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Neuroanatomical and cognitive correlates of visual hallucinations in Parkinson's disease and dementia with Lewy bodies: voxel-based morphometry and neuropsychological meta-analysis

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ABSTRACT

Visual hallucinations (VH) are common in Parkinson's disease and dementia with Lewy bodies, two forms of Lewy body disease (LBD), but the neural substrates and mechanisms involved are still unclear. We conducted meta-analyses of voxel-based morphometry (VBM) and neuropsychological studies investigating the neuroanatomical and cognitive correlates of VH in LBD. For VBM (12 studies), we used Seed-based d Mapping with Permutation of Subject Images (SDM-PSI), including statistical parametric maps for 50% of the studies. For neuropsychology (35 studies), we used MetaNSUE to consider non-statistically significant unreported effects. VH were associated with smaller grey matter volume in occipital, frontal, occipitotemporal, and parietal areas (peak Hedges' g -0.34 to -0.49). In patients with Parkinson's disease without dementia, VH were associated with lower verbal immediate memory performance (Hedges' g -0.52). Both results survived correction for multiple comparisons. Abnormalities in these brain regions might reflect dysfunctions in brain networks sustaining visuo-perceptive, attention, and executive abilities, with the latter also being at the basis of poor immediate memory performance.

Keywords: Lewy body disease, visual hallucinations, dementia with Lewy bodies, Parkinson's disease, meta-analysis, VBM, MRI, grey matter volume, neuropsychology, memory.

1. Introduction

Recurrent and complex visual hallucinations (VH) are involuntary and repetitive visual perceptions experienced in the absence of external sensory inputs (Collerton et al., 2005; Ffytche, 2007; Waters et al., 2014). VH are a common symptom across the Lewy body disease (LBD) spectrum occurring in Parkinson's disease (PD), Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB) (McKeith et al., 2017; Onofrj et al., 2013). Other related minor hallucinatory phenomena, such as false sensations of presence and sensations of passage, are also frequently observed and may be experienced in conjunction with more complex VH (Aarsland et al., 2009; McKeith et al., 2017; Onofrj et al., 2013). VH can be severe and disabling symptoms, with a deleterious impact on the overall quality of life of patients and are associated with significantly higher caregiver distress (Onofrj et al., 2013; Swann and O'Brien, 2018). This is especially the case for those VH which are frightening (such as patients "seeing" robbers in the house) or emotionally upsetting (such as patients "seeing" deceased children). Previous studies suggest that VH in LBD are associated with structural brain abnormalities, evident in brain imaging, mainly in frontal, parietal, and occipitotemporal areas (Pezzoli et al., 2017). Other studies including patients with LBD reported an association between VH and specific cognitive deficits, including visual perception/construction, visual attention, memory, and executive functioning (Barnes and Boubert, 2011; Cagnin et al., 2013; Grossi et al., 2005; Hepp et al., 2013; Koerts et al., 2010; Manganeli et al., 2009). However, findings are often inconsistent and even contradictory, suggesting the need for further research to widen our current knowledge of the neuroanatomical and neuropsychological correlates of this symptom. Within this framework, meta-analyses are unique tools to summarize and integrate quantitatively findings from individual studies.

Previous reviews provided a critical overview of neuroimaging studies that investigated the neural bases of VH in PD and DLB, although results were not combined using meta-analytic methods (Lenka et al., 2015; Pezzoli et al., 2017). Meta-analyses of voxel-based morphometry studies (VBM) investigating the structural brain correlates of auditory hallucinations in

schizophrenia have been performed previously (Modinos et al., 2013; Palaniyappan et al., 2012), and a meta-analysis of hallucinations has been published recently, which included patients with psychiatric and neurodegenerative disorders and hallucinations in different sensory modalities (Rollins et al., 2019). Nevertheless, as the aim of the latter meta-analysis was to investigate transdiagnostic structural brain correlates of hallucinations, it was not specific for VH nor LBD (Rollins et al., 2019). Even though hallucinations in different sensory modalities often occur in conjunction, they may potentially result from distinct and independent pathophysiological mechanisms.

Similarly, we should note that neuropsychological meta-analyses have been already performed on data from different neurological and psychiatric conditions (Demakis, 2006), including PD (Henry and Crawford, 2004; Kudlicka et al., 2011; Ramanan and Kumar, 2013) and DLB (Collerton et al., 2003). However, to our knowledge, no neuropsychological meta-analysis has been carried out to investigate differences between patients with and without VH in LBD.

Neuropsychological assessment represents an important tool in both research and clinical settings for the investigation and understanding of behavioral features that are manifestations of underlying neuropathology (Lezak et al., 2012). In this context, understanding the cognitive features related to VH may aid our knowledge of the neural mechanisms underlying this symptomatology, complementing structural, and functional brain imaging results.

In this study, we aimed to investigate the neuroanatomical and cognitive correlates of complex and/or minor VH in LBD through two separate meta-analyses, respectively on VBM and neuropsychological studies. For the VBM meta-analysis, we aimed to include as many t-maps (statistical parametric maps) as possible, to minimize the imputation associated with the use of only peak coordinates in voxel-based meta-analyses (Radua and Mataix-Cols, 2012). T-maps contain the results of statistical comparisons for every single voxel in the brain, increasing accuracy and statistical power (Radua et al., 2012). We used the software Seed-based d Mapping (SDM) that allows the combination of peak coordinates and t-maps in the same meta-analysis (Albajes-Eizagirre et al., 2019b; Radua et al., 2012). This approach allows a

comprehensive inclusion of studies, and more accurate meta-analyses than those including coordinate data only. For the neuropsychological meta-analysis, we used MetaNSUE, which allows the unbiased inclusion of studies with unreported non-statistically significant effects (Albajes-Eizagirre et al., 2019a; Radua et al., 2015).

2. Meta-analysis of grey matter VBM studies

2.1. Literature search and inclusion criteria for studies

The search strategy followed the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009). A systematic search was carried independently by two authors (SP and NV) in November 2020 using the PubMed and Web of Science databases to identify VBM studies comparing grey matter volume (GMV) between patients with LBD with VH and patients with LBD without VH, using the following keywords: "visual hallucinations", "visual hallucination", "Lewy body", "dementia with Lewy bodies", "Parkinson's disease", "magnetic resonance imaging", "MRI", "voxel-based morphometry", "VBM". The reference section of the identified studies, review articles, and meta-analyses were also screened to search for additional records. The following exclusion criteria were used to select relevant studies: (1) pathologies other than DLB, PD, or PDD; (2) neuroimaging techniques other than MRI whole-brain VBM; (3) analysis of GMV not comparing LBD patients with and without VH and/or minor VH; (4) peak coordinates were not reported or t-maps were not available (5) studies restricting the analysis to *a priori* small volume corrections; (6) case studies; (7) review and theoretical articles; (8) articles not in English; and (9) non-peer-reviewed articles. VBM studies could report whole-brain MRI findings at any level of statistical significance (when including a study from which only peak information is available, SDM uses its effect size independently of its statistical significance); however, studies using small volume correction were excluded. We also excluded studies reporting findings from multiple ROIs instead of the whole brain. Authors of VBM studies were contacted for the full data (i.e., the statistical parametric map), or otherwise for the data required to recreate them (peak coordinates and t-values or equivalent).

2.2. Selection of studies

The initial literature search of keywords produced 372 studies of which 162 were duplicate publications that were found in both the PubMed and Web of Science databases. Among the 210 unique studies screened for eligibility, 17 met eligibility criteria and the authors of these VBM studies were contacted asking for additional or unpublished data (n=17). Additionally, two studies had performed voxel-based ROI analyses (Ibarretxe-Bilbao et al., 2008; Sanchez-Castaneda et al., 2010), two had compared patients with VH and controls (Gama et al., 2014; Nishio et al., 2017), and one had investigated the progression of brain atrophy (Ibarretxe-Bilbao et al., 2010). The authors of these latter studies were also contacted to ask for unpublished whole-brain analyses comparing patients with and without VH. A flow chart summarizing the selection process is shown in Figure 1. Peak coordinates reported on the published papers were included for 6 studies, all on PD (Lee et al., 2017; Meppelink et al., 2011; Pagonabarraga et al., 2014; Ramirez-Ruiz et al., 2007b; Shin et al., 2012; Watanabe et al., 2013). The authors of four studies agreed to send the t-maps of their analyses for the comparison between hallucinating and non-hallucinating patients, three on PD (Bejr-Kasem et al., 2019; Firbank et al., 2018; Goldman et al., 2014) and one on DLB (Blanc et al., 2016). We found no sample overlap between studies. We also included two VBM analyses, one on DLB and one on PD, recently published by our group (Pezzoli et al., 2019). The meta-analysis included a total of 11 studies, including 12 VBM analyses (Table 1), consisting of 210 LBD patients with VH and 259 without VH. Different structured and semi-structured questionnaires and interviews had been used to assess VH, such as the Neuropsychiatric Inventory hallucination score (NPI-hall) and the Unified Parkinson's Disease Rating Scale Part I (UPDRS-I). We report this information and the frequency, severity, and duration of these symptoms for each study in Table 1. Four studies clearly stated that they had considered only complex VH, and two were on minor hallucinatory phenomena; the remaining studies did not provide clear information about the severity of hallucinatory experiences.

2.3. Assessment of study quality

We assessed the quality of the studies in the meta-analysis with the Newcastle-Ottawa Scale (Wells et al., last accessed 2020) for case-control studies (Supplementary Table S1).

2.4. Seed-based d Mapping meta-analysis

We pooled VBM data using Seed-based d Mapping (formerly Signed Differential Mapping) (Radua and Mataix-Cols, 2009; Radua et al., 2012; Radua et al., 2014) with Permutation of Subject Images (SDM-PSI) (Albajes-Eizagirre et al., 2019b) using the default parameters. The main advantage of this method is that it directly tests whether there are differences between patients with and without hallucinations, rather than conducting indirect tests such as whether peaks tend to converge in some regions more than in others (Albajes-Eizagirre and Radua, 2018). First, all coordinates were converted to a common MNI space using the Lancaster method (taking into account the small changes in MNI space between SPM and FSL, and undoing the MNI conversions conducted with the old Brett method) (Lancaster et al., 2007). Second, the map of the potential lower and upper bounds of possible effect sizes was created for each study based on the level of statistical significance, the coordinates and effect size of the reported peaks, and the anisotropic covariance between adjacent voxels (Radua et al., 2014). Third, multiple effect size maps (and the corresponding variance maps) were imputed voxelwise for each study, adding normal spatially correlated noise to the maximum likely effect sizes (Albajes-Eizagirre et al., 2019b). Fourth, images of each dataset of imputed effect size maps were combined using a standard random-effects meta-analysis, and the meta-analytic maps resulting from the different imputations were combined using Rubin's rules (Albajes-Eizagirre et al., 2019a). Finally, images were imputed for each study, and statistical significance was assessed via a permutation test of the subject images (Albajes-Eizagirre et al., 2019b). We considered statistically significant those voxels with threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) family-wise error rate (FWER) of $p < 0.05$. We assessed the between-study heterogeneity and conducted tests to evaluate potential publication bias in the

main findings. Finally, in a sensitivity analysis, we repeated the analyses after excluding two studies with DLB (Blanc et al., 2016; Pezzoli et al., 2019), as well as after excluding three studies that did not report MMSE scores or presented statistically significant differences in the MMSE (Blanc et al., 2016; Meppelink et al., 2011; Ramirez-Ruiz et al., 2007b). We also aimed to repeat the analyses after only including the studies that reported only complex VH, but there were too few studies.

3. Meta-analysis of neuropsychological studies

3.1. Literature search and inclusion criteria for studies

A systematic search was carried independently by two authors (SP and NV) in November 2020 using the PubMed and Web of Science databases to identify neuropsychological studies of VH in LBD using the terms "visual hallucinations", "visual hallucination", "Lewy body", "dementia with Lewy bodies", "Parkinson's disease", "cognit*", "neuropsycholog*". The following exclusion criteria were applied: (1) pathologies other than DLB, PD, or PDD; (2) studies not using neuropsychological tests to investigate cognitive functioning; (3) statistical analysis not comparing LBD patients with and without VH and/or minor VH; (4) mean and standard deviation for the neuropsychological tests not available for each group of patients; (5) studies combining different neuropsychological tests into general cognitive domains (6) case studies; (7) review and theoretical articles; (8) articles not in English; (9) non-peer-reviewed articles; (10) studies for which each neuropsychological test had been included in less than three studies. Finally, we contacted the authors of the VBM studies to ask for neuropsychological data when not available in the published article.

3.2. Selection of studies

The initial search of keywords yielded 1229 studies, of which 408 were duplicate publications. Additionally, four studies were identified by searching the reference lists of the articles obtained, and four were obtained from the authors of VBM studies. Of the 821 records

screened, 35 studies met inclusion criteria and were included in the meta-analysis (the selection process is described in Figure 1). Each neuropsychological test to be included in the meta-analysis had to have been used by three or more studies, which resulted in a total of 35 datasets (Table 2) assessing different cognitive domains. Different questionnaires and interviews had been used to assess VH, including the NPI-hall, the UPDRS-I, and the Scales for Outcomes in Parkinson's Disease – Psychiatric Complications (SCOPA-PC). We report this information and the frequency, severity, and duration of these symptoms for each study in Table 2. Nine datasets only included patients with complex VH and two patients with minor hallucinations; the remaining studies included both or did not provide clear information about the severity of hallucinatory experiences.

When overlapping samples of patients were detected, we only took the comparisons performed on the largest sample into account for the meta-analysis (Barnes and Boubert, 2008; Barnes et al., 2003; Cagnin et al., 2013; Grossi et al., 2005; Pezzoli et al., 2019; Santangelo et al., 2007). For two studies (Lenka et al., 2018; Thota et al., 2017), we could not assess whether there was sample overlap; thus, we conducted the meta-analysis twice: first considering no overlap, and second considering an overlap (i.e., discarding the smaller study). For longitudinal studies, only data collected at baseline were used (Santangelo et al., 2007). Wang et al. (2010) included three groups of patients with PD: 1) patients with VH and REM sleep behavior disorder (RBD), 2) patients with RBD but no VH, 3) patients with neither VH nor RBD. In the meta-analysis, we only included the first two groups, to consider the presence of RBD as a potential confounding factor. Llebaria et al. (2010) reported separate statistics for patients with minor VH, patients with major VH without insight, and patients with major VH with insight. The three samples were combined in a single global sample, calculating the global means and standard deviations of the three samples. Note that to calculate global standard deviations, both the standard deviations of the three samples and the square differences between the means of the three samples and the global means were used. We used the same methodology to combine internally driven and externally driven hallucinators in Boubert and Barnes (2015). The

neuropsychological tests included in the meta-analysis were as follows: Trail Making Test (TMT) part A and B, Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed recall, Rey figure copy and delayed recall, phonemic and semantic fluency, clock drawing test, digit span forward and backward, Boston naming test, Stroop test, Frontal Assessment Battery (FAB), Wisconsin card sorting test and the Visual Object and Space Perception Battery (VOSP) subtests (incomplete letters, silhouettes, object decision, progressive silhouettes, number location, position discrimination, dot counting, and cube analysis). Only a few studies included covariates of no interest in statistical analyses (Chang et al., 2016; Gasca-Salas et al., 2016; Grossi et al., 2005; Imamura et al., 2008; Katzen et al., 2010; Koerts et al., 2010; Pezzoli et al., 2019; Ramirez-Ruiz et al., 2006), including only two studies controlling for a measure of global cognitive impairment, namely the MMSE (Imamura et al., 2008; Ramirez-Ruiz et al., 2006). In addition, in one study, patients were matched for their executive functioning (assessed with the FAB) (Koerts et al., 2010).

3.3. Assessment of study quality

We assessed the qualities of the studies included in the meta-analysis with the Newcastle-Ottawa Scale (Wells et al., last accessed 2020) for case-control studies (Supplementary Table S2).

3.4. Statistical analysis

We pooled neuropsychological data using a separate random-effects meta-analysis for each test. For the sake of simplicity, we only report those tests for which we could include at least three studies. Still, results were nearly identical when we repeated the analyses after including tests for which there were only two studies. In addition to the main results (effect size, confidence interval, and p-value), we calculated the I^2 statistic that describes which percentage of the variability between studies might be due to between-study heterogeneity, and the p-value from the test for funnel plot asymmetry that is useful to assess potential publication or reporting bias (a version of the Egger test based on a meta-regression) (Sterne and Egger, 2005).

We carried out meta-regressions by mean age, percentage of females, disease duration, education, Mini-Mental State Examination (MMSE), Hoehn and Yahr (H&Y) scores, UPDRS-III (assessing motor symptoms), and Montreal cognitive assessment (MoCA) for those tests with statistically significant differences between patients with and without visual hallucinations. We could not conduct meta-regression by the NPI hallucinations score because there were too few studies reporting the score for the statistically significant neuropsychological tests. We used the package “MetaNSUE” for R (Albajes-Eizagirre et al., 2019a; Radua et al., 2015) to allow an unbiased inclusion of studies that did not report statistics for results that were non-statistically significant. Finally, in a sensitivity analysis, we repeated the analyses after excluding thirteen studies that did not report MMSE scores or presented statistically significant differences in the MMSE (Barnes and Boubert, 2008; Bejr-Kasem et al., 2019; Bronnick et al., 2011; Cagnin et al., 2013; Cho et al., 2017; Dauwan et al., 2019; Llebaria et al., 2010; Marques et al., 2020; Nishio et al., 2018; Ozer et al., 2007; Pagonabarraga et al., 2014; Ramirez-Ruiz et al., 2006; Walpola et al., 2020), after excluding four studies with LBD patients with dementia, namely PDD (Bronnick et al., 2011) and DLB (Cagnin et al., 2013; Heitz et al., 2015; Zarkali et al., 2019), and after only including the nine studies that reported only complex HV (Cagnin et al., 2013; Dauwan et al., 2019; Firbank et al., 2018; Imamura et al., 2008; Marques et al., 2020; Ozer et al., 2007; Pezzoli et al., 2019; Ramirez-Ruiz et al., 2006; Shin et al., 2012).

4. Results

4.1. Neuroanatomical correlates of visual hallucinations based on imaging studies

The demographic, clinical, and methodological characteristics available for each study are summarized in Table 1. Visual hallucinations have been assessed using different questionnaires and interviews, which varied between studies (see Table 1 for a detailed description

Table 3 and Figure 2 show the findings of the VBM meta-analysis. The analysis revealed several clusters of statistically significantly lower GMV.

The largest cluster (1904 voxels, peak Hedges' $g = -0.46$) covered principally posterior midline regions including the calcarine fissure, the lingual gyrus, and the cuneus. Anteriorly there were three other smaller midline clusters in the precuneus/medial cingulate (234 voxels, peak Hedges' $g = -0.34$), supplementary motor area (594 voxels, peak Hedges' $g = -0.40$), and medial superior frontal cortex (889 voxels, peak Hedges' $g = -0.38$).

We also found two regions of smaller GMV in the left inferior parietal gyrus (excluding supramarginal and angular gyri; 321 voxels, peak Hedges' $g = -0.49$), left middle occipital gyrus (203 voxels, peak Hedges' $g = -0.47$), and right fusiform gyrus (286 voxels, peak Hedges' $g = -0.38$). No peaks showed between-study heterogeneity ($I^2 < 10\%$) and there was no indication of potential publication bias.

The findings were similar when we repeated the analyses after discarding the three datasets with potential differences in MMSE between groups or the two datasets from studies of patients with DLB (Table 3). The Hedges' g in the voxels of the coordinates of the peaks of the main analysis were similar. However, these comparisons could be biased because we selected the peaks from the main analysis and voxels other than peaks from the subgroup analyses. To avoid this bias, we selected peaks from the subgroup analyses close to the peaks of the main analysis. This comparison showed that Hedges' g was potentially larger in nearly all findings (Table 3, right column).

4.2. Cognitive correlates of visual hallucinations

Clinical and demographic features for each neuropsychological study are summarized in Table 2. Results from the comparison between hallucinating and non-hallucinating patients for each neuropsychological test are reported in Table 4.

The only neuropsychological test that showed statistically significant differences after FWER-correction was the immediate recall of the RAVLT. Patients with visual hallucinations showed a significantly lower score on this test (Hedges' $g = -0.52$, FWER = 0.001), with no indications of heterogeneity between studies or publication bias ($I^2 = 0\%$, Egger test not statistically significant). Only studies on PD without dementia used the RAVLT to explore memory impairments (no study on DLB/PDD used the RAVLT).

Several other neuropsychological tests showed statistically significant differences that, however, did not survive correction for multiple comparisons: the delayed recall of the RAVLT (Hedges' $g = -0.42$), the phonemic fluency test (Hedges' $g = -0.18$), the TMT-A test (Hedges' $g = 0.24$), the FAB test (Hedges' $g = -0.39$), and the semantic fluency test (Hedges' $g = -0.17$). In all cases, there were no indications of heterogeneity between studies or publication bias ($I^2 < 40\%$, Egger test not statistically significant). To exclude the possibility to include potentially overlapping samples, we repeated the meta-analysis excluding the study by Thota et al. (2017). The FAB was no longer significant. All the other results remained unchanged.

Meta-regressions by education and MMSE were statistically significant only for the FAB test ($\beta = 5.2$ and $\beta = -0.13$), although these findings did not survive correction for multiple comparisons. No other meta-regression analyses reached statistical significance.

When we repeated the analyses after discarding the four studies in patients with dementia (either PDD or DLB), the results were identical except for the FAB test that remained statistically significant after correction for multiple comparisons and the TMT-B that was significant without correction for multiple comparisons. Moreover, the phonemic fluency and the TMT-A tests lost statistical significance. When we repeated the meta-analysis after discarding those studies that presented statistically significant differences in the MMSE, the RAVLT immediate and delayed recall were statistically significant even after correction for multiple comparisons. The phonemic fluency was no longer statistically significant. Finally, when we repeated the meta-analysis after only including studies that included only complex VH, the findings were only statistically significant at the uncorrected level (Rey figure recall, TMT-A, and semantic

fluency). However, this loss of significance should be taken with caution because this subgroup analysis included only 25% of studies.

5. Discussion

These meta-analyses provide evidence of the presence of structural GMV alterations and neuropsychological deficits associated with the presence of VH in LBD. Specifically, we found regions of smaller GMV in hallucinating patients in occipital, occipitotemporal, medial frontal, and inferior parietal areas that were predominant over the entire midline of the brain. The neuropsychological meta-analysis revealed verbal immediate memory deficits in LBD patients with visual hallucinations compared with those without. Hallucinating patients presented a poorer performance on the RAVLT immediate recall, a result that remained significant after correction for multiple comparisons. More severe deficits were also found in executive functioning (phonemic fluency and FAB), visual attention (TMT-A), semantic memory (semantic fluency) as well as on the RAVLT delayed recall, although these emerged using an uncorrected threshold of significance.

Previous neuroimaging research using a complementary approach has also found evidence of the involvement of posterior regions in hallucinating patients. Functional imaging studies have reported occipital and occipitotemporal hypometabolism or hypoperfusion in hallucinating patients with PD (Gasca-Salas et al., 2016; Matsui et al., 2006; Oishi et al., 2005), and DLB (Heitz et al., 2015; Pasquier et al., 2002; Pernecky et al., 2008). Similarly, an association between the severity/frequency of VH and occipital/occipitotemporal metabolism in LBD has been detected using FDG-PET (Firbank et al., 2016; Iaccarino et al., 2018; Kantarci et al., 2012; Park et al., 2013). Functional MRI studies have also found altered activity in the occipital lobe. Specifically, decreased activity in occipital and temporal regions have been identified in response to visual stimuli in hallucinating patients with PD, compared with the non-

hallucinating ones (Holroyd and Wooten, 2006; Lefebvre et al., 2016; Stebbins et al., 2004). In a resting-state fMRI study, Yao et al. (2016) found that patients with VH in PD had decreased functional connectivity between the hippocampus and occipitotemporal areas. Despite these findings, occipital Lewy body pathology has not been associated with the presence of VH so far (Kalaitzakis et al., 2009), but significantly higher Lewy body burden has been found mainly in temporal and frontal regions (Gallagher et al., 2011; Harding et al., 2002a; Harding et al., 2002b; Kalaitzakis et al., 2009; Papapetropoulos et al., 2006). In this context, we speculate that occipital/occipitotemporal atrophy may represent a structural hallmark of disrupted functional and structural neural circuits contributing to VH in LBD, especially involving visual areas. The findings outlined above, together, suggest a contribution to VH of impaired ventral visual pathways, involved in the formation of object visual representations (Kravitz et al., 2013). This is in line with one of the leading models of VH, proposed by Collerton et al. (2005). Briefly, the authors proposed that recurrent, complex VH may generate from combined deficits in visual attention and object perception, the latter supported by impaired activity in the ventral visual stream (Collerton et al., 2005). Although individual neuropsychological studies reported worse performance in visual perception in hallucinating patients with LBD (Barnes et al., 2003; Ibarretxe-Bilbao et al., 2010; Koerts et al., 2010; Ramirez-Ruiz et al., 2006, 2007a), no evidence of visual perception deficits and their association with VH was identified in the present meta-analysis. Heterogeneity in the tests used by different studies might partially account for this negative result. None of the neuropsychological tests included was specific for studying the cognitive correlations of VH in LBD and, therefore, may not be sensitive enough to detect deficits in specific visuoperceptive aspects linked to this symptomatology. Furthermore, patients may perform at ceiling in some cognitive tests, such as the VOSP cube analysis and dot counting. However, we could not formally assess this possibility in the present dataset. Moreover, distinct cognitive mechanisms may underlie VH across different diagnoses. In support of this view, when including only patients with PD, differences in executive functioning (assessed with the FAB test) reached significance after correction for multiple comparisons.

However, this analysis included the two studies for which we could not verify sample overlap (Lenka et al., 2018; Thota et al., 2017). This result, therefore, should be interpreted with caution. Significant differences in visual attention in patients with VH disappeared when repeating the meta-analysis after removing studies on DLB. In this context, visual attention deficits might be driven by the inclusion of patients with dementia, while executive dysfunction may be more distinctive of hallucinating patients without dementia. Executive dysfunction may be present from an early stage in PD, and it has been shown to worsen with the progression of the disease (Dirnberger and Jahanshahi, 2013). Dopaminergic dysfunction due to disrupted fronto-striatal circuits reflecting nigrostriatal dopaminergic depletion, typical of PD, is thought to underlie, at least in part, these deficits (Kehagia et al., 2010; Lewis et al., 2003). We could suggest that differential patterns of cognitive deficits might lead to VH across diagnosis: executive dysfunction in PD and visual attention impairment in DLB. Nevertheless, this interpretation remains purely speculative. Thus, future studies need to clarify the role of top-down control mechanisms in the development of VH across different LBD diagnoses and patterns of phenomenological features. Therefore, the pathophysiological processes underlying VH in PD and DLB may differ. In this context, differential neuropathological features between conditions may play a role. For example, most DLB cases have LB pathology reflecting an advanced Braak stage with cortical LBs, and DLB patients do not necessarily follow the neuropathological progression typical of PD, suggesting that different trajectories may be taken in terms of LBs progression and distribution (Donaghy and McKeith, 2014; Walker et al., 2015). Moreover, β -amyloid load has been found to be higher in DLB compared to PDD, and in PDD compared to PD patients without dementia (Hepp et al., 2016). When we repeated the VBM meta-analysis including only patients with PD without dementia, the effect sizes Hedges' g were potentially larger in nearly all findings. We may speculate, therefore, that DLB has a different distribution of abnormalities and thus, when we added the two DLB studies to the meta-analysis, the PD-related abnormalities showed a smaller effect size. However, we could

not formally explore this hypothesis, given the limited number of studies including patients with DLB (only two).

On the other hand, the neuropsychological meta-analysis revealed more severe immediate verbal memory deficits in hallucinating patients compared with non-hallucinating ones. None of the studies included used the RAVLT immediate and delayed recall to explore differences in memory deficits between patients with and without VH in DLB/PDD. Thus, the interpretation of such findings cannot be extended to LBD hallucinating patients with concomitant dementia. Although less severe than those observed in Alzheimer's disease (AD), memory deficits have been shown in PDD, as well as PD with mild cognitive impairment (Emre et al., 2007; Fields, 2017; Goldman et al., 2018; Goldman and Litvan, 2011). Studies on PD have shown medial temporal lobe-related deficits, namely storing and learning difficulties, which have been linked to a higher risk of developing dementia, while frontal-related dysfunctions appeared more stable over the progression of the disease (Aarsland, 2016; Chiaravalloti et al., 2014). Evidence has suggested that memory impairment (Galtier et al., 2016; Hobson and Meara, 2004; Levy et al., 2002; Pedersen et al., 2013), as well as the presence of VH at baseline (Aarsland et al., 2003; Anang et al., 2014), significantly predict the development of dementia at follow-up in PD. In this context, the presence of this cognitive profile in hallucinating PD patients may be driven by the presence of early signs of dementia, of which the RAVLT may represent a more sensitive measure than others assessing visuoperceptive abilities (e.g. VOSP). On the other hand, lower scores on the RAVLT immediate recall may be explained by more severe global cognitive impairment. However, in five out of six studies, there were no significant differences in MMSE or MoCA scores between groups. In the remaining study, MMSE was included as a covariate in the statistical analyses. Moreover, meta-regression analysis by MMSE scores was not significant, suggesting that more severe memory performance may be independent of more severe global cognitive impairment. Interestingly, Lewy body pathology in limbic areas has been related to both dementia and VH in PD (Kalaitzakis et al., 2009). In another study on PD, the presence of VH has been associated with both Lewy body and AD pathology, and their

comorbidity was significantly more common in hallucinating patients (Jacobson et al., 2014). In addition, it has been found that PD patients progressing to PDD showed hippocampal atrophy at baseline that predicted conversion to dementia over time (Delgado-Alvarado et al., 2016; Sarasso et al., 2020). PDD converters are also characterized by cortical thinning in frontal, temporal, parietal, and occipital areas (Sarasso et al., 2020). These findings suggest that VH and dementia in PD may share some underlying pathological mechanisms, including the presence of Lewy bodies with or without concomitant AD-related pathology, which may foster the development of more severe memory deficits, as well as VH and dementia. We could include only a few studies in both meta-analyses (Bejr-Kasem et al., 2019; Firbank et al., 2018; Goldman et al., 2014; Pagonabarraga et al., 2014; Pezzoli et al., 2019; Shin et al., 2012). Thus, interpretations inferring a direct correspondence between GMV alterations and cognitive deficits should be formulated with caution. Unknown confounding variables, including clinical features, may influence the apparent contrasting findings between the neuropsychological and VBM meta-analyses. For example, patients included in the neuropsychological studies may have more advanced cognitive decline, reflected by greater impairment of memory abilities. Future studies including patients comprehensively examined with both structural MRI analysis and neuropsychological assessment might provide more insight into the link between smaller GMV and cognitive deficits associated with VH in LBD.

It should be noted that the main finding of the present meta-analysis highlights the presence of more severe deficits in the RAVLT immediate recall, a test that might be influenced by working memory impairments. Working memory abilities also influence episodic memory performance by facilitating an efficient encoding of information (Wolk and Dickerson, 2011). In AD, early immediate recall of information, assessed with the initial encoding trials of the RAVLT, has been associated with regions supporting working memory, including frontal and parietal areas, while delayed memory performance has been found associated with the medial temporal lobe (Wolk and Dickerson, 2011). Executive dysfunction and working memory deficits have been related to impaired frontostriatal dopaminergic circuits in PD (de la Fuente-Fernandez, 2012;

Kehagia et al., 2010). Within this framework, impaired memory abilities in immediate recall might be explained by working memory difficulties due to frontostriatal dysfunctions in LBD that, in turn, might constitute a susceptibility to VH. This may also account for the smaller frontal GMV found in the present meta-analysis. However, no differences were detected in working memory abilities, assessed with the digit span backward, suggesting the need for further studies to corroborate this hypothesis. Within this framework, the nature of the memory deficits specifically characterizing LBD patients with VH needs to be explored more in depth. The present voxel-based meta-analysis reported evidence of smaller GMV in hallucinating patients in medial superior frontal, and anterior and median cingulate cortices, and in the inferior parietal lobule. Consistently, studies have shown frontal (Boecker et al., 2007; Heitz et al., 2015; Pernecky et al., 2008), and parietal (Boecker et al., 2007; Gasca-Salas et al., 2016; Matsui et al., 2006; Park et al., 2013) hypometabolism/perfusion in hallucinating LBD patients compared with non-hallucinating ones. The role of a frontoparietal network of regions in the top-down control of spatial attention (Gazzaley and Nobre, 2012; Nobre and Mesulam, 2014) might account for the results of the present meta-analysis, in line with multifactorial models of VH (Collerton et al., 2005; Shine et al., 2011; Shine et al., 2014). As mentioned above, Collerton et al. (2005) proposed a contribution of visual attention deficits in the development of VH, along with disrupted visual processing impairments. In addition, Shine et al. (2011) proposed that VH may be the result of dysfunctional attention networks, specifically an overactivity of the default mode network (DMN) and the ventral attention network, and an inappropriate engagement of the dorsal attention network. The DMN, activated at rest and deactivated during goal-directed activities, has been associated with internal self-referential thoughts, and the retrieval and manipulation of episodic memories (Shine et al., 2011). Regions within the DMN include the posterior cingulate, precuneus, inferior parietal lobule, medial prefrontal cortex, and temporal areas (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001; Rosazza and Minati, 2011; Utevsky et al., 2014), some of which have also been detected by the present voxel-based meta-analysis (i.e. inferior parietal, medial frontal, cingulate and

temporal cortices). Smaller GMV in these regions might result in dysfunctional compensatory mechanisms, including DMN overactivity. Dysfunctional attention networks may lead to the emergence of false images originating from previously recorded percepts in the DMN (Shine et al., 2011). Increased DMN-related connectivity, mainly in fronto-parietal regions, has been found in PD patients with VH (Pezzoli et al., 2017). When compared to controls, however, both patients with and without VH showed a pattern of decreased connectivity (Pezzoli et al., 2017). In another study, overlapping regions of decreased functional connectivity compared with controls were found in paracentral and occipital areas in both PD with and without VH (Hepp et al., 2017). Additional regions of decreased functional connectivity were shown in patients with VH in frontal, temporal, occipital, and striatal areas related to cognitive performance (Hepp et al., 2017). Other findings reported a pattern of increased connectivity between the hippocampus and occipitotemporal areas, while connectivity was increased between the hippocampus and fronto-parietal regions (Yao et al., 2016).

To our knowledge, these are the first meta-analyses investigating structural brain abnormalities and neuropsychological features associated with VH in LBD. However, several limitations should be considered when interpreting the results of the present meta-analyses. Firstly, the present meta-analyses showed a substantial lack of studies comprising patients with dementia, highlighting the need for future investigations focused on systematically exploring potentially distinct patterns of alteration across different diagnoses. Moreover, both meta-analyses included a relatively small number of studies. Despite these limitations, the robustness of the meta-analytic method allowed a comprehensive summary of our current knowledge on the neural correlates of VH in LBD. Individual studies are often low-powered and include small sample sizes, increasing the likelihood of false-negative results (Button et al., 2013; Muller et al., 2018). This is complicated further by the common use of not particularly stringent thresholds leading to higher rates of false-positive results, an issue that has been highlighted as particularly problematic in neuroimaging studies (Muller et al., 2018; Wager et al., 2009). Thus, reproducibility and consistency of findings represent a controversial issue of the current

scientific research, highlighting the importance to detect those findings that have been replicated by different studies (Muller et al., 2018; Wager et al., 2009). Heterogeneity and publication bias were excluded from the main results. Nevertheless, between-study differences in demographics and other clinical features, and the implementation of different methodologies may have an impact on the results. Due to the low number of studies, meta-regression analyses exploring the association between regional smaller GMV and other sample characteristics were not performed in the VBM meta-analysis. Thus, the influence of other clinical and demographic features cannot be completely excluded. Moreover, although publication bias cannot be completely ruled out, we also included studies not reporting significant differences in individual analyses (Meppelink et al (2011), and subthreshold results through the use of T-maps (Bejr-Kasem et al., 2019; Blanc et al., 2016; Firbank et al., 2018; Goldman et al., 2014), ensuring that negative results were also well represented. In the literature, the limited availability of T-maps has generally led to the use of peak coordinates in most meta-analyses (Radua and Mataix-Cols, 2012). We included peak coordinate data for six studies; however, the combination of both T-maps and coordinates in the same meta-analyses represents a well-validated method, which has been shown to improve meta-analyses, even when T-maps are included for only one sample (Radua et al., 2012).

In the neuropsychological meta-analysis, the number of studies included for each neuropsychological test was relatively small ($n \leq 20$ studies for each test). To decrease between-study heterogeneity in the tasks used, we only meta-analyzed data available for single neuropsychological tests, instead of combining multiple measures for similar cognitive constructs. This approach allows more precise analyses to be undertaken for each test, although it might have contributed to decreasing the number of studies included. Due to the limited amount of studies available, no subgroup analyses including only patients with concomitant dementia were performed. Therefore, differences between clinical diagnoses could not be tested. Despite this, our results suggest that memory impairments may be distinctive of PD patients with VH regardless of other demographic and clinical features, as shown by meta-regression

analyses. However, not all studies included such information and therefore, the influence of other variables cannot be completely ruled out. Moreover, this result could not be extended to patients with DLB/PDD, since none of the studies including a sample of patients with dementia used the RAVLT to investigate memory impairments.

The present study provides evidence of the presence of significantly smaller occipital, occipitotemporal, frontal, and parietal GMV in LBD patients with VH compared with those without. This pattern of smaller GMV may represent a structural hallmark of dysfunctions in brain networks sustaining visuo-perceptive and attention abilities, which may be contributing factors to VH.

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Figure 1. Modified PRISMA flow charts adapted from Moher et al. (2009) describing the selection process of the studies included in the VBM meta-analysis (left) and neuropsychological meta-analysis (right).

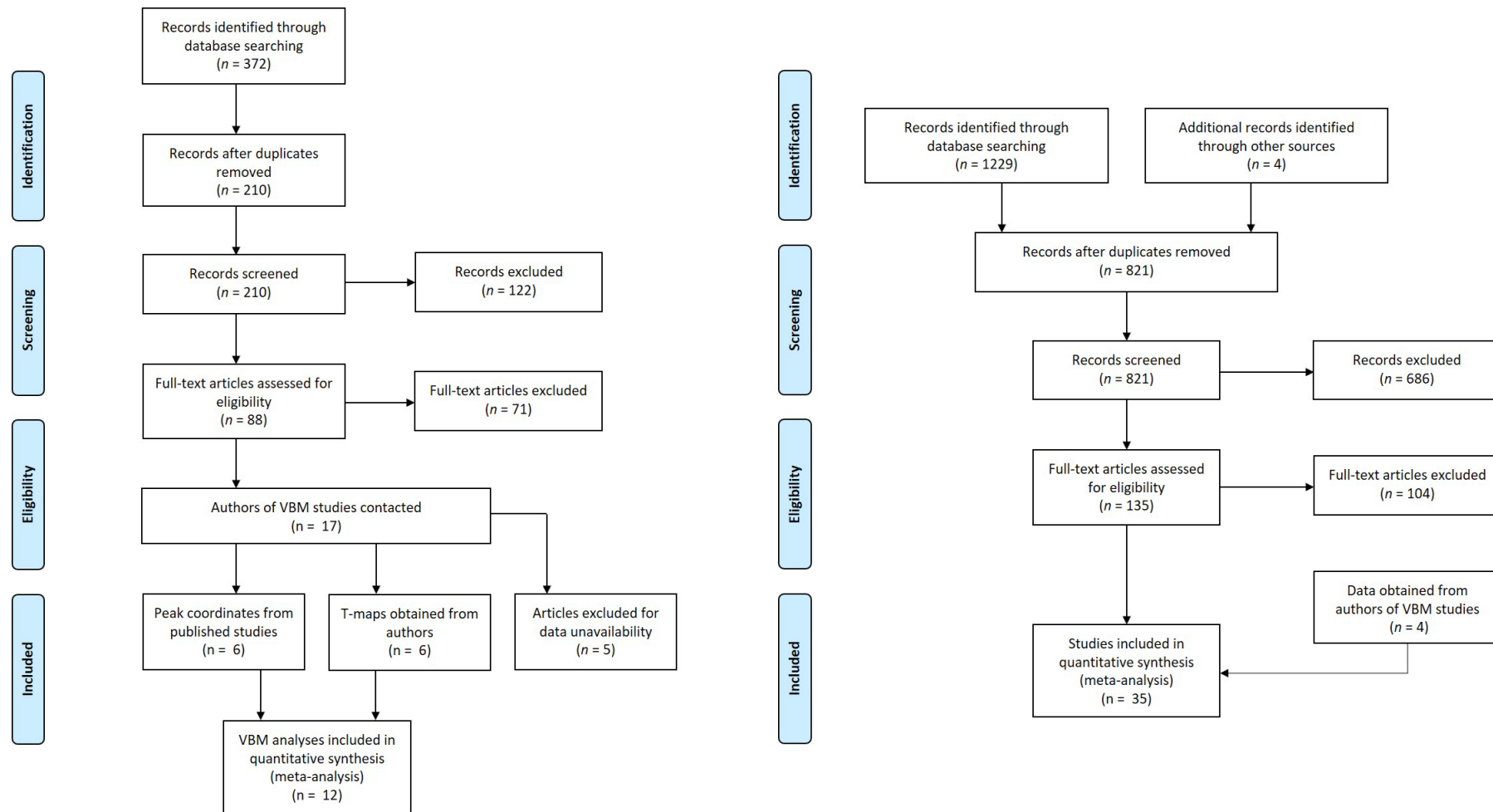


Figure 2. Areas of statistically significantly smaller grey matter volume in patients with LBD with visual hallucination compared to those without. Red-to-yellow colors indicate smaller grey matter volume in patients with visual hallucinations compared to those without. The clusters show regions with threshold-free cluster enhancement (TFCE) family-wise error rate (FWER) < 0.05, with red-to-yellow colors proportional to the Z-values.

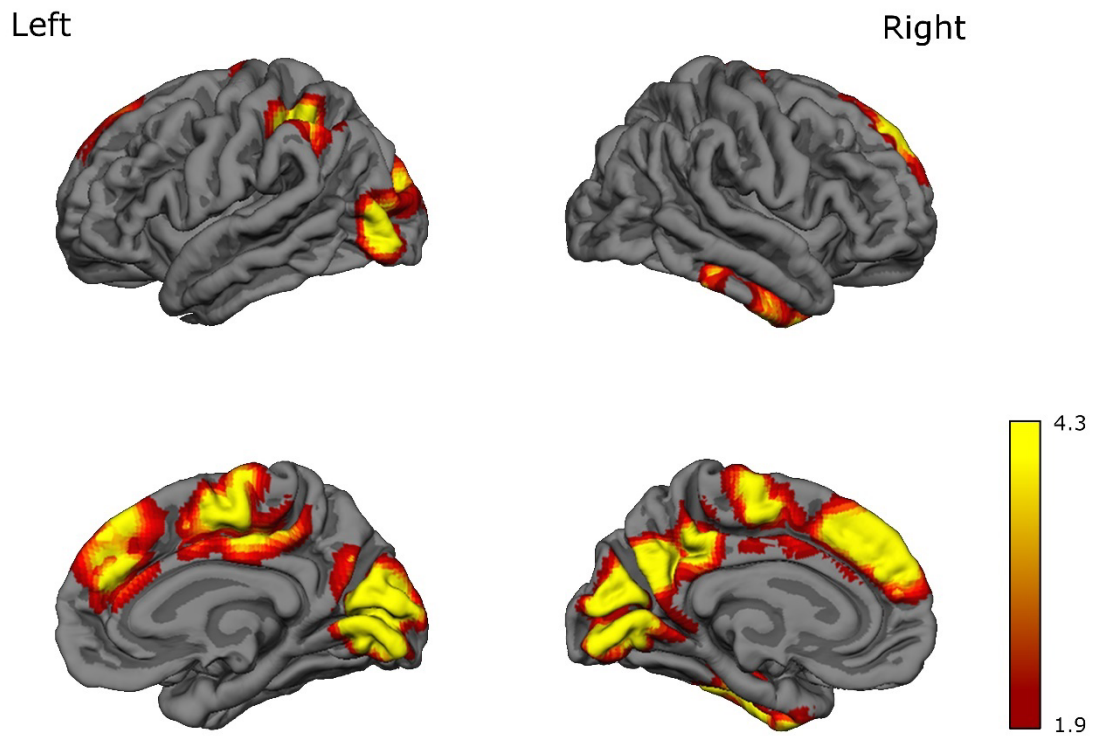


Table 1 Characteristics of the 11 studies (12 VBM analyses) included in the SDM meta-analysis. Mean and (SD) are reported for each variable unless otherwise specified.

Study	LBD patients	Age	MMSE	H&Y	UPDRS-III	Definition and characteristics of the VH	Covariates	Data
Bejr-Kasem et al. (2019)	18 PD mH	70.4 (5.5) ^a	25.2 (2.8) ^{a,c}	2.1 (0.3) ^a	21.9 (8.6) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I, and a semi-structured interview covering the types of minor hallucinations	Age, sex, education, TIV	T-map
	14 PD NH	65.8 (7.8) ^a	23.9 (4.5) ^{a,c}	2.1 (0.4) ^a	25.8 (9.2) ^a	Minor hallucinations (sense of presence, passage hallucinations, visual illusions, and/or pareidolias) at least weekly during the last month and stable for three months		
Blanc et al. 2016)	17 DLB VH	68.5 (8.4)	27.5 (2.5)	NA	NA	Structured questionnaire composed of ten qualitative items on hallucinations, minor phenomena, and delusions	TIV, age, sex	T-map
	11 DLB NVH	66.0 (10.6)	27.8 (1.5)					
Firbank et al. (2018)	17 PD VH	75.5 (4.5) ^a	23.1 (4.9) ^a	NA	55.9 (19.3) ^b	NPI-hall and screening questions from the North-East Visual Hallucinations Interview III	Age, TIV, CAMCOG	T-map
	19 PD NVH	72.3 (5.1) ^a	25.6 (4.1) ^a		34.7 (18.8) ^b	Active visual hallucinators (PD VH) if they had complex visual hallucinations in the month preceding their interview; otherwise, they were classed as PD NVH		
Goldman et al. 2014)	25 PD VH	74.8 (6.0) ^a	23.9 (5.4) ^a	3 (2-5) ^{a,d}	39 (13.8) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I	TIV	T-map
	25 PD NVH	75.4 (6.1) ^a	25.1 (4.4) ^a	3 (2-5) ^{a,d}	43.5 (13.2) ^a	Chronic VH for at least a month, and fulfilling diagnostic criteria for PD-associated psychosis proposed by the National Institute of Health/National Institute of Mental Health		
Lee et al. 2017)	10 PD VH	69.4 (5.3)	27.6 (1.8) ^a	2.2 (0.3) ^b	22.5 (5.8) ^a	The definition of VH, including minor hallucinations, was based on a semi-structured interview	TIV, age, sex	Coordinates
	21 PD NVH	66.2 (6.8)	28.2 (1.4) ^a	1.8 (0.5) ^b	16.4 (5.1) ^a	Persistent VH were present for at least three months		

Meppelink et al. 2011)	11 PD VH 13 PD NVH	NA	NA	NA	NA	NPI-hall VH experienced at least weekly during the previous month	Total GM volume	Coordinates
Pagonabarraga et al. 2014)	15 PD mH 27 PD NH	64.1 (9) ^a 66.3 (8) ^a	87.2 (13) ^{a, f} 90.3 (13) ^{a, f}	1.9 (0.3) ^a 1.9 (0.4) ^a	21.7 (8) ^a 18.6 (8) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I Minor hallucinations (sense of presence and/or passage hallucinations) at least weekly during the last month	Total GM volume, age, sex	Coordinates
Pezzoli et al. (2019)	11 DLB VH 17 DLB NVH 9 PD VH 15 PD NVH	75.1 (5.0) ^a 73.7 (6.5) ^a 67.0 (10.6) ^a 67.3 (8.1) ^a	22.5 (3.5) ^a 25.0 (3.5) ^a 26.2 (2.1) ^a 27.6 (1.7) ^a	NA NA 2.0 (1.0) ^{a, e} 2.3 (1.0) ^{a, e}	8.0 (11.9) ^a 4.6 (5.9) ^a NA NA	NPI-hall Patients with recurrent, complex VH. Sensory modality was ascertained with a qualitative assessment of reported patients' experiences	TIV, age	T-maps (2 VBM analyses)
Ramirez-Ruiz et al. 2007b)	18 PD VH 20 PD NVH	NA	27.0 (2.1) ^b 29.1 (1.4) ^b	3.2 (1.0) ^b 2.5 (0.7) ^b	29.3 (11.7) ^a 24.5 (14.0) ^a	NPI-hall and semi-structured questionnaire Formed VH in the previous year (people, animals, objects)	TIV, MMSE, HDRS, H&Y	Coordinates
Shin et al. 2012)	46 PD VH 64 PD NVH	71.3 (5.9) ^a 70.7 (5.7) ^a	25.2 (3.0) ^a 25.7 (2.9) ^a	NA	24.1 (10.4) ^a 21.6 (11.0) ^a	VH (people, animals, objects) assessed using the NPI-hall	TIV, age, sex, MMSE, PD duration	Coordinates
Watanabe et al. 2013)	13 PD VH 13 PD NVH	66.6 (5.5) ^a 63.6 (10.7) ^a	27.9 (1.9) ^a 29.0 (1.5) ^a	2.9 (0.6) ^a 2.4 (0.8) ^a	23.4 (9.0) ^a 28.6 (19.9) ^a	VH assessed using the UPDRS-I	TIV, age, sex	Coordinates

^a no statistically significant differences between groups; ^b statistically significant differences between groups; ^c Montreal cognitive assessment (MoCA); ^d median (range), ^e Missing data for 4 VH patients and 8 without VH; ^f PD-CRS. CAMCOG: Cambridge Cognition Examination; DLB: dementia with Lewy bodies; GM: grey matter; H&Y: Hoehn and Yahr; HDRS: Hamilton depression rating scale; LBD: Lewy body disease; MDS: Movement Disorder Society; MMSE: Mini-Mental State Examination; mH: minor hallucinations; NA: not available; NPI-hall: Neuropsychiatric Inventory – hallucination score; NH: no hallucinations; NVH: no VH; PD: Parkinson's disease; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; TIV: total intracranial volume; UPDRS: Unified Parkinson's Disease Rating Scale; VH: visual hallucinations.

Table 2 Characteristics of the 35 studies included in the meta-analysis of neuropsychological studies. Mean, and SD are reported for each variable unless otherwise specified.

Study	LBD patients	Age	Ed. (y)	Disease duration (y)	MMSE	H&Y	UPDRS-III	Definition and characteristics of the VH
Barnes and Boubert 2008)	17 PD VH	67.5 (4.7)	NA	11.9 (4.8)	26.4 (1.1)	3.8 (0.5) ^b	NA	NA
	20 PD NVH	63.7 (9.5)		9.7 (4.8)	27.2 (1.2)	2.9 (0.7) ^b		
Barnes and Boubert 2011)	36 PD VH	68.5 (4.3) ^a	NA	10.0 (4.4) ^a	27.3 (1.9) ^a	3.8 (0.3) ^b	NA	Questionnaire about VH and visual disturbances
	32 PD NVH	67.4 (6.5) ^a		9.5 (4.32) ^a	27.6 (1.6) ^a	2.5 (0.4) ^b		Frequency of VH > 1 per day
Barnes et al. 2003)	17 PD VH	67.9 (5.9) ^a	NA	11.9 (4.3) ^a	26.7 (1.1) ^b	3.4 (0.6) ^b	NA	Hallucinations' questionnaire covering the nature and properties of VH
	20 PD NVH	62.8 (10.9) ^a		8.8 (4.4) ^a	27.5 (1.4) ^b	2.9 (0.5) ^b		VH in the last three months
Bejr-Kasem et al. (2019)	18 PD mH	70.4 (5.5) ^a	12.5 (4.6) ^a	NA	25.2 (2.8) ^{a,c}	2.1 (0.3) ^a	21.9 (8.6) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I, and a semi-structured interview covering the types of minor hallucinations
	14 PD NH	65.8 (7.8) ^a	11.6 (4.9) ^a		23.9 (4.5) ^{a,c}	2.1 (0.4) ^a	25.8 (9.2) ^a	Minor hallucinations at least weekly during the last month and stable for three months
Boubert and Barnes (2015)	35 PD VH	73.9 (7.89)	NA	11.8 (5.4)	27.2 (1.7)	3.7 (0.8)	NA	Questionnaire about VH and visual disturbances
	20 PD NVH	72.2 (10.3)		10.7 (4.5)	27.6 (1.9)	3.34 (0.41)		Frequency of VH > 1 per day VH occurred in the last month
Bronnick et al. 2011)	86 PDD VH	73.2 (5.9) ^a	8.8 (3.9) ^a	11.5 (6.4) ^b	19.4 (3.8) ^b	NA	35.2 (13.7) ^b	NPI-hall
	86 PDD NVH	73.2 (6.1) ^a	8.7 (3.8) ^a	9.15 (5.1) ^b	20.8 (3.0) ^b			
Cagnin et al. 2013)	45 DLB VH	76.6 (5.5) ^b	6.8 (3.9) ^a	2.3 (1.5) ^a	21.7 (4.8) ^a	NA	7.9 (10.0) ^a	NPI-hall, clinical records, information from each patient and/or caregiver
	36 DLB NVH	72.4 (6.2) ^b	8.5 (4.6) ^a	2.1 (1.6) ^a	23.9 (4.1) ^a			

									Frequency and severity in the past four weeks. Recurrent complex VH. Visual illusions, feeling of presence, and passage were not considered
Chang et al. (2016)	12 PD VH 23 PD NVH	67.8 (7.9) ^a 66.4 (9.7) ^a	9.3 (6.7) ^a 10.9 (4.2) ^a	11.7 (6.4) ^b 6.2 (4.9) ^b	27.7 (2.2) ^a 27.6 (1.4) ^a	2.7 (0.9) ^b 1.5 (0.7) ^b	27.9 (13.0) ^b 14.2 (8.4) ^b		VH experienced in the last year
Cho et al., (2017)	11 PD VH 8 PD NVH	64.1 (9.1) ^a 63.0 (6.4) ^a	16.2 (2.5) ^a 15.9 (2.9) ^a	8.7 (4.6) ^a 6.7 (4.0) ^a	26.0 (1.8) ^{a, c} 26.9 (1.9) ^{a, c}	2.09 (0.7) ^a 1.87 (0.4) ^a	24.5 (15.1) ^a 14.3 (7.0) ^a		NPI-hall and Parkinson Psychosis Questionnaire Diagnostic criteria for PD-associated psychosis Illusions, sense of presence, and/or intermittent, well-formed VH with maintained insight At least once a week for at least a month
Creese et al. (2018)	24 PD VH 45 PD NVH	67.8 (7.8) ^a 65.9 (8.5) ^a	2 (2) ^{a, d, e} 2 (2) ^{a, d, e}	5.38 (8.25) ^{b, e} 3.45 (3.17) ^{b, e}	NA	NA	NA		NPI-Clinician Rating Scale hallucination score Persistent VH: present for more than one occasion in the last year; transient VH: present on one occasion
Dauwan et al. (2019)	20 PD VH 20 PD NVH	72.2 (6.2) ^b 70.5 (6.5) ^b	4 (3-7) ^{a, e, f} 7 (6-7) ^{a, e, f}	7.7 (4.3-12.7) ^{a, e} 4.5 (2.8-9.4) ^{a, e}	26.0 (21.8-27.8) ^{b, e} 28.5 (27.0-29.0) ^{b, e}	3.0 (3.0-4.0) ^{a, e} 3.0 (3.0-3.0) ^{a, e}	NA		Questionnaire for Psychotic Experiences and SCOPA-PC Recurrent complex VH (people, animals, inanimate objects) experienced at least in the previous month
Firbank et al. (2018)	17 PD VH 19 PD NVH	75.5 (4.5) ^a 72.3 (5.1) ^a	11.6 (2.2) ^a 11.1 (1.5) ^a	11.0 (7.4) ^a 9.6 (6.5) ^a	23.1 (4.9) ^a 25.6 (4.1) ^a	NA	55.9 (19.3) ^b 34.7 (18.8) ^b		NPI-hall and screening questions from the North-East Visual Hallucinations Interview III regarding VH occurring in the previous month

Gasca-Salas et al. 2016)	9 PD VH 12 PD NVH	70.7 (3.9) ^a 70.8 (3.4) ^a	12 (4) ^a 9 (2.5) ^a	14.7 (5.4) ^a 14.3 (6.3) ^a	27 (1.7) ^a 25.9 (2.7) ^a	NA	33.2 (8.7) ^a 32.6 (12.9) ^a	UPDRS-I
Goldman et al. 2014)	25 PD VH 25 PD NVH	74.8 (6.0) ^a 75.4 (6.1) ^a	15.4 (3.3) ^a 15.7 (2.9) ^a	13.1 (4.6) ^a 10.8 (4.4) ^a	23.9 (5.4) ^a 25.1 (4.4) ^a	3 (2-5) ^{a, g} 3 (2-5) ^{a, g}	39 (13.8) ^a 43.5 (13.2) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I Chronic VH for at least a month, and fulfilling diagnostic criteria for PD-associated psychosis proposed by the National Institute of Health/National Institute of Mental Health
Grossi et al. 2005)	14 PD VH 34 PD NVH	67.4 (10.7) ^a 66.9 (9.2) ^a	12.7 (4.1) ^b 8.5 (4.4) ^b	10.4 (7.3) ^b 6.3 (4.2) ^b	26.6 (2.2) ^a 27 (2.1) ^a	2.8 (0.6) ^a 2.5 (0.8) ^a	NA	Questionnaire to investigate the present or past occurrence of visual or auditory hallucinations, content, frequency and duration, and emotional reaction VH: fully formed images of people, animals, objects, or shades Two patients out of 14 had only auditory hallucinations
Heitz et al. 2015)	36 DLB VH 30 DLB NVH	71.7 (10.2) ^a 73.5 (6.9) ^a	NA	NA	21.7 (5.6) ^a 23.3 (4.3) ^a	NA	NA	Clinically assessed by neurology experts. Question: "Have you ever seen things that do not exist?"
Hepp et al. 2013)	31 PD VH 31 PD NVH	66 (11) ^a 65 (11) ^a	NA	7 (5) ^a 8 (5) ^a	27 (2) ^a 28 (2) ^a	2.5 (1-4) ^{a, g} 2.5 (1-4) ^{a, g}	32 (15) ^a 26 (11) ^a	SCOPA-PC VH within the previous month
Imamura et al. 2008)	11 PD VH 23 PD NVH	74.2 (10.4) 69.3 (6.9)	NA	9.5 (7.8) 5.7 (4.2)	26.5 (2.7) 28.1 (2.0)	NA	28.9 (9.0) 24.6 (7.1)	Patients and caregivers were asked whether the patients could see people, animals, insects, or inanimate objects that did not exist, over the preceding few months

Katzen et al., (2010)	47 PD VH 105 NVH	65.6 (8.9) ^a 64.6 (9.0) ^a	14.0 (3.7) ^a 14.1 (3.8) ^a	11.7 (5.8) ^b 9.9 (4.9) ^b	26.5 (3.1) ^a 27.2 (2.5) ^a	2.3 (0.7) ^a 2.3 (1.2) ^a	NA	Hallucinations' questionnaire VH: history of one or more episodes of visual hallucinations currently or in the past
Koerts et al. 2010)	14 PD VH 14 PD NVH	69.0 (5.0) ^a 67.1 (6.8) ^a	4.4 (1.7) ^a 4.2 (1.9) ^a	10.7 (4.9) 6.0 (5.7)	26.2 (1.3) 26.4 (1.6)	NA	NA	NPI-hall and questionnaire based on the characteristics of VH
Lenka et al. (2018)	42 PD VH 51 PD NVH	58.7 (7.7) ^a 57.8 (6.9) ^a	NA	6.6 (3.2) ^a 5.8 (2.4) ^a	25.8 (2.7) ^{a, c} 25.4 (2.6) ^{a, c}	2.4 (0.2) ^a 2.3 (0.3) ^a	35.2 (8.4) ^a 34.6 (8.2) ^a	Semi-structured interviews and a scale to assess psychosis in PD VH and/or minor hallucinations
Llebaria et al. 2010)	29 PD VH 28 PD NVH	74.96 (5.2) 72.7 (6)	8.5 (4.8) 8.4 (5)	8.6 (4.1) 7.9 (5)	NA	2.5 (0.7) 2 (0.5)	24.4 (4.2) 26.7 (3.0)	MDS-UPDRS-I Minor VH, major VH without insight, major VH with insight
Manganelli et al. 2009)	10 PD VH 12 PD NVH	70.4 (5.3) ^a 65.5 (10.1) ^a	12 (6) ^a 12 (5) ^a	8.7 (6.3) ^a 9 (5.5) ^a	27.4 (1.6) ^a 27.8 (1.9) ^a	NA	16.1 (6.9) ^a 17.6 (4.2) ^a	Structured interview including the Parkinson Psychosis Questionnaire, Part B
Marques et al. (2020)	28 PD VH 28 PD NVH	71.3 (6.8) ^a 69.3 (8.5) ^a	17.8 (3.8) ^a 18.4 (4.2) ^a	11.1 (5.1) ^b 6.5 (4.9) ^b	24.8 (2.5) ^{b, c} 26.2 (2.4) ^{b, c}	3.0 (0.8) ^b 2.5 (1.0) ^b	35.5 (18.2) ^a 28.8 (18.4) ^a	SCOPA-PC, patient and caregiver interviews and Psycho-Sensory Hallucinations Scale Patients with minor hallucinations only were excluded VH occurring at least once a week within the past three months
Nishio et al. (2018)	19 PD VH 53 PD NVH	69.4 (6.3) ^b 65.7 (6.4) ^b	12.7 (1.9) ^a 11.2 (2.1) ^a	7.3 (4.5) ^a 6.7 (4.2) ^a	26.6 (2.9) ^b 28.4 (1.7) ^b	NA	27.2 (11.0) ^b 16.2 (6.6) ^b	NPI-hall
Ozer et al. 2007)	33 PD VH 30 PD NVH	67.4 (8.3) ^a 65.5 (9.4) ^a	NA	6.8 (4.4) ^a 5.9 (3.2) ^a	NA	NA	21.9 (11.5) ^a 16.5 (11.1) ^a	UPDRS Several episodes of definite VH in the past three months

Pagonabarraga et al. 2014)	15 PD mH	64.1 (9) ^a	11.1 (6) ^a	9.8 (7) ^a	87.2 (13) ^{a, h}	1.9 (0.3) ^a	21.7 (8) ^a	Hallucinations and Psychosis item of the MDS-UPDRS-I Minor hallucinations (sense of presence and/or passage hallucinations) at least weekly during the last month
	27 PD NH	66.3 (8) ^a	9.2 (5) ^a	7.3 (4) ^a	90.3 (13) ^{a, h}	1.9 (0.4) ^a	18.6 (8) ^a	
Pezzoli et al. (2019)	9 PD VH	67.0 (10.6) ^a	11.3 (5.3) ^a	9.9 (5.7) ^a	26.2 (2.1) ^a	2.0 (1.0) ^{a, i}	NA	NPI-hall Patients with recurrent, complex VH. Sensory modality was ascertained with a qualitative assessment of reported patients' experiences
	15 PD NVH	67.3 (8.05) ^a	11.3 (4.2) ^a	10.0 (4.2) ^a	27.6 (1.7) ^a	2.3 (1.0) ^{a, i}		
Ramirez-Ruiz et al. 2006)	24 PD VH	74.7 (5.4) ^a	7.3 (3.4) ^a	NA	26.7 (2.1) ^b	3.3 (1.1) ^b	30.6 (14.5) ^a	VH: well-formed images of people, faces, or animals. Insight was maintained in 63% of patients VH in the previous year
	21 PD NVH	73.3 (6.1) ^a	7.7 (3.4) ^a		29.2 (1.4) ^b	2.5 (0.7) ^b	24.9 (13.7) ^a	
Santangelo et al. 2007)	9 PD VH	72.1 (9) ^a	11.7 (4.7) ^a	10.5 (5) ^a	23.3 (6.2) ^a	2.8 (0.9) ^a	25.8 (11.6) ^a	Parkinson Psychosis Questionnaire, part B, NPI-hall
	15 PD NVH	70.1 (8.6) ^a	10.3 (4.3) ^a	6.2 (2.9) ^a	26.2 (2.7) ^a	2 (0.5) ^a	19 (9.8) ^a	
Shin et al. 2012)	46 PD VH	71.3 (5.9) ^a	8.3 (5.1) ^a	0.28 (0.25) ^a	25.2 (3.0) ^a	NA	24.1 (10.4) ^a	NPI-hall
	64 PD NVH	70.7 (5.7) ^a	8.4 (5.2) ^a	0.23 (0.25) ^a	25.7 (2.9) ^a		21.6 (11.0) ^a	
Thota et al. (2017)	34 PD VH	58.7 (8.4) ^a	NA	NA	28.2 (1.9) ^a	2.3 (0.3) ^a	36.7 (8.8) ^a	18 patients had only minor hallucinations, six had only formed VH, two had VH and auditory hallucinations, and one had only auditory hallucinations
	35 PD NVH	55.7 (8.2) ^a			28.7 (1.2) ^a	2.2 (0.3) ^a	35.4 (13.2) ^a	
Walpola et al. (2020)	18 PD VH	67.5 (6.7) ^a	13.3 (3.3) ^a	7.6 (5.0) ^a	27.9 (1.3) ^a	2.2 (0.6) ^a	33.4 (15.9) ^a	MDS-UPDRS Complex VH or minor hallucinations
	20 PD NVH	63.7 (6.6) ^a	14.6 (2.4) ^a	5.7 (3.2) ^a	27.9 (1.1) ^a	2.1 (0.4) ^a	28.4 (13.4) ^a	
Wang et al. 2010)	10 PD VH	68.4 (7.1) ^a	NA	7.6 (4.3) ^a	25.7 (1.6) ^b	2.1 (0.6) ^a	27.7 (3.7) ^b	Self-designed VH questionnaire 10, 6, and 2 had VH every day, less than six times per week, and
	10 PD NVH	67 (8.98) ^a		5.9 (2.2) ^a	26.9 (1.1) ^b	1.8 (0.6) ^a	21.7 (4.6) ^b	

less than once a week, respectively. Most were of overlapping, blurred human image rather than objects in daily life.

Zarkali et al. (2019)	17 PD+DLB VH 20 PD+DLB NVH	68.0 (6.9) ^a 68.9 (7.1) ^a	15.4 (2.9) ^a 15.9 (2.3) ^a	4.6 (2.7) ^a 4.5 (4.6) ^a	28.0 (2.1) ^a 29.0 (1.5) ^a	NA	30.5 (10.6) ^a 24.7 (7.5) ^a	MDS-UPDRS, and University of Miami Parkinson's Disease Hallucinations Questionnaire
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^a no statistically significant differences between groups; ^b statistically significant differences between groups; ^c MoCA; ^d this reflects the three main levels of education in the United Kingdom; ^e median, interquartile range; ^f Verhage coding system for education; ^g median range; ^h PD-CRS; ⁱ Missing data for 4 VH patients and 8 without VH. DLB: dementia with Lewy bodies; Ed.: education; H&Y: Hoehn and Yahr Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal cognitive assessment; NA: not available; NVH: no VH; PD: Parkinson's disease; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; PDD: Parkinson's disease dementia; SCOPA-PC: Scales for Outcomes in Parkinson's Disease – Psychiatric Complications; VH: visual hallucinations; y= years.

Table 3 Regions with smaller regional grey matter volume in patients with Lewy body disease with visual hallucinations compared with those without visual hallucinations. Subgroup analyses included patients with PD without dementia only (excluding patients with DLB).

Structure	Main analysis						Cluster		Only studies on PD		Only studies with no differences in MMSE	
	Peak						Voxels	Breakdown (Voxels)	Coordinate of the main analysis' peak	Coordinate of the subgroup analysis' peak	Coordinate of the main analysis' peak	Coordinate of the subgroup analysis' peak
	MNI	Hedges' <i>g</i>	<i>Z</i>	FWER	<i>p</i>	Egger <i>p</i>						
Calcarine fissure	-4,-84,12	-0.46	4.26	0.001	0%	n.s.	1904	B calcarine fissure (571) B lingual gyrus (331) B cuneus (179) B precuneus (109) Cerebellum vermis (96)	MNI: -4,-84,12 Hedges' <i>g</i> = -0.45 (<i>Z</i> = 3.72) FWER = 0.001	MNI: 0,-72,14 Hedges' <i>g</i> = -0.52 (<i>Z</i> = 4.44) FWER = 0.001	MNI: -4,-84,12 Hedges' <i>g</i> = -0.42 (<i>Z</i> = 3.38) FWER = 0.001	MNI: -2,-84,8 Hedges' <i>g</i> = -0.46 (<i>Z</i> = 3.84) FWER = 0.001
L middle occipital	-44,-86,0	-0.47	4.24	0.003	1%	n.s.	203	L middle occipital gyrus (155) L inferior occipital gyrus (16)	MNI: -44,-86,0 Hedges' <i>g</i> = -0.56 (<i>Z</i> = 4.78) FWER = 0.001	MNI: -44,-86,0 Hedges' <i>g</i> = -0.56 (<i>Z</i> = 4.78) FWER = 0.001	MNI: -44,-86,0 Hedges' <i>g</i> = -0.52 (<i>Z</i> = 4.25) FWER = 0.001	MNI: -44,-86,0 Hedges' <i>g</i> = -0.52 (<i>Z</i> = 4.25) FWER = 0.001
L inferior parietal	-42,-44,48	-0.49	4.12	0.003	8%	n.s.	321	L inferior parietal gyrus (286) L postcentral gyrus (10)	MNI: -42,-44,48 Hedges' <i>g</i> = -0.40 (<i>Z</i> = 2.94) FWER = 0.003	MNI: -50,-58,42 Hedges' <i>g</i> = -0.50 (<i>Z</i> = 4.16) FWER = 0.001	MNI: -42,-44,48 Hedges' <i>g</i> = -0.46 (<i>Z</i> = 3.39) FWER = 0.003	MNI: -42,-44,48 Hedges' <i>g</i> = -0.46 (<i>Z</i> = 3.39) FWER = 0.003
Supplementary motor area	0,-6,54	-0.40	3.51	0.004	0%	n.s.	594	B supplementary motor area (351) B median cingulate cortex (164) L paracentral lobule (54)	MNI: 0,-6,54 Hedges' <i>g</i> = -0.43 (<i>Z</i> = 3.47) FWER = 0.001	MNI: -4,-8,54 Hedges' <i>g</i> = -0.43 (<i>Z</i> = 3.60) FWER = 0.001	MNI: 0,-6,54 Hedges' <i>g</i> = -0.47 (<i>Z</i> = 3.70) FWER = 0.001	MNI: -2,-6,54 Hedges' <i>g</i> = -0.48 (<i>Z</i> = 3.77) FWER = 0.001
Medial superior frontal	0,32,48	-0.38	3.34	0.004	1%	n.s.	889	B medial superior frontal gyrus (638) B anterior cingulate cortex (131) B supplementary motor area (58) R median cingulate cortex (39)	MNI: 0,32,48 Hedges' <i>g</i> = -0.37 (<i>Z</i> = 3.01) FWER = 0.003	MNI: -2,34,52 Hedges' <i>g</i> = -0.38 (<i>Z</i> = 3.11) FWER = 0.003	MNI: 0,32,48 Hedges' <i>g</i> = -0.45 (<i>Z</i> = 3.69) FWER = 0.001	MNI: -2,34,48 Hedges' <i>g</i> = -0.48 (<i>Z</i> = 3.71) FWER = 0.001
R fusiform	44,-34,-24	-0.38	3.21	0.023	2%	n.s.	191	R fusiform gyrus (104) R inferior temporal gyrus (52)	MNI: 44,-34,-24 Hedges' <i>g</i> = -0.33 (<i>Z</i> = 2.39) FWER = 0.151	MNI: 42,-24,-28 Hedges' <i>g</i> = -0.41 (<i>Z</i> = 3.39) FWER = 0.025	MNI: 44,-34,-24 Hedges' <i>g</i> = -0.39 (<i>Z</i> = 2.98) FWER = 0.001	MNI: 44,-34,-24 Hedges' <i>g</i> = -0.39 (<i>Z</i> = 2.98) FWER = 0.001
R inferior temporal	34,4,-46	-0.36	3.22	0.028	0%	n.s.	95	R inferior temporal gyrus (35) R fusiform gyrus (29)	MNI: 34,4,-46 Hedges' <i>g</i> = -0.36 (<i>Z</i> = 2.99) FWER = 0.150	MNI: 44,-12,-30 Hedges' <i>g</i> = -0.46 (<i>Z</i> = 3.70) FWER = 0.010	MNI: 34,4,-46 Hedges' <i>g</i> = -0.42 (<i>Z</i> = 3.43) FWER = 0.001	MNI: 34,4,-46 Hedges' <i>g</i> = -0.42 (<i>Z</i> = 3.43) FWER = 0.001
Median cingulate	0,-42,54	-0.34	2.89	0.036	0%	n.s.	234	B median cingulate cortex (135) B precuneus (72)	MNI: 0,-42,54 Hedges' <i>g</i> = -0.40 (<i>Z</i> = 3.18) FWER = 0.001	MNI: -4,-42,50 Hedges' <i>g</i> = -0.45 (<i>Z</i> = 3.74) FWER = 0.001	MNI: 0,-42,54 Hedges' <i>g</i> = -0.40 (<i>Z</i> = 3.29) FWER = 0.001	MNI: -2,-44,52 Hedges' <i>g</i> = -0.48 (<i>Z</i> = 3.87) FWER = 0.001

B: bilateral; FWER: familywise error rate of the peak, derived from the distribution of the maximum threshold-free cluster enhancement (TFCE) statistic in a permutation test; L: left; MNI: coordinates of the peak in the Montreal Neurological Institute space; R: right.

Table 4 Results of the meta-analysis of neuropsychological differences between patients with Lewy body disease with and without visual hallucinations.

Test	K	N		Hedges' <i>g</i>	p	FWER	<i>I</i> ²	Egger p
		VH	NVH					
RAVLT immediate recall	6	127	160	-0.52 (-0.76, -0.28)	<0.001	0.001	0%	n.s.
RAVLT delayed recall	5	103	139	-0.42 (-0.68, -0.16)	0.002	n.s.	0%	n.s.
Phonemic fluency	16	429	519	-0.18 (-0.31, -0.05)	0.007	n.s.	0%	n.s.
Semantic fluency	16	379	483	-0.17 (-0.31, -0.03)	0.02	n.s.	0%	n.s.
TMT-A	11	201	222	0.24 (0.04, 0.43)	0.02	n.s.	0%	n.s.
TMT-B	7	119	151	0.21 (-0.11, 0.53)	0.20	n.s.	35%	n.s.
TMT-B minus TMT-A	4	76	77	0.22 (-0.10, 0.54)	0.19	n.s.	0%	n.s.
FAB	6	122	137	-0.39 (-0.72, -0.06)	0.02	n.s.	33%	n.s.
WCST	3	92	158	-0.05 (-0.31, 0.21)	0.70	n.s.	0%	n.s.
Stroop color-word	4	74	61	-0.01 (-0.36, 0.33)	0.94	n.s.	0%	n.s.
Similarities	3	61	69	-0.02 (-0.36, 0.33)	0.93	n.s.	0%	n.s.
Clock copying	3	67	81	-0.04 (-0.37, 0.28)	0.80	n.s.	0%	n.s.
Clock drawing	6	155	159	-0.07 (-0.29, 0.16)	0.56	n.s.	0%	n.s.
Rey figure copy	10	244	280	-0.15 (-0.36, 0.06)	0.17	n.s.	27%	n.s.
Rey figure recall	7	202	233	-0.25 (-0.51, 0.02)	0.07	n.s.	44%	n.s.
BFRT	3	68	59	-0.10 (-0.45, 0.25)	0.58	n.s.	0%	n.s.
RMF	3	52	49	-0.08 (-0.47, 0.32)	0.71	n.s.	0%	n.s.
JLO	5	113	168	-0.13 (-0.37, 0.12)	0.31	n.s.	0%	n.s.
VOSP incomplete letters	5	123	118	-0.20 (-0.46, 0.05)	0.12	n.s.	0%	n.s.
VOSP silhouettes	4	95	90	-0.04 (-0.32, 0.25)	0.81	n.s.	0%	n.s.
VOSP object decision	4	95	90	-0.21 (-0.51, 0.08)	0.15	n.s.	0%	n.s.
VOSP progressive silhouettes	4	95	90	0.14 (-0.15, 0.43)	0.35	n.s.	0%	n.s.
VOSP dot counting	4	95	90	-0.14 (-0.43, 0.15)	0.35	n.s.	0%	n.s.
VOSP position discrimination	5	113	104	-0.18 (-0.45, 0.08)	0.18	n.s.	0%	n.s.
VOSP number location	5	113	104	-0.03 (-0.30, 0.24)	0.84	n.s.	0%	n.s.
VOSP cube analysis	4	95	90	-0.08 (-0.37, 0.21)	0.61	n.s.	0%	n.s.
Digit span forward	12	312	356	0.0003 (-0.16, 0.16)	1.00	n.s.	0%	n.s.
Digit span backward	11	278	352	-0.07 (-0.23, 0.09)	0.42	n.s.	0%	n.s.
BNT	8	211	280	0.06 (-0.12, 0.24)	0.52	n.s.	0%	n.s.
MDR attention	3	71	84	-0.002 (-0.32, 0.32)	0.99	n.s.	0%	n.s.
MDRS initiation	3	71	84	-0.10 (-0.42, 0.22)	0.54	n.s.	0%	n.s.
MDRS construction	3	71	84	-0.02 (-0.34, 0.30)	0.90	n.s.	0%	n.s.
MDRS conceptualization	3	71	84	-0.03 (-0.35, 0.29)	0.85	n.s.	0%	n.s.

FAB: Frontal Assessment Battery; BFRT: Benton Facial Recognition Test; BNT: Boston Naming Test; FWER: familywise error; JLO: Judgment of Line Orientation Test; K: number of studies; MDRS: Mattis Dementia Rating Scale; n.s.: not significant; NVH: no VH; RAVLT: Rey Auditory Verbal Learning Test; RMF: Warrington's Recognition Memory Test for Faces; TMT: Trail Making Test; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery; WCST: Wisconsin Card Sorting Test.