DOI:
10.1016/j.cortex.2021.11.001

Document Version
Peer reviewed version

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, online-only 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. Effect-sizes (Hedges' g) were calculated for all comparisons and synthesized in random-effects meta-analyses 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 between-group 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[1], an estimate that is likely to rise with increased longevity in the world population [2,3] . Despite motor symptoms being characteristic features of this disorder, non-motor symptoms are also recognised[4]. These include sleep behaviour disorders[5], dementia[4] and PD psychosis[6]. These non-motor symptoms adversely and substantially impact patients' and carers' quality of life[7].

PD psychosis (PDP)[8] refers to a spectrum of symptoms that can affect around half of patients with PD[9] 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[10] for rates of multimodal hallucinations). For an overview of their clinical presentation and progression see work by ffytche and colleagues[6]. The presence of hallucinations in PD has been identified as a significant predictor of dementia and has been associated with steeper cognitive decline[11] , especially in those with pre-existent dementia[12]. 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[13], sustained attention[14] and visuo-perceptual functions[15,16]. 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[17]), although there are some studies suggesting that they are present (see [18] and [19]). To date, memory deficits are not incorporated in models of VH in PD (such as the PAD model[20] or the attentional networks dysfunction model[21]). 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 (https://osf.io/zu7kp/) 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 co-

authors. 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,[22] 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[23] 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[24]. 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[25] and then applied robust-variance-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[26]. Participants are described at the first level, within-study variance at the second, and between-study variance at the third[27].

Heterogeneity was assessed using both the τ^2 test and the Higgins and Thompson I^2 statistic. Publication bias was checked via funnel plots and Egger's tests. We ran random-effects meta-analytic models with DerSimonian-Laird estimator for τ^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[28]).

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*), 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[29].

* 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.

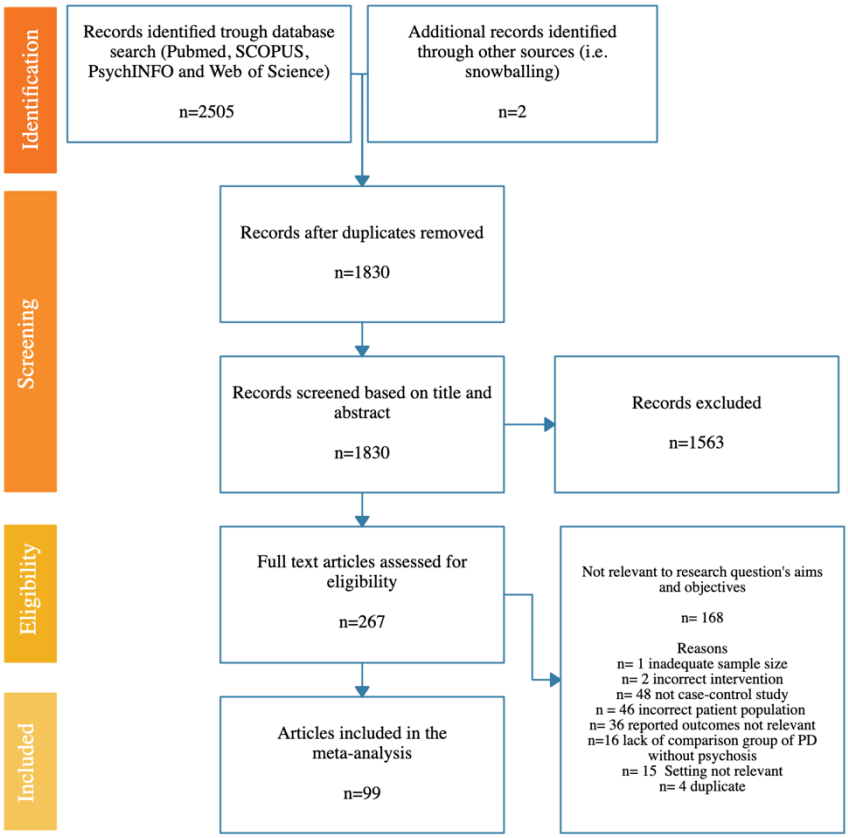


Figure 1- PRISMA flowchart of study selection

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

Variable	**PD noVH (overall N= 5318)**		**PD VH (overall 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.

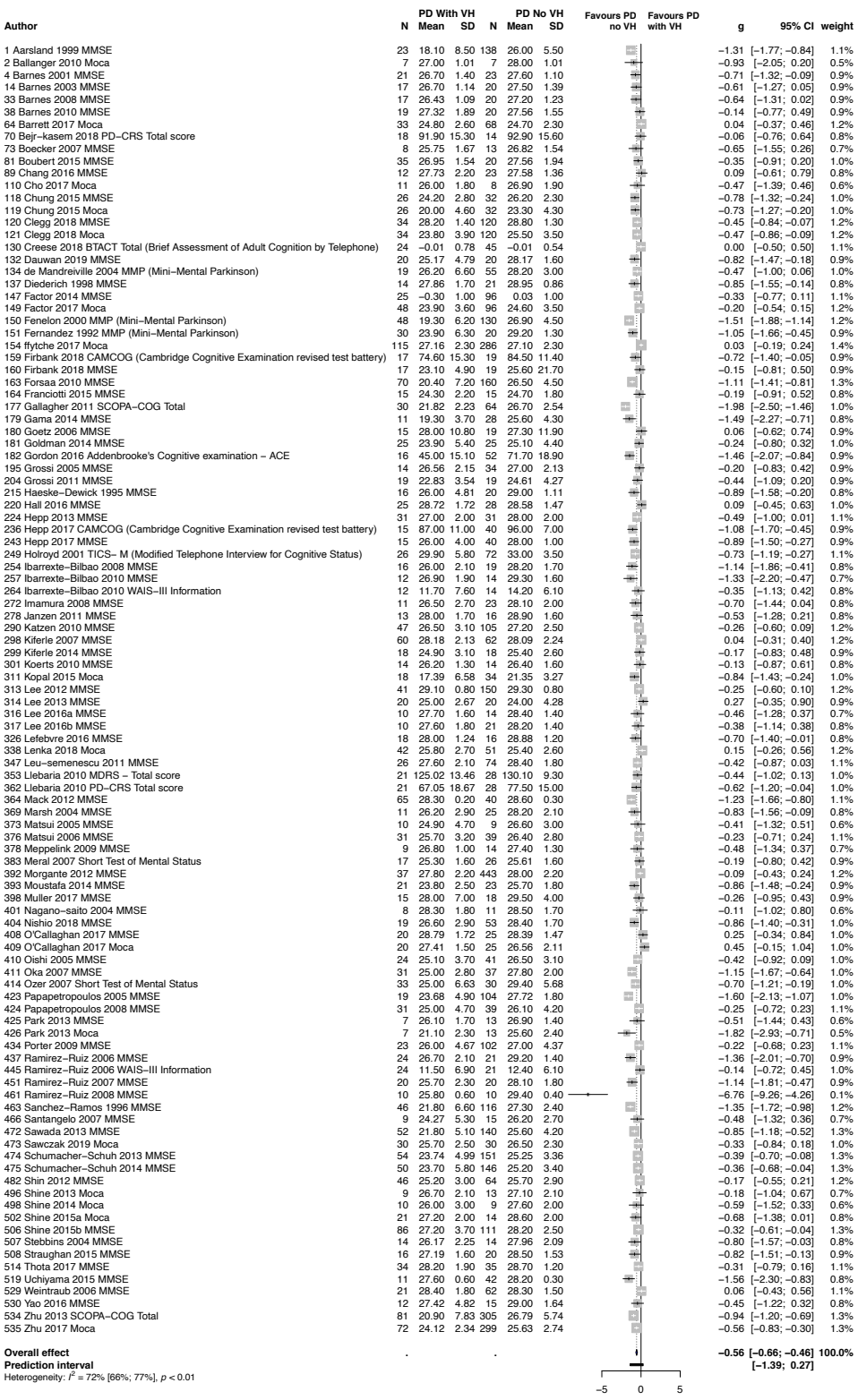
Table 2- Comparison of effect sizes (negative means favouring PDnoVH, positive favours PDVH) ordered from greatest to smallest.

	g (95%CI), p-value	**I^2 (95 %)**	**N studies (Sample size PDVH, PDnoVH)**	**Type**
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

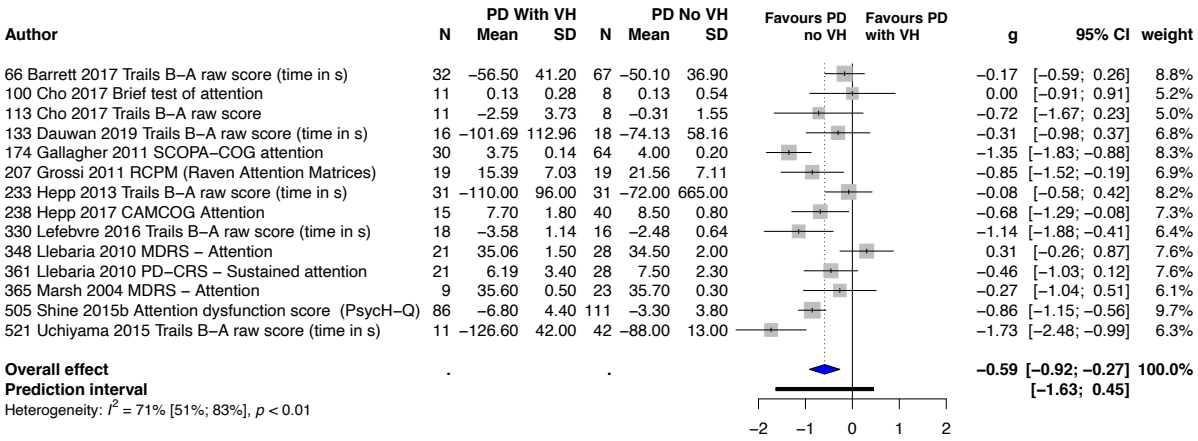
g = Hedges' g; I^2 = Heterogeneity measure; BS = Between-studies; WC= Within-studies; SEV= Sampling error variance

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



b) Attention



c) Language

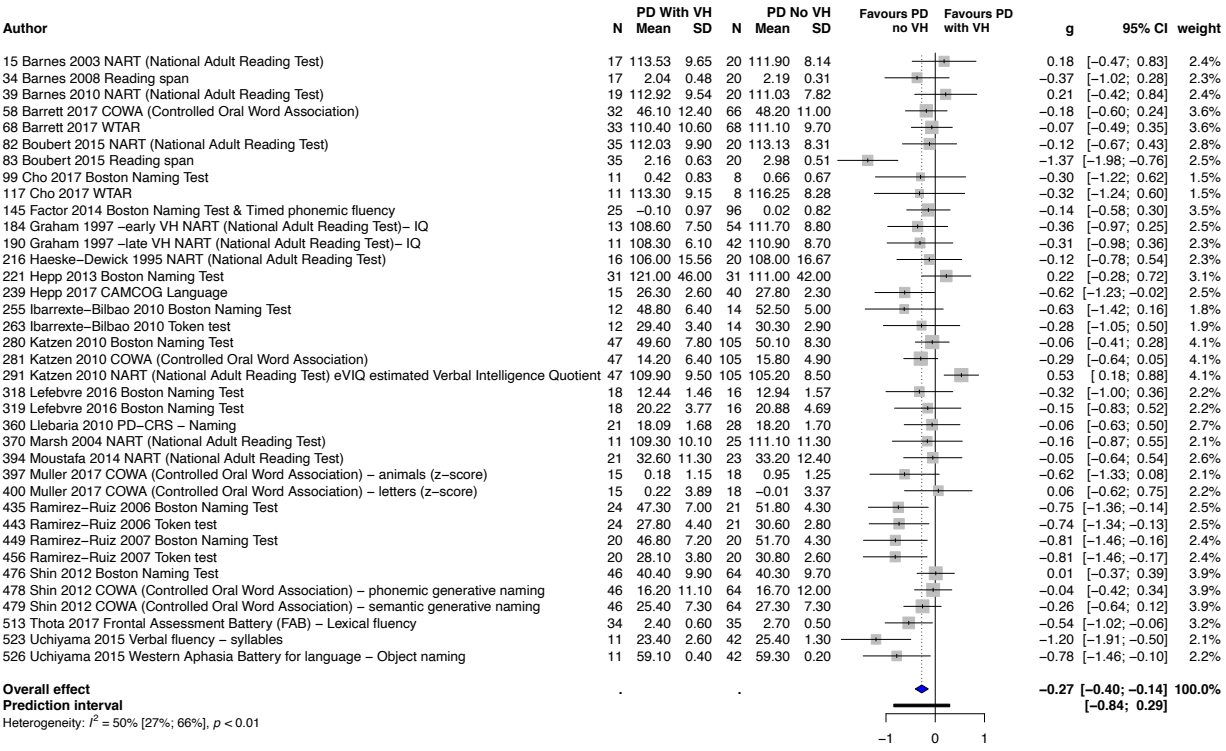
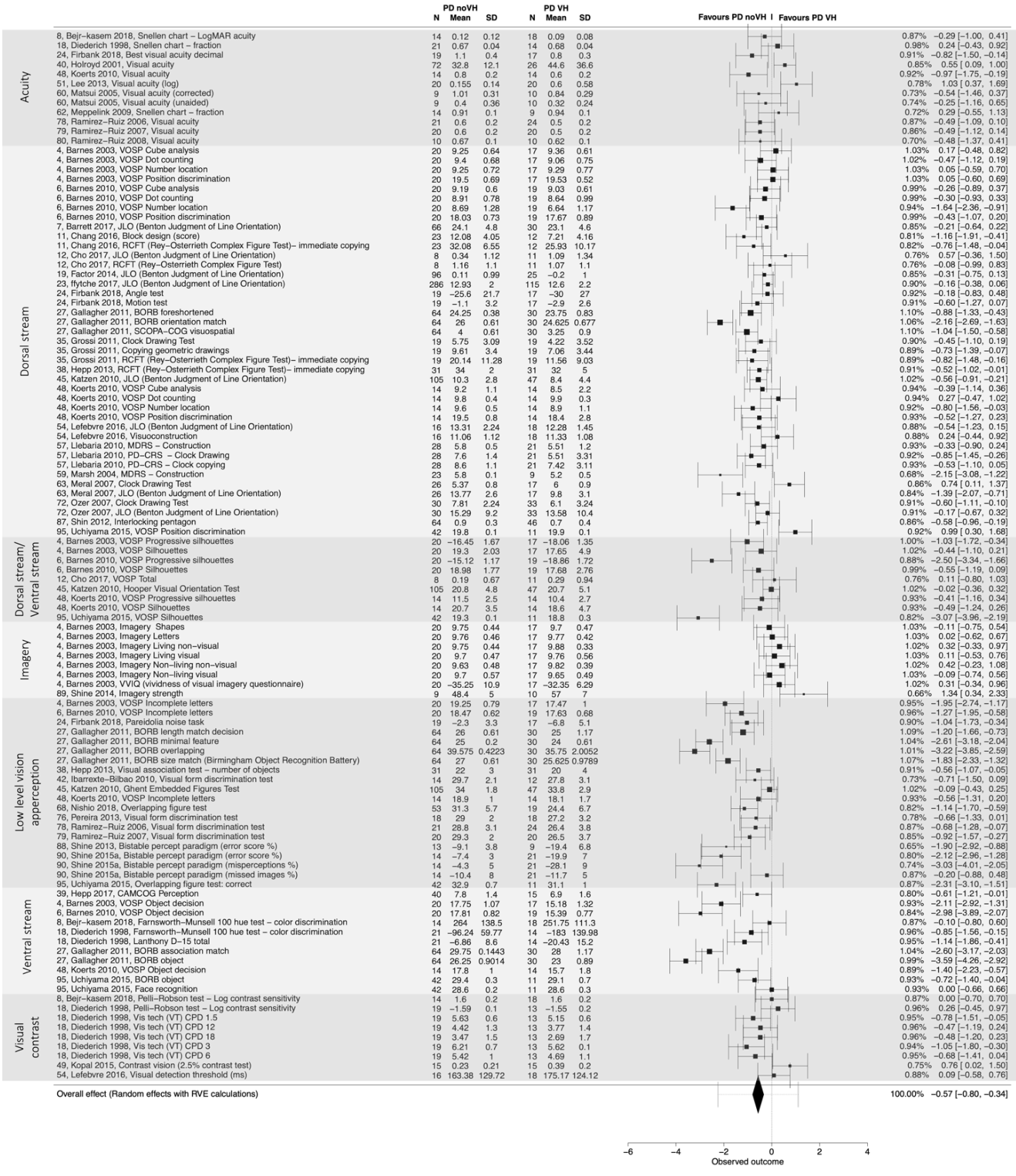
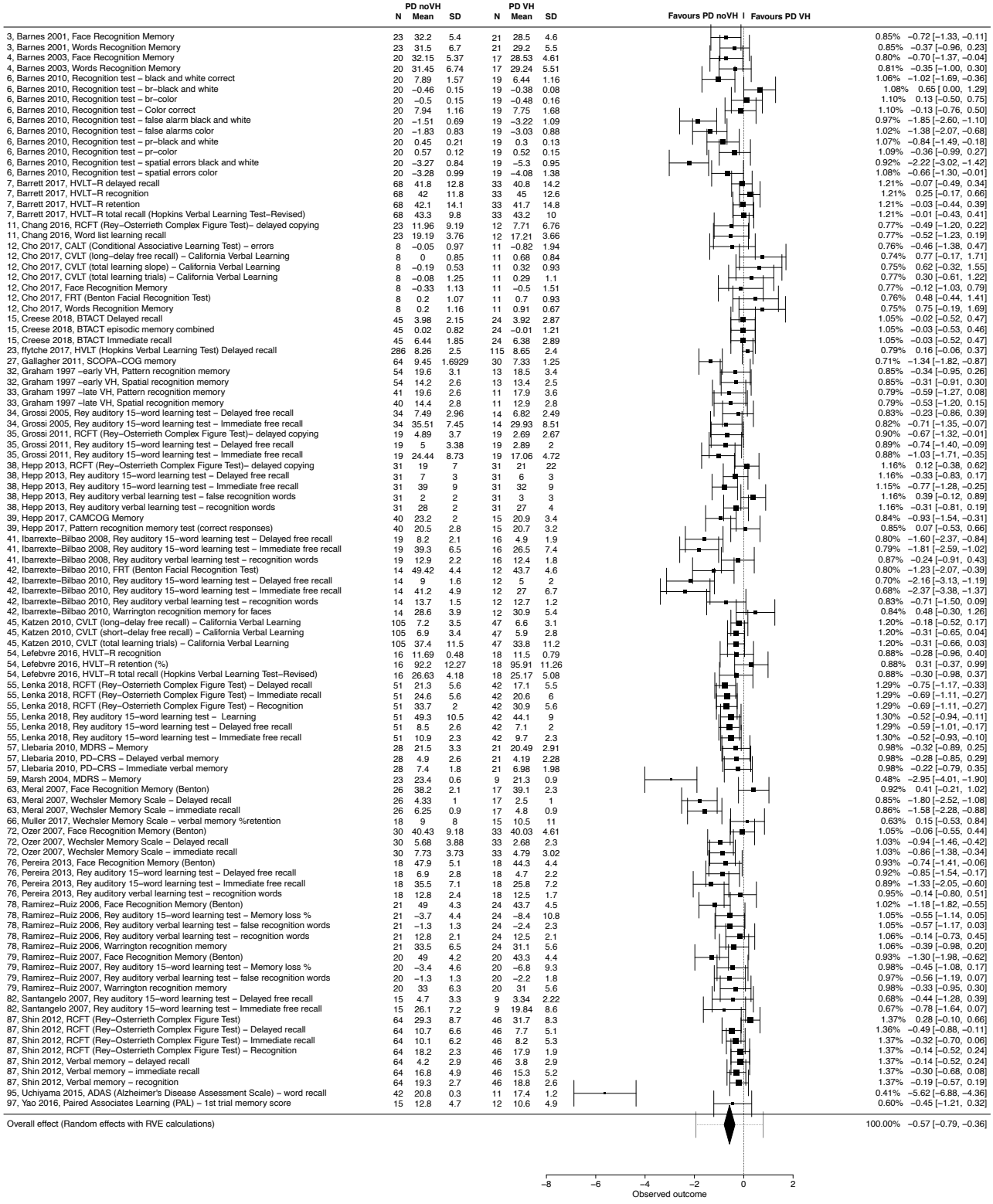


Figure 3 - Results from multi-level meta-analysis with robust variance method correction (RVM) are shown in the forest plot for the domains of d) visual processing (and its subdomains shaded in grey), e) episodic memory, f) working memory and g) executive functions. Each forest plot shows the standardized 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.

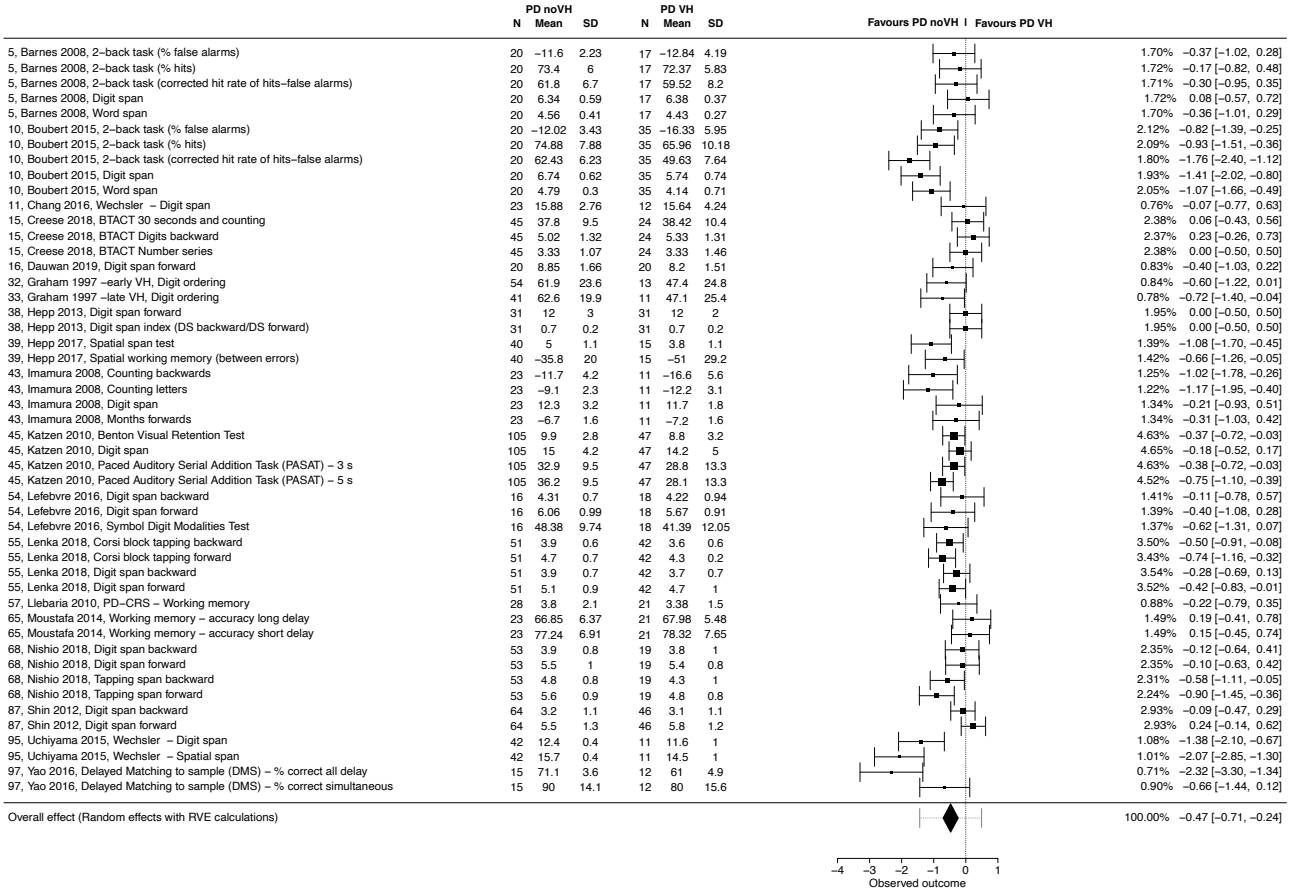
d) Visual processing



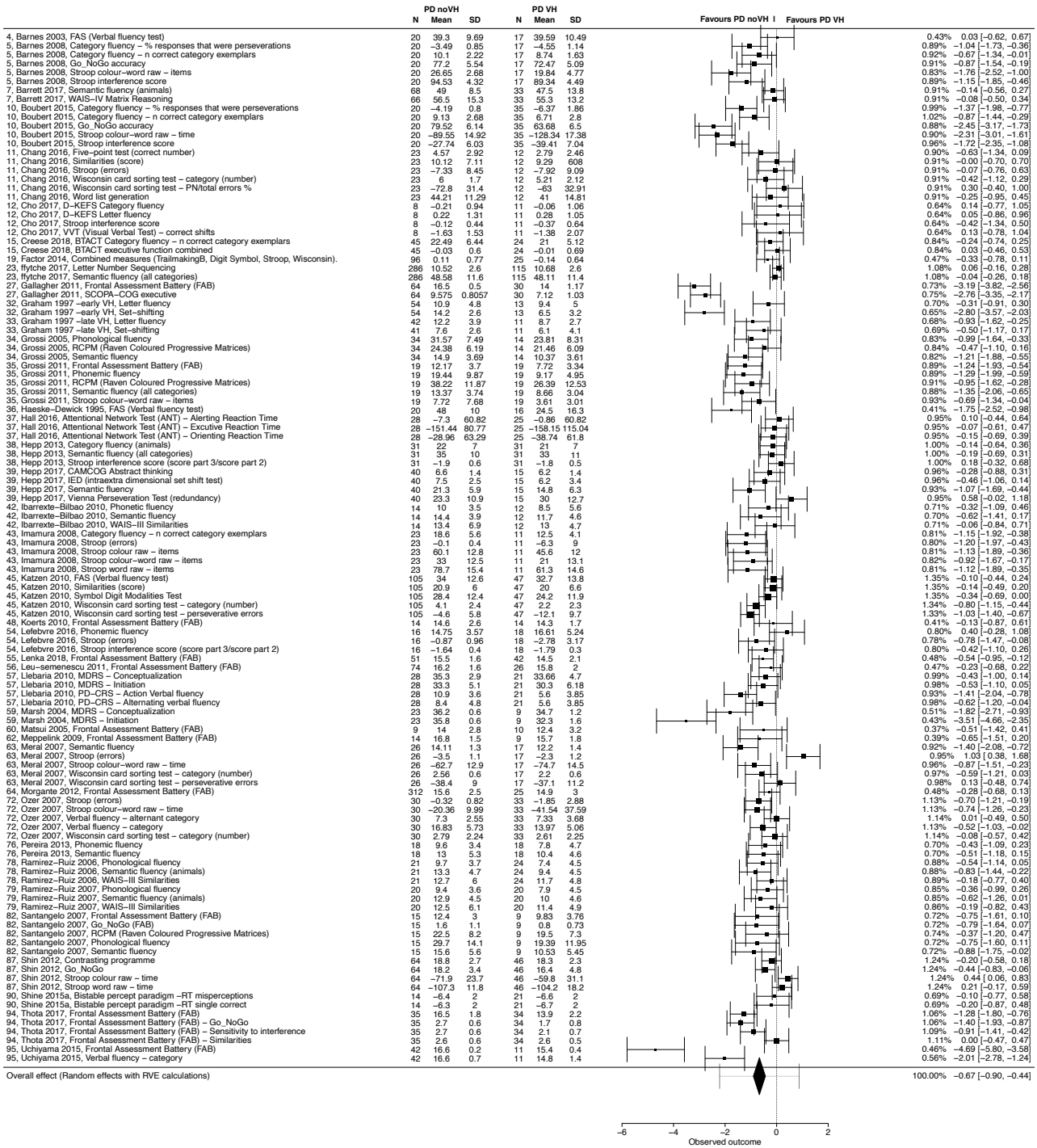
e) Episodic memory



f) Working memory



g) Executive functions



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.

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)

Domain	Model variables[a]	Beta	SE	P-value	t-value	CI (95%)	N studies (Sample size PDVH, PDnoVH)
General cognition	Age	-0.059	0.027	**0.036***	-2.148	(-0.115 -0.004)	56 (1544, 3146)
	Levodopa dose	0.0007	0.0007	0.302	1.040	(-0.0007, 0.002)	
	Illness duration (y)	-0.047	0.039	0.238	-1.191	(-0.127, 0.032)	
	Illness severity [b]	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)	
Episodic Memory	Age	-0.268	0.136	0.054	-1.963	(-0.541, 0.005)	23 (543, 961)
	Levodopa dose	-0.001	0.001	0.369	-0.903	(-0.004, 0.002)	

	Illness duration (y)	0.118	0.145	0.420	0.811	(-0.173, 0.409)	
	Illness severity [b]	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)	
Executive functions	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)	
	Illness duration (y)	-0.005	0.081	0.947	-0.066	(-0.167, 0.156)	
	Illness severity [b]	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)	
Attention	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)	
	Illness severity [b]	-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)	
Language	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)	
	Illness duration (y)	-0.014	0.072	0.847	-0.195	(-0.165, 0.137)	
	Illness severity [b]	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)	
Visual processing	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)	
	Illness duration (y)	-0.024	0.070	0.730	-0.345	(-0.163, 0.115)	
	Illness severity [b]	-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 [b]	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[30] and others[31,32] 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[33] 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[6]. Functional activation of the lateral visual cortex is modulated by cholinesterase inhibitors[34] suggesting a link to the cholinergic system, while 5-HT2A receptor

upregulation has been found in the inferior occipital cortex[35]. Firbank and colleagues[36] 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[37]. 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[38]. 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[39], while in PD more generally, a reduction in thickness of retinal layers with dopaminergic A18 amacrine cells has been found (inner nuclear layer, INL) [39]. These retinal changes might account for visual acuity, spatial contrast sensitivity, and colour discrimination deficits in PD[40]. Poor visual acuity might be a factor in developing VHs in PD[16], highlighting similarities with VHs in eye disease (Charles Bonnet syndrome[41]) and thought to depend upon de-afferentation of the visual cortex[42]. 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)[20] and Shine's Attentional network dysfunction[21] (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[6]. 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[20]. 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[43], although given the widespread network and neurotransmitter dysfunction[44,45] 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 top-down mechanisms in the process of encoding uncertainty [20,46]. In this view, there could be a dysfunction in the ventral visual stream, with the temporal lobe being affected by alpha-synuclein pathology in LBD and dysfunctional cholinergic signalling to occipital regions[47]. 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[21,48,49]. 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 cognitive-visual 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[50] 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

Author Contributions: *Concept and design:* Marcella Montagnese and Mitul Mehta. *Acquisition of data:* Marcella Montagnese. *Drafting of the manuscript:* Marcella Montagnese, Mitul Mehta, Dominic ffytche. *Figures*: Marcella Montagnese. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Marcella Montagnese and Mitul Mehta. *Supervision:* Mitul Mehta, Dominic ffytche and Miriam Vignando.
All authors approved the final version of the manuscript.

Conflict of Interest Disclosures: We declare no competing interests

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

Acknowledgments:
We thank Dr Daniel Williams for the valuable discussion during the revision of this work. The overall funding bodies for each of the authors are as follows: Marcella Montagnese is supported by the NIHR Maudsley Biomedical Research Centre. This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
MV is funded by the Medical Research Council (MRC) – MR/R005931/1
M. Mehta is funded by the Medical Research Council (MRC)
DHFF was funded by the NIHR Programme Grants for Applied Research (SHAPED: RP-PG-0610-10100).

5. References

1. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nature reviews Disease primers. 2017 Mar 23;3(1):1-21.

2. Dorsey E, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007 Jan 30;68(5):384-6.

3. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement disorders. 2014 Nov;29(13):1583-90.

4. Poewe W. Non-motor symptoms in Parkinson's disease. European journal of neurology. 2008 Apr;15:14-20.

5. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. BMC neurology. 2017 Dec;17(1):1-6.

6. ffytche DH, Creese B, Politis M, Chaudhuri KR, Weintraub D, Ballard C, Aarsland D. The psychosis spectrum in Parkinson disease. Nature Reviews Neurology. 2017 Feb;13(2):81-95.

7. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease?. Journal of Neurology, Neurosurgery & Psychiatry. 2000 Sep 1;69(3):308-12.

8. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, Aarsland D, Babcock D, Cummings J, Endicott J, Factor S. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Movement Disorders. 2007 Jun 15;22(8):1061-8.

9. Chang A, Fox SH. Psychosis in Parkinson's disease: epidemiology, pathophysiology, and management. Drugs. 2016 Jul 1;76(11):1093-118.

10. Marcella Montagnese, Pantelis Leptourgos, Charles Fernyhough, Flavie Waters, Frank Larøi, Renaud Jardri, Simon McCarthy-Jones, Neil Thomas, Rob Dudley, John-Paul Taylor, Daniel Collerton, Prabitha Urwyler, A Review of Multimodal Hallucinations: Categorization, Assessment, Theoretical Perspectives, and Clinical Recommendations. Schizophrenia Bulletin. 2020 Aug 09; https://doi.org/10.1093/schbul/sbaa101

11. Williams-Gray CH, Foltynie T, Lewis SJ, Barker RA. Cognitive deficits and psychosis in Parkinson's disease. CNS drugs. 2006 Jun 1;20(6):477-505.

12. Aarsland D, Ballard CG, Halliday G. Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? Journal of geriatric psychiatry and neurology. 2004 Sep;17(3):137-45.

13. Imamura K, Wada-Isoe K, Kitayama M, Nakashima K. Executive dysfunction in non-demented Parkinson's disease patients with hallucinations. Acta Neurologica Scandinavica. 2008 Apr;117(4):255-9.

14. Lenka A, Hegde S, Arumugham SS, Pal PK. Pattern of cognitive impairment in patients with Parkinson's disease and psychosis: a critical review. Parkinsonism & Related Disorders. 2017 Apr 1;37:11-8.

15. Diederich NJ, Goetz CG, Raman R, Pappert EJ, Leurgans S, Piery V. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clinical neuropharmacology. 1998 Sep 1;21(5):289-95.

16. Matsui H, Udaka F, Tamura A, Oda M, Kubori T, Nishinaka K, Kameyama M. Impaired visual acuity as a risk factor for visual hallucinations in Parkinson's disease. Journal of geriatric psychiatry and neurology. 2006 Mar;19(1):36-40.

17. Katzen, H., Myerson, C., Papapetropoulos, S., Nahab, F., Gallo, B., & Levin, B. (2010). Multi-modal hallucinations and cognitive function in Parkinson's disease. *Dementia and geriatric cognitive disorders*, *30*(1), 51-56.

18. Barnes, J., & Boubert, L. (2011). Visual memory errors in Parkinson's disease patient with visual hallucinations. *International Journal of Neuroscience*, *121*(3), 159-164.

19. Ramírez-Ruiz, B., Junqué, C., Martí, M. J., Valldeoriola, F., & Tolosa, E. (2006). Neuropsychological deficits in Parkinson's disease patients with visual hallucinations. *Movement disorders: official journal of the Movement Disorder Society*, *21*(9), 1483-1487.

20. Collerton, D., Perry, E., & McKeith, I. (2005). Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. *Behavioral and Brain Sciences*, *28*(6), 737-757.

21. Shine JM, Halliday GM, Naismith SL, Lewis SJ. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? Movement Disorders. 2011 Oct;26(12):2154-9.

22. ffytche, D.H.,Blom, J. D., & Catani, M. (2010). Disorders of visual perception. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(11), 1280-1287.

23. Schünemann H, editor. The GRADE handbook. Cochrane Collaboration; 2013 Oct.

24. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-Analysis John Wiley & Sons. Ltd, Chichester, UK. 2009.

25. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of statistical software. 2010;36(3):1-48.

26. Tanner-Smith EE, Tipton E, Polanin JR. Handling complex meta-analytic data structures using robust variance estimates: A tutorial in R. Journal of Developmental and Life-Course Criminology. 2016 Mar 1;2(1):85-112.

27. Cheung MW. Modeling dependent effect sizes with three-level meta-analyses: a structural equation modeling approach. Psychological Methods. 2014 Jun;19(2):211.

28. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2011 Aug 24.

29. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Statistics in medicine. 2004 Jun 15;23(11):1663-82.

30. Simmonds, M. (2015). Quantifying the risk of error when interpreting funnel plots. *Systematic reviews*, *4*(1), 1-7.

31. Terrin, N., Schmid, C. H., & Lau, J. (2005). In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *Journal of clinical epidemiology*, *58*(9), 894-901.

32. Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., ... & Higgins, J. P. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj, 343.

33. Forsaa, E. B., Larsen, J. P., Wentzel-Larsen, T., Goetz, C. G., Stebbins, G. T., Aarsland, D., & Alves, G. (2010). A 12-year population-based study of psychosis in Parkinson disease. *Archives of Neurology*, *67*(8), 996-1001.

34. Kumari V, Aasen I, ffytche DH, Williams SC, Sharma T. Neural correlates of adjunctive rivastigmine treatment to antipsychotics in schizophrenia: a randomized, placebo-controlled, double-blind fMRI study. Neuroimage. 2006 Jan 15;29(2):545-56.

35. Ballanger B, Strafella AP, van Eimeren T, Zurowski M, Rusjan PM, Houle S, Fox SH. Serotonin 2A receptors and visual hallucinations in Parkinson disease. Archives of neurology. 2010 Apr 12;67(4):416-21.

36. Firbank MJ, Parikh J, Murphy N, Killen A, Allan CL, Collerton D, Blamire AM, Taylor JP. Reduced occipital GABA in Parkinson disease with visual hallucinations. Neurology. 2018 Aug 14;91(7):e675-85.

37. Kalaitzakis, M. E., Christian, L. M., Moran, L. B., Graeber, M. B., Pearce, R. K. B., & Gentleman, S. M. (2009). Dementia and visual hallucinations associated with limbic pathology in Parkinson's disease. *Parkinsonism & related disorders*, *15*(3), 196-204.

38. Harding, A. J., Stimson, E., Henderson, J. M., & Halliday, G. M. (2002). Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. *Brain*, *125*(11), 2431-2445.

39. Lee JY, Kim JM, Ahn J, Kim HJ, Jeon BS, Kim TW. Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's disease. Movement Disorders. 2014 Jan;29(1):61-7.

40. Davidsdottir S, Cronin-Golomb A, Lee A. Visual and spatial symptoms in Parkinson's disease. Vision research. 2005 May 1;45(10):1285-96.

41. Diederich NJ, Pieri V, Goetz CG. Visual hallucinations in Parkinson and Charles Bonnet Syndrome patients. A phenomenological and pathogenetic comparison. Fortschritte der Neurologie-psychiatrie. 2000 Mar 1;68(3):129-36.

42. ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nature neuroscience. 1998 Dec;1(8):738-42.

43. Lenka, A., Ingalhalikar, M., Shah, A., Saini, J., Arumugham, S. S., Hegde, S., ... & Pal, P. K. (2018). Hippocampal subfield atrophy in patients with Parkinson's disease and psychosis. Journal of Neural Transmission, 125(9), 1361-1372

44. Yao, N., Shek-Kwan Chang, R., Cheung, C., Pang, S., Lau, K. K., Suckling, J., ... & McAlonan, G. M. (2014). The default mode network is disrupted in Parkinson's disease with visual hallucinations. Human brain mapping, 35(11), 5658-5666.

45. Factor, S. A., McDonald, W. M., & Goldstein, F. C. (2017). The role of neurotransmitters in the development of Parkinson's disease-related psychosis. European journal of neurology, 24(10), 1244-1254.

46. Collerton D, Mosimann UP, Perry EK, editors. The neuroscience of visual hallucinations. Oxford: Wiley Blackwell; 2015 Feb 23.

47. Friston K, Kiebel S. Predictive coding under the free-energy principle. Philosophical Transactions of the Royal Society B: Biological Sciences. 2009 May 12;364(1521):1211-21.

48. Muller AJ, Shine JM, Halliday GM, Lewis SJ. Visual hallucinations in Parkinson's disease: theoretical models. Movement Disorders. 2014 Nov;29(13):1591-8.

49. Shine JM, O'Callaghan C, Halliday GM, Lewis SJ. Tricks of the mind: visual hallucinations as disorders of attention. Progress in neurobiology. 2014 May 1;116:58-65.

50. Reijnders, J. S. A. M., Ehrt, U., Lousberg, R., Aarsland, D., & Leentjens, A. F. G. (2009). The association between motor subtypes and psychopathology in Parkinson's disease. *Parkinsonism & related disorders*, *15*(5), 379-382.