.8	11 -6.3 9 11 45.6 12	┞╤╼╤┦╷	0.80% -1.20 [-1.97, -0.43 0.81% -1.13 [-1.89, -0.36
nura 2008, Stroop colour-word raw - items nura 2008, Stroop word raw - items	23 33 12.5 23 78.7 15.4	11 21 13.1 11 61.3 14.6		0.82% -0.92 [-1.67, -0.1] 0.81% -1.12 [-1.89, -0.3
en 2010, FAS (Verbal fluency test) en 2010, Similarities (score)	105 34 12.6 105 20.9 6	47 32.7 13.8 47 20 6.6		1.35% -0.10 [-0.44, 0.24 1.35% -0.14 [-0.49, 0.26
n 2010, Symbol Digit Modalities Test n 2010, Wisconsin card sorting test – category (number)	105 28.4 12.4 105 4.1 2.4	47 24.2 11.9 47 22 23		1.35% -0.34 (-0.69, 0.00 1.34% -0.80 (-1.15, -0.4
n 2010, Wisconsin card sorting test – perseverative errors s 2010, Frontal Assessment Battery (FAB)	105 -4.6 5.8 14 14.6 2.6	47 –12.1 9.7 14 14.3 1.7		1.33% -1.03 [-1.40, -0.6] 0.41% -0.13 [-0.87, 0.6]
ovre 2016, Phonemic fluency ovre 2016, Stroop (errors)	16 14.75 3.57 16 -0.87 0.96	18 16.61 5.24 18 -2.78 3.17		0.80% 0.40 [-0.28, 1.0 0.78% -0.78 [-1.47, -0.0
vre 2016, Stroop interference score (score part 3/score part 2) a 2018 Frontal Assessment Battery (FAB)	16 -1.64 0.4 51 155 1.6	18 -1.79 0.3 42 14.5 2.1		0.80% -0.42 [-1.10, 0.2
semenescu 2011, Frontal Assessment Battery (FAB) aria 2010, MDBS – Conceptualization	74 16.2 1.6	26 15.8 2		0.47% -0.23 [-0.68, 0.2 0.99% -0.43 [-1.00, 0.1
aria 2010, MDRS – Initiation aria 2010, PD-CRS – Action Verbal fluency	28 33.3 5.1 28 10.9 3.6	21 30.3 6.18		0.98% -0.53 [-1.10, 0.0
paria 2010, PD-CRS – Alternating verbal fluency rsh 2004 MDBS – Concentualization	28 8.4 4.8	21 5.6 3.85	╷──└───	0.98% -0.62 [-1.20, -0.0 0.51% -1.82 [-2.71 -0.0
rsh 2004, MDRS – Initiation tsui 2005 Frontal Assessment Battery (FAB)	23 35.8 0.6	9 32.3 1.6		0.43% -3.51 [-4.66, -2.3 0.37% -0.51 [-1.42 0.4
appelink 2009, Frontal Assessment Battery (FAB)	14 16.8 1.5	9 15.7 1.8		0.39% -0.65 [-1.51, 0.2
eral 2007, Stroop (errors) eral 2007, Stroop (errors)	20 14.11 1.3 26 -3.5 1.1	17 -2.3 1.2		0.95% 1.03 [ 0.38, 1.6
and 2007, Wisconsin card sorting test – category (number)	26 2.56 0.6	17 -74.7 14.5 17 2.2 0.6	│ <u>│</u> │ │ │ │	0.97% -0.59 [-1.21, 0.0
argante 2012, Frontal Assessment Battery (FAB)	20 -38.4 9 312 15.6 2.5	25 14.9 3	¦ <u>⊦</u> ∓₁ <u></u> ⊤⊺	0.48% -0.28 [-0.68, 0.1
zer 2007, Stroop colour-word raw - time	30 -0.32 0.82 30 -20.36 9.99	33 -1.85 2.88 33 -41.54 37.59	<b>₽</b> ₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽₽	1.13% -0.74 [-1.26, -0.2
er 2007, verbal fluency – alternant category er 2007, Verbal fluency – category 2007, Verbal fluency – category	30 7.3 2.55 30 16.83 5.73	33 7.33 3.68 33 13.97 5.06	╵┝╼╪┱╷	1.14% U.U1 [-U.49, 0.5 1.13% -0.52 [-1.03, -0.0
zer 2007, wisconsin card sorting test – category (number) areira 2013, Phonemic fluency	30 2.79 2.24 18 9.6 3.4	33 2.61 2.25 18 7.8 4.7	<u> </u>	1.14% -0.08 [-0.57, 0.4 0.70% -0.43 [-1.09, 0.2
eira 2013, Semantic fluency mirez-Ruiz 2006, Phonological fluency	18 13 5.3 21 9.7 3.7	18 10.4 4.6 24 7.4 4.5	╷╠╤ <del>╸</del> ╤╡╢╹	0.70% -0.51 [-1.18, 0.1 0.88% -0.54 [-1.14, 0.0
amirez-Ruiz 2006, Semantic fluency (animals) amirez-Ruiz 2006, WAIS-III Similarities	21 13.3 4.7 21 12.7 6	24 9.4 4.5 24 11.7 4.8	┝╄ <mark>╋╤┧</mark> ╝┥	0.88% -0.83 [-1.44, -0.2 0.89% -0.18 [-0.77, 0.4
amirez-Ruiz 2007, Phonological fluency amirez-Ruiz 2007, Semantic fluency (animals)	20 9.4 3.6 20 12.9 4.5	20 7.9 4.5 20 10 4.6	│ <del>│↓</del> ∎= <u>↓</u> ┤↓	0.85% -0.36 -0.99, 0.3 0.85% -0.62 -1.26, 0.0
amirez-Ruiz 2007, WAIS-III Similarities antangelo 2007, Frontal Assessment Battery (FAB)	20 12.5 6.1 15 12.4 3	20 11.4 4.9 9 9.83 3.76		0.86% -0.19 -0.82, 0.4 0.72% -0.75 -1.61. 0.1
antangelo 2007, Go_NoGo (FAB) antangelo 2007, RCPM (Raven Coloured Progressive Matrices)	15 1.6 1.1 15 22.5 8.2	9 0.8 0.73 9 19.5 7.3		0.72% -0.79 [-1.64, 0.0 0.74% -0.37 [-1.20 0.4
ntangelo 2007, Phonological fluency ntangelo 2007, Semantic fluency	15 29.7 14.1 15 15.6 5.6	9 19.39 11.95 9 10.53 5.45		0.72% -0.75 [-1.60, 0. 0.72% -0.88 [-1.75 -0
in 2012, Contrasting programme	64 18.8 2.7 64 18.2 24	46 18.3 2.3		1.24% -0.20 [-0.58, 0. 1.24% -0.44 [-0.93 -0
in 2012, Stroop colour raw – time	64 -71.9 23.7	46 -59.8 31.1		1.24% 0.44 [ 0.06, 0.1
ine 2015a, Bistable percept paradigm –RT misperceptions	04 -107.3 11.8 14 -6.4 2	40 -104.2 18.2 21 -6.6 2	, <u>  <del> </del>  </u>	0.69% -0.10 [-0.77, 0.1
nine zu isa, sistable percept paradigm –H i single correct nota 2017, Frontal Assessment Battery (FAB)	14 -6.3 2 35 16.5 1.8	21 -6.7 2 34 13.9 2.2	┟╼╫╼┊╴╢	0.09% -0.20 [-0.87, 0. 1.06% -1.28 [-1.80, -0.
nota 2017, Frontal Assessment Battery (FAB) – Go_NoGo hota 2017, Frontal Assessment Battery (FAB) – Sensitivity to interference	35 2.7 0.6 35 2.7 0.6	34 1.7 0.8 34 2.1 0.7		1.06% -1.40 [-1.93, -0.8 1.09% -0.91 [-1.41, -0.4
nota 2017, Frontal Assessment Battery (FAB) – Similarities chiyama 2015, Frontal Assessment Battery (FAB)	35 2.6 0.6 42 16.6 0.2	34 2.6 0.5 11 15.4 0.4	┝───┤╷╵╷┞╪┤	1.11% 0.00 [-0.47, 0.4 0.46% -4.69 [-5.80, -3.5
Jchiyama 2015, Verbal fluency – category	42 16.6 0.7	11 14.8 1.4		0.56% -2.01 [-2.78, -1.2
all effect (Random effects with RVE calculations)			· · · · · · · · · · · · · · · · · · ·	100.00% -0.67 [-0.90, -0.4
			· • • ·	
			-6 -4 -2 0 2	
			Observed outcome	

### 3.3. Meta-regression analyses of sample characteristics

When looking at the meta-regression analyses, the difference in age (PDVH minus PDnoVH) was significant for the following domains – general cognition, working memory and executive functions (*Table 3*), indicating that group age-difference was associated with changes in performance in those domains. This can be partly explained by the fact that there is a significant difference in mean age between the PDVH and the PDnoVH groups. Further exploratory analyses showed no significant correlation between age and task performance in these three cognitive domains when looking at each group separately, but there was a trend indicating a decline in performance with older age (*Supplementary - eTable1*).

Finally, despite summary statistics showing significant group differences in average levodopa medication and illness duration (see *Table 1*), the meta-regression analysis showed no significant results with regards to these covariates across the 7 domains of interest. There was also no relation between difference in general cognition and task performance across domains, suggesting that deficits in the PDVH group in these domains are not related to generalised cognitive decline.

Domain	Model variables <sup>a</sup>	Beta	SE	P- value	t-value	CI (95%)	N studies (Sample size PDVH, PDnoVH)
	Age	-0.059	0.027	0.036*	-2.148	(-0.115 -0.004)	56 (1544, 3146)
General	Levodopa dose	0.0007	0.0007	0.302	1.040	(-0.0007, 0.002)	
cognition	Illness duration (y)	-0.047	0.039	0.238	-1.191	(-0.127, 0.032)	
	Illness severity <sup>b</sup>	0.004	0.014	0.798	0.256	(-0.024, 0.031)	
	M/F ratio (%)	-0.003	0.0005	0.539	-0.062	(-0.001, 0.0007)	
Fairedia	Age	-0.268	0.136	0.054	-1.963	(-0.541, 0.005)	23 (543, 961)
Episodic Memory	Levodopa dose	-0.001	0.001	0.369	-0.903	(-0.004, 0.002)	

*Table 3-* Meta-regression analyses of sample characteristics on task performance in each of the cognitive/visual domains. Illness duration is in years (y) and daily levodopa-equivalent dose in milligrams (mg)

	Illness duration (y)	0.118	0.145	0.420	0.811	(-0.173, 0.409)	
	Illness severity <sup>b</sup>	0.020	0.057	0.726	0.351	(-0.094, 0.134)	
	General cognition	-0.019	0.032	0.569	-0.572	(-0.084, 0.047)	
	M/F ratio (%)	0.0008	0.002	0.719	0.361	(-0.004, 0.005)	
	Age	-0.208	0.091	0.025*	-2.285	(-0.390, -0.026)	27 (614, 1044)
	Levodopa dose	-0.0009	0.001	0.391	-0.862	(-0.003, 0.001)	
Executive	Illness duration (y)	-0.005	0.081	0.947	-0.066	(-0.167, 0.156)	
functions	Illness severity <sup>b</sup>	0.024	0.041	0.548	0.604	(-0.057, 0.107)	
	General cognition	0.009	0.024	0.703	0.381	(-0.039, 0.058)	
	M/F ratio (%)	-0.0004	0.001	0.747	-0.323	(-0.003, 0.002)	
	Age	0.135	0.407	0.771	0.331	(-1.610, 1.888)	8 (141, 242)
	Levodopa dose	-0.002	0.006	0.751	-0.363	(-0.028, 0.023)	
	Illness duration (y)	0.002	0.308	0.995	0.006	(-1.326, 1.330)	
Attention	Illness severity <sup>b</sup>	-0.353	0.821	0.709	-0.429	(-3.887, 3.181)	
	General cognition	-0.231	0.599	0.736	-0.386	(-2.809, 2.346)	
	M/F ratio (%)	0.001	0.006	0.789	0.305	(-0.025, 0.029)	
	Age	0.009	0.068	0.886	0.145	(-0.133, 0.153)	16 (302, 472)
	Levodopa dose	-0.0008	0.0008	0.339	-0.983	(-0.002, 0.0009)	
Languaga	Illness duration (y)	-0.014	0.072	0.847	-0.195	(-0.165, 0.137)	
Language	Illness severity <sup>b</sup>	0.008	0.070	0.904	0.121	(-0.140, 0.157)	
	General cognition	0.002	0.024	0.933	0.084	(-0.048, 0.052)	
	M/F ratio (%)	-0.0008	0.0007	0.291	-1.087	(-0.002, 0.0008)	
	Age	-0.122	0.081	0.134	-1.512	(-0.283, 0.038)	25 (547, 893)
	Levodopa dose	-0.0006	0.001	0.581	-0.553	(-0.003, 0.002)	
Visual	Illness duration (y)	-0.024	0.070	0.730	-0.345	(-0.163, 0.115)	
processing	Illness severity <sup>b</sup>	-0.011	0.032	0.710	-0.372	(-0.075, 0.052)	
	General cognition	-0.022	0.081	0.787	-0.270	(-0.185, 0.141)	
	M/F ratio (%)	-0.001	0.001	0.403	-0.840	(-0.003, 0.001)	

Working memory	Age	-0.420	0.195	0.044*	-2.149	(-0.828, 0.012)	13 (271, 473)
	Levodopa dose	-0.001	0.001	0.416	-0.829	(-0.003, 0.001)	
	Illness duration (y)	0.105	0.121	0.395	0.867	(-0.148, 0.359)	
	Illness severity <sup>b</sup>	0.099	0.050	0.064	1.963	(-0.006, 0.204)	
	General cognition	0.003	0.019	0.858	0.181	(-0.036, 0.043)	
	M/F ratio (%)	-0.002	0.001	0.172	-1.417	(-0.005, 0.0009)	

 $^{a}$  = the difference in these values between the groups (PDVH minus PDnoVH).

 $^{b}$  = the difference in these values between the groups (PDVH minus PDnoVH), including values from both H&Y and UPDRS-III scales as absolute differences.

For the subgroup analyses in the visual processing domain (*Table 4*), significant group differences were found for the subdomain of low-level visual apperception (the formation of a coherent visual perceptual gestalt, impaired for example in the ability to recognise fragmented letters or incomplete figures) and ventral stream, but not for the other subdomains investigated.

*Table 4-* Meta-regression analyses of visual subdomains (after RVE correction) on task performance in the visual domain. Each of the tests that make up the different relevant subdomains can be found in the forest plot in Figure 3 d)

Domain	Subdomain variable	Beta	SE	P-value	t-value	CI (95%)	N studies (Sample size PDVH, PDnoVH)
Visual processing	Acuity	-0.221	0.202	0.283	-1.093	(-0.633, 0.191)	12 (192, 243)
	Dorsal stream	-0.151	0.219	0.496	-0.689	(-0.600, 0.297)	20 (542, 1000)
	Dorsal stream/Ventral stream	-0.656	0.413	0.122	-1.588	(-1.500, 0.187)	6 (119, 209)
	Imagery	0.502	0.295	0.098	1.703	(-0.100, 1.105)	2 (27, 29)
	Low level vision apperception	-0.928	0.274	0.002*	-3.384	(-1.488, -0.368)	15 (309, 468)
	Ventral stream	-1.067	0.434	0.020*	-2.455	(-1.954, -0.179)	8 (138, 235)
	Visual contrast	-0.086	0.365	0.815	-0.236	(-0.832, 0.659)	5 (73, 77)

### 3.4. Publication Bias and Risk of Bias Evaluation

For all domains, publication bias was examined via visual examination of funnel plots and also using Egger intercept. Indeed, Simmonds<sup>30</sup> and others<sup>31,32</sup> argue that correct identification of publication bias upon visual inspection of funnel plots alone can be limited, due to the subjectivity of the interpretation and thus the Egger intercept provided an additional quantitative measure. Publication bias by these methods was significant for all domains except for general cognition and attention. Risk of bias was evaluated according to the principles detailed in the Methods and the results can be found in the *Supplementary eFigure10*, where the weighted bar chart (summarising the distribution of risk of bias for all studies within the different bias domain) and the traffic light chart (showing domain-level judgements for each study) both show an overall main issue of missing data across studies, alongside some lack of appropriate matching between groups in disease severity and illness duration (for a more detailed commentary, see *Supplementary section 1.4 and Supplementary eFigure10*,).

### 4. Discussion

Cognitive and visual perceptual dysfunction associated with VHs in PD has been documented before, but never quantified on such a wide scale spanning different domains of cognition and visual processing. The ability to pool tests from different studies in a meta-analysis provides a perspective not available to individual studies.

In these seven meta-analyses comprising 99 studies and an overall 7826 patients, we found that those with PDVH perform worse on a wide range of visual and cognitive domains compared to patients with PDnoVH. While it was not possible to statistically compare the differences between effect size pertaining to different cognitive domains across separate meta-analyses, we note that the domains with the greatest group-difference effect size were executive function, attention, episodic memory and visual processing, with less of a group-difference effect size for language and working memory.

### 4.1. Covariate contributions to visual and cognitive functions

#### 4.1.1. Summary

We investigated relationships between a range of potential confounding factors and differences in cognitive and visual performance. In summary, our meta-regression results showed that study characteristics (namely gender, Levodopa-equivalent dose, illness duration and illness severity) were not significantly associated with observed between-group differences in the visual and cognitive domains of interest. The only effect was found for age, whereby age differences were significantly associated with performance differences in the domain of general cognition, working memory and executive functions.

### 4.1.2. Interpretation

General cognition (as measured by MMSE/MOCA) might be considered a proxy measure of neurodegeneration and the stage of progression from PD-Mild Cognitive Impairment to PD Dementia. Performance in all cognitive and visual domains is likely to be impaired in patients with lower general cognition scores through factors such as the ability to engage with the test, understand its requirements and sustain attention for its completion. The fact that in the meta-regression analyses, general cognitive score was *not* related to differences in performance between PDVH and PDnoVH across cognitive and visual perceptual domains indicates the deficits found cannot simply be accounted for by a non-specific effect of general cognitive decline.

It is also noteworthy that across all domains, lower performance in the PDVH group could not be explained by group differences in daily levodopa-equivalent medication. This does not exclude the possible interaction of dopaminergic medication and PD neurodegeneration in the mechanism of VHs but demonstrates that dopaminergic medication dose is not related to the difference in the degree of cognitive/visual deficit in the PDVH group. Similarly, variations in disease duration between groups did not explain the differences across the domains under investigation. The prevalence of VH in PD increases with longer PD duration<sup>33</sup> so that case-control studies selecting participants based on the presence of VH will be biased towards longer duration of PD (and potentially also higher levodopa-equivalent doses) unless this is specifically considered in the study design. What our results suggest is that differences in disease duration does not account by itself for the cognitive/visual deficts through non-specific factors such as those suggested for general cognition. Finally, age difference was found to be associated with the degree of deficit in general cognition, episodic memory, and executive functions. This finding could reflect either disease-specific processes related to age (or age at PD onset), which was not evaluable in the meta-analyses, or a greater dependence of performance in these domains on age.

### 4.2. Visual domains

Focusing on the visual domains studied, the results show a variability in visual impairments (See *Figure* 3.d) with significant subdomain differences in performance for low-level vision-apperception and ventral stream.

The observed dysfunction in these domains implies dysfunction in the lateral occipital lobe and ventral-occipito-temporal cortex, with a relative sparing of the visual parietal lobe. Why this pattern of dysfunction should occur in PDVH is unclear. One possibility is that it reflects the distribution of modulatory cholinergic and serotonergic inputs to visual processing thought to be disrupted in PDVH<sup>6</sup>. Functional activation of the lateral visual cortex is modulated by cholinesterase inhibitors<sup>34</sup> suggesting a link to the cholinergic system, while 5-HT2A receptor

upregulation has been found in the inferior occipital cortex<sup>35</sup>. Firbank and colleagues<sup>36</sup> described a reduced GABA-spectroscopy signal in the occipital lobe and this may be related to the performance deficits described. In the few studies that have examined neuropathological changes in the visual cortex of patients with visual hallucinations in PD, Lewy body and tau pathologies have been found to be absent, and amyloid burden rated as mild<sup>37</sup>. Notably, an early study of PD patients with visual hallucinations and MMSE >25 (equivalent to the average MMSE in this study) found increased Lewy body load in the basolateral nucleus of the amygdala but only sparse Lewy bodies in the cortex and hippocampus<sup>38</sup>. It thus seems unlikely the visual performance deficits identified here reflect localised neuropathology in the occipital lobe, supporting the view that they reflect wider functional network changes related to neurotransmitter systems.

Patients with PDVH have reduced retinal nerve fibre layer thickness<sup>39</sup>, while in PD more generally, a reduction in thickness of retinal layers with dopaminergic A18 amacrine cells has been found (inner nuclear layer, INL) <sup>39</sup>. These retinal changes might account for visual acuity, spatial contrast sensitivity, and colour discrimination deficits in PD<sup>40</sup>. Poor visual acuity might be a factor in developing VHs in PD<sup>16</sup>, highlighting similarities with VHs in eye disease (Charles Bonnet syndrome<sup>41</sup>) and thought to depend upon de-afferentation of the visual cortex<sup>42</sup>. However, differences in acuity and contrast sensitivity were not significant between groups in the meta-regression, suggesting impaired vision related to eye dysfunction is not directly implicated in the mechanism of VHs in PD in these studies.

### 4.3. Cognitive domains

When looking at the results from general cognitive ability and from the other five domains investigated (*Figure 2* a to c and *Figure 3* e to g) we see that there is some variability in the performance of the PDVH group, with greater group-differences in some domains, such as

executive function, compared to others. A common idea among different theoretical models of PDVH, such as the Perception-Attention-Deficit (PAD)<sup>20</sup> and Shine's Attentional network dysfunction<sup>21</sup> (more details in Supplementary section 1.7), is that hallucinations might result from a disruption in the processing of information across attentional networks (with the implication of dorsal, ventral attentional and default-mode networks). These networks, and the 'Attention' component in the PAD model, do not map to specific neuropsychological tests but our results are broadly in line with these model predictions. In particular, we found that both the attention and the executive function domains, considered part of attention in the PAD model, had the greatest group-difference effect sizes, with PDVH patients performing worse than the PDnoVH ones across these tasks. How these cognitive differences relate to neurotransmitters activity and to the underlying structural and functional dysfunction in PDVH has still not been fully determined. However, our results are in accordance with what we know from neuroimaging findings on the greater atrophy in PDVH patients across frontal and parietal cortices<sup>6</sup>. Furthermore, it is important to note that these results were not explainable by overall group differences in general cognition, as shown by the meta-regression analyses in Table 3.

We also found that patients with hallucinations performed worse than PDnoVH on memory and language tasks, domains that were not thought to be linked to changes in VH prevalence across neurodegenerative diseases in the PAD model<sup>20</sup>. Interestingly, the memory group-effect was greater for episodic memory tasks compared to working memory ones. This pattern of findings might speculatively reflect the presence of greater hippocampal pathology in the PDVH group<sup>43</sup>, although given the widespread network and neurotransmitter dysfunction<sup>44,45</sup> in PDVH it is not possible to specify what might have contributed the most to deficits in this domain. Finally, we found a group difference in the language domain, with PDVH once again performing worse than the PDnoVH group. It is difficult to understand exactly why PDVH patients showed impairments in language, but this result could be driven by the fact that the tests that were included in this domain related to naming, word association and premorbid IQ (NART), thus containing a mixture of language-related cognitive domains, although no single one appeared to be driving the observed impairment in the hallucinating group.

### 4.4. Implications for models of visual hallucinations in PD

According to the PAD model proposed for Lewy-body dementia (LBD), hallucinations relate to dysfunction of cholinergic mechanisms regulating the interaction of bottom-up and topdown mechanisms in the process of encoding uncertainty <sup>20,46</sup>. In this view, there could be a dysfunction in the ventral visual stream, with the temporal lobe being affected by alphasynuclein pathology in LBD and dysfunctional cholinergic signalling to occipital regions<sup>47</sup>. This model fits well with our results regarding both the ventral visual and the executive domains which suggests it applies more widely across Lewy body disorders, including PD in its early stages. As noted above, other models argue for altered regulation of the dorsal and ventral attentional system and their interaction with the default mode network and salience network<sup>21,48,49</sup>. Although specific tests of these functions are not included in the battery of cognitive tests typically performed, the general deficits of attention found are consistent with this view.

An important contribution of the meta-analysis is the suggestion that deficits in memory and language need to be incorporated into current theories of PDVH. Our findings tell us that memory and language deficits are associated with PDVH, but they do not reveal if a) they contribute to the formation of hallucinations, or b) they are a result of experiencing hallucinations, or c) they might be an epi-phenomenon associated with the pathology in the PDVH group. Memory deficits, in particular those of episodic memory, can be accommodated within existing models as they are likely to be linked to the hippocampal deficits found in PDVH and could be considered part of the default mode network that is already included. How language deficts fit into existing models is more difficult to determine. Further consideration should be paid to this domain in future research to understand its contribution to PDVH.

### 4.5. Clinical implications

Our current work indicates that a broader range of cognitive and visual domains are affected in PDVH than previously suspected. There may therefore not be a specific visuo-cognitive profile of PD patients at risk of VHs detectable by standard neuropsychological tests. Based on current findings, tests focussing on the ventral visual stream, apperception, attention and executive function may best discriminate those at risk of VHs. The findings may help direct research to earlier stages of PD to better understand the first cognitive changes in patients that go on to develop VHs. A better understanding of the temporal evolution of these cognitivevisual deficits might help a) predict who is at-risk and b) develop interventions to mitigate later poor cognitive outcomes, such as dementia.

### 4.6. Strengths and Limitations

To our knowledge, this is the first meta-analysis comparing the cognitive and visual profile of both PDVH and PDnoVH patients, allowing a breadth of coverage not possible in individual studies. We have included data from around 7826 patients (2508 with PDVH) and this gave us a substantial increase in statistical power for detecting small group differences compared to previous work. Finally, we successfully examined the effects of various important clinical and demographic factors on PDVH. The limitations include high between-study heterogeneity, driven by both between-study differences and within-study heterogeneity, indicating additional sources of noise from the original studies (e.g. sampling biases). Another limitation is that while we were able to group tasks by cognitive domain, none of the tests can be considered pure measures of a given domain and thus our labels at best reflect an important component of the tests included, with substantial overlap between domains. Nonetheless, our grouping approach allowed us to increase power and combine more conservative and robust checks to limit Type I errors. The ability to describe deficits with greater statistical power in meta-analyses of cognition does not extend to understanding what the impact of these deficits are in the day-to-day life of the patients. An important future goal is to understand the link between these deficits ranging from small to moderate effect sizes (0.27 to 0.57) in the daily functioning of patients with PDVH. Finally, medication other than dopamine-replacement therapy was not included in the analysis. Treatment for VHs with atypical-antipsychotics and cholinesterase-inhibitors may therefore have had a significant impact on general cognition or on individual domains and was not accounted for in the analysis. Similarly, exploratory and confirmatory cluster analysis of a large PD dataset has revealed associations between non-tremor-dominant PD and psychopathology, including hallucinations and cognitive impairment<sup>50</sup> but we were unable to examine this factor as the PD subtype was not described for most of the studies.

### 4.7. Conclusion

We conclude that a broad range of cognitive and visual processing deficits are associated with PDVH that do not seem to be explained by overall cognitive decline, dopaminergic medication or duration of illness. Overall, we suggest that current models and theories of VHs in PD need to be updated or developed to accommodate a wider spectrum of cognitive domains than previously suspected.

### **Article information**

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