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Frontal and subcortical contribution to visual hallucinations in dementia with Lewy bodies and Parkinson's disease

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Abstract

Objectives. Visual hallucinations (VH) are common in Lewy body disease (LBD), and have been associated with cognitive and structural brain alterations. Evidence so far concerns mainly Parkinson's disease (PD), but little is known about symptom-specific pathophysiological mechanisms across the LBD spectrum, especially related to the presence of dementia. The aim of the present pilot study was to investigate the neuroanatomical, and neuropsychological characteristics related to VH in two forms of LBD, namely dementia with Lewy bodies (DLB) and PD without dementia. **Methods.** Whole brain voxel-based morphometry (VBM) analyses on 3D MRI acquired structural brain scans, and neuropsychological testing were performed on 28 clinically diagnosed DLB (11 with VH, 17 NVH), and 24 PD (9 with VH, and 15 NVH) patients. In order to assess differences in grey matter (GM) regional volumes, and cognitive performance, hallucinating patients for each group were compared with corresponding non-hallucinating ones. **Results.** DLB patients with VH presented significantly worse visual attention deficits compared to those without, which persisted even when controlling for visual perception. Whole brain VBM analysis revealed decreased GM volume in DLB with VH in the right superior and medial frontal gyri, putamen, caudate nucleus and insula. Subcortical regional volumes were also significantly associated with visual attention performance. Hallucinating PD patients, instead, presented more severe executive dysfunction, but VBM showed no volumetric differences between the two PD subgroups. *Post hoc* region of interest analyses revealed striatal GM loss in PD with VH. **Conclusion.** Frontal and striatal GM atrophy may contribute to the emergence of VH in DLB, which may be fostered by the more severe attention deficits. Striatal GM loss and executive dysfunction, instead,

appeared to underlie VH in PD without dementia.

Keywords: visual hallucinations; Lewy body; Parkinson's disease; dementia with Lewy bodies; MRI; VBM; grey matter; frontal; striatum; attention; executive dysfunction

1.0 Introduction

The main pathological feature of Lewy body disease (LBD) is the inclusion of pathologic α-synuclein aggregates called Lewy bodies (LBs) [1,2]. Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) are clinical manifestations of LB pathology, and share clinical features, among which visual hallucinations (VH). VH are among the core characteristics for a diagnosis of DLB, and they have been identified as the more specific clinical feature differentiating DLB from Alzheimer's disease (AD) at early stages [3,4]. VH may be considered a marker of LB pathology, being a strong predictor of LBs accumulation [4-6].

VH are often present since the early stages of DLB, and are considered an important hallmark of the disorder [3]. On the other hand, they tend to occur later in the progression of PD, with longer disease duration identified as independent predictor of VH in this disease [7,8]. VH tend to be more frequent, complex and severe in patients with DLB and PD-dementia (PDD), who are often unaware of the unreal nature of their sensory experience [6].

Despite the high rate of VH in DLB, their cognitive and neuroanatomical correlates in this disorder have not been studied extensively, while more evidence is available for PD. Collerton et al. [9] suggested that VH generate from a combined deficit in top-down and bottom-up processes, respectively in visual attention and visual perception. Visuoperceptive and visuoconstructive deficits have been found in patients with VH by several neuropsychological studies in PD [10-17], and some in DLB and PDD [18,19]. On the other hand, contrasting findings are available for visual attention, some showing poorer performance in PD [11,13,20] and DLB [21] with VH, but not others [22,23]. To our knowledge, no study so far has taken into account the interaction between these deficits, investigating whether there is an interplay between disruptions in these two aspects of cognition in LBD patients with VH.

Neuroimaging techniques have been used to explore *in vivo* functional and structural brain features related to VH in LBD [24]. Among structural anatomical features, grey matter (GM) loss in occipito-temporal regions represents one of the most consistent findings characterising PD with VH, while the scarce evidence available for DLB suggests a greater involvement of frontal areas [25-29]. Some findings have also been confirmed by FDG-PET and SPECT studies that identified reduced glucose metabolism/perfusion in occipito-temporal, occipital, and parietal regions in hallucinating LBD patients with and without dementia, but inconsistencies have been reported about frontal hypometabolism [22-24,30-32]. Neuropathological studies, however, have reported high concentration of LBs in hallucinating patients, mainly in temporal and frontal regions [8,33,34]. In this context, VH may generate from concomitant impairments of large-scale functional networks for visual attention, with frontal atrophy as structural marker, and dysfunctional visual processes, underlined by occipito-temporal atrophy and hypometabolism [24]. However, due to the limited amount of studies in the field, this hypothesis needs further investigation. Moreover, VH in LB dementia have been investigated by a few studies only, making difficult to infer if and how neuroanatomical and neurocognitive features associated with VH differ across the LBD spectrum, especially relative to the presence of dementia. Despite the relationship between VH and cognitive impairment, the association between specific cognitive domains and brain regions and networks altered in LBD patients with VH is still a poorly investigated area [24].

Top-down modulation refers to the goal-based neural modulation of cortical sensory areas to prioritise the processing of task-relevant information [35]. The neural mechanism underlying the top-down control of spatial attention has been shown to rely on a fronto-parietal network of brain regions, directly interconnected to each other, and indirectly through subcortical hubs located in the striatum, and the pulvinar nucleus of the thalamus [35,36]. The role that these subcortical nuclei play in top-down attentional control suggests that their alteration may also constitute a vulnerability to VH.

In an attempt to reconcile findings in the current literature, the present pilot study aimed at investigating the cognitive and anatomical brain features related to VH in separate samples of patients with DLB and PD without dementia. Firstly, we explored whether there was an interplay between deficits in top-down (visual attention) and bottom-up (visual perception) mechanisms in the expression of VH. Then, a whole brain VBM approach was used to detect brain volumetric differences between patients with and without VH (VH versus NVH) within each diagnostic group, and correlational analyses were run to identify regional brain volumes associated with visual attention and visual perception/construction. We expected GM loss in fronto-parietal regions and subcortical nuclei (pulvinar and striatum), sustaining attention deficits, and occipito-temporal areas, related to impaired perception abilities.

2.0 Materials and Methods

2.1 Sample

The present study involved 28 clinically diagnosed patients with DLB (11 VH and 17 NVH), and 24 patients with idiopathic PD[1] (9 VH, and 15 NVH). In order to assess further structural brain abnormalities in PD with and without VH, 15 healthy controls were also included in the neuroimaging section of the study. This study was approved by the ethical committee of Padua Teaching Hospital, Padua, Italy, where data for the DLB group were collected and by the Institutional Review Board of the IRCCS Fondazione Ospedale San Camillo, Venice, Italy, where data for the PD group were collected. Informed consent was obtained from each participant.

Clinical diagnosis of DLB was based on the consensus criteria proposed by the DLB consortium [3]. DLB patients were included in the study if they presented mild to moderate cognitive

[1] Data for the PD sample were collected while Angelo Antonini was employed by the IRCCS Fomdazione Ospedale San Camillo, Venice, Italy

decline, as assessed using a Mini-Mental State Examination (MMSE) test score cut-off of 18 or above. None of the patients presented severe cerebrovascular disease, assessed by brain CT or MRI scan, history of psychiatric disorders, and severe eye pathology impairing visual acuity (cataract, glaucoma, macular degeneration). Specifically, a neuro-ophthalmologic assessment was carried out including external inspection of the eyes, pupil reactions, penlight reflex, measure of near vision acuity, ocular movements and estimation of the visual field by confrontation test. Visual acuity and visual field were normal (or corrected to normal for visual acuity) in all patients. Medications used included: cholinesterase inhibitors, benzodiazepines, antidepressants. Neuroleptic drugs were taken by 45% of patients with VH and by one without VH. Only patients on a stable dose of cholinesterase inhibitors and/or levodopa for at least 3 months were included in the analyses.

Diagnosis of PD was based on the UK PD Brain Bank Criteria [37]. Patients with mild/moderate and severe cognitive decline were excluded from the study, using a MMSE cut-off of 24. According to the Hoehn and Yahr (H&Y) staging system, all patients were in the mild stage of the disease (between stage 1 and 3) [38]. Patients had no previous history of psychiatric or other neurological disorders, except for one patient with VH who had a history of depressive symptoms. All patients in this group also had a neuro-ophthalmologic assessment as describef above. Visual acuity and visual field were normal (or corrected to normal for visual acuity) in all patients. All PD patients were treated with levodopa and 75% of them with dopamine agonists. Besides levodopa, dopaminergic therapy included pramipexole (n=13), pergolide (n=1) and ropinirole (n=4). Levodopa equivalent dose (LED) in mg/d was calculated for each antiparkinsonian medication as described by Moller et al. [39]. Other medications used were: monoamine oxidase inhibitors, antidepressants and benzodiazepines.

The healthy control sample included 15 participants with no previous history of psychiatric or neurological diseases.

All participants underwent a comprehensive neurological and clinical examination. In DLB, the following were administered: Unified Parkinson's Disease Rating Scale motor score subsection III (UPDRS-III) [40], Mayo Fluctuations Questionnaire [41], and the Mayo Sleep Questionnaire [42]. Disease severity for patients with PD was measured using the Hoehn and Yahr (H&Y) scale [38]. Behavioural disorders were evaluated with the Neuropsychiatric Inventory (NPI) questionnaire [43]. The NPI subsection for hallucinations was used to assess the presence, severity and frequency of VH. Only patients with recurrent, complex VH were included in the study. The sensory modality of hallucinatory phenomena was ascertained with a qualitative assessments of reported patients' experiences.

2.2 Neuropsychological assessment

Global cognitive functioning was evaluated with the MMSE [44]. Each patient underwent a comprehensive neuropsychological assessment using the Italian version of each test. Visual attention deficits were evaluated with the digit cancellation test [45], and the Trail Making Test part A (TMT-A) [46]. Assessment of visuoperceptive/visuo-spatial and visuoconstructive abilities was performed with the Visual and Object Space Perception (VOSP) Battery [46,47], and Rey-Osterrieth Complex Figure (ROCF) [48], respectively.

An extensive battery of neuropsychological tests was used for screening for cognitive impairment and to ensure that patients with and without VH were comparable in severity. This battery included: Frontal Assessment Battery (FAB) [49,50], letter fluency [46], and a short version of the Stroop colour-word test [51] test for executive functioning; prose memory test [52] and Rey Auditory Verbal Learning Test (RAVLT) [46] for verbal long-term memory; clock drawing test [53] for visuospatial and executive abilities; digit span forward and backward [46,54] for short-term and working memory.

The following tests were administered to DLB patients only: digit cancellation, clock drawing test and VOSP; while the following just to PD patients: RAVLT, Stroop test and FAB. Scores for all the remaining tests were available for both groups.

2.3 MRI acquisition

Three dimensional T1 weighted structural scans were all acquired with the same MRI scanner, a 1.5 Tesla Philips Achieva running the same software release. The sequence used was a Turbo Field Echo and acquisition was sagittal. The following acquisition parameters were applied: TR=7.4 ms, TE=3.4 ms, field of view (FOV): 220 mm for DLB and 230 for PD, flip angle: 8°, 160 slices, voxel dimension 1.04x1.04x0.66 mm, gap 0.6.

2.4 VBM pre-processing

Whole brain VBM was carried out using the Statistical Parametric Mapping (SPM) 12 software (Wellcome Centre for Human Neuroimaging, London, UK), running on MATLAB R2014a, version 8.3 (The MathWorks, Icn, Natick, Massachussetts), including pre-processing and statistical analyses. First, structural MRI data were manually reoriented to the Anterior Commissure-Posterior Commissure line, segmented into GM, white matter (WM) and cerebrospinal fluid (CSF), spatially normalised to MNI space, and modulated to preserve absolute volumes. Images were, then, smoothed using a FWHM 8mm isotropic Gaussian kernel. Total GM, WM, and CSF volumes were determined using the MATLAB "get_totals" script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) from each image in native space. Total intracranial volume (TIV) was calculated for each patient by summing GM, WM and CSF total volumes.

2.5 Statistical analyses

IBM SPSS Statistics 22 was used to assess differences in demographic, clinical and neuropsychological characteristics, and total brain volumes within each diagnostic group. For the DLB group, differences between patients with and without VH were investigated using the following statistics: independent sample t-test and Mann-Whitney U test for normally and non-normally distributed numerical variables respectively; Fisher's Exact Test was used for categorical variables. Differences in demographics between PD subgroups and healthy controls were assessed using one-way ANOVA and Kruskal-Wallis tests for normally and non-normally distributed numerical variables respectively. Categorical variables were analysed with the Pearson Chi-Square test. Statistical analyses of neuropsychological tests were conducted as detailed above for the DLB group. Bonferroni correction was applied to account for multiple comparisons, by which statistical significance is reached with a p value $< \alpha/n$, where α is equal to the p value for each comparison (p=0.05) and n the number of comparisons. Corrections were applied independently to the screening set and to the experimental set. For DLB group comparisons, significance level was lowered to p = 0.0033 for the screening set and to p = 0.0125 for the experimental set. For the PD group comparisons, significance level was lowered to p = 0.0055 for the screening set and to p = 0.025 for the experimental set. Non-parametric correlations (Spearman's rho test) were run between VH severity and frequency, and attention and visuospatial tests within each diagnostic group.

A general linear model (GLM) was used to assess attentional deficits in patients with VH controlling for visuoperceptive/visuoconstructive deficits, separately for each patient group. Specifically, ANCOVA analyses were performed by entering performance on a relevant attention test as the dependent variable, performance on a visuoperceptive/visuoconstructive test as a covariate of no interest, and the presence of VH as a fixed factor. Moreover, in order to investigate changes in visuoperceptive/visuoconstructive deficits accounting for visual

attention deficits, an ANCOVA design was used with a visuoperceptive/visuoconstructive test as the dependent variable, an attention test as covariate of no interest, and the presence of VH as a fixed factor.

In the VBM analyses, GLM with TIV and age as covariates of no interest was used to determine differences between groups in GM and WM volumes. TIV was included in the model to account for individual global differences while investigating regional changes. Within each diagnostic group, the following contrasts were performed: VH < NVH and VH > NVH. Each PD subgroup was further compared to a group of healthy controls. The same procedure was performed for whole brain correlation analyses, undertaken to assess the association between regional GM volumes, cognitive functions and VH severity and frequency.

To exclude voxels outside the brain, relative threshold masking of 0.2 and 0.8 were applied for GM and WM analyses, respectively. Significance level was set at $p<0.001$ uncorrected for multiple comparisons (set-level). A cluster-level threshold of $p<0.05$ FWE (family wise error) corrected for multiple comparisons was chosen to report significant results in all the analyses.

Montreal Neurological Institute (MNI) coordinates were converted into Talairach coordinates using GingerALE, version 2.3.6 (available online at http://www.brainmap.org/ale/). Then, the Talairach Client, version 2.4.3 (available online at http://www.talairach.org/client.html) was used to determine brain region labels for each significant cluster. White matter regions were determined using the following atlases: the JHU white-matter tractography and ICBM-DTI-81 white-matter labels atlases, available on FSL [55-57].

2.6 Post hoc region of interest analyses

To assess our *a priori* hypothesis of an involvement of the pulvinar and the striatum in the mechanisms underlying VH, ROIs were placed *post-hoc* in the left and right pulvinar, putamen and caudate nucleus, and other control regions, namely the left and right lateral geniculate

body, hippocampus and primary motor cortex. The lateral geniculate body was chosen as control nucleus of the thalamus, the hippocampus as control region involved in cognitive processing, and the primary motor cortex as control region not involved in high cognitive functioning. ROIs were created with the WFU PickAtlas toolbox, version 3.0.5 [58,59], specifically using the Brodmann Area atlas based on the Talairach Daemon (TD) database [60,61]. In order to investigate whether the VBM results were associated with cognitive performance, ROI masks were generated *post hoc* based on the significant clusters from the VBM analysis. Further *post hoc* analyses were undertaken within the PD sample to assess group differences in line with our *a priori* hypotheses. The ROIs were chosen in frontal, parietal, occipital and occipito-temporal regions. Specifically, differences between PD patients with and without VH were investigated in the following ROIs: left and right frontal eye field (BA 8), superior parietal lobule (BA 7), primary visual cortex, secondary visual cortex (BA 18), visual associative cortex (BA 19), inferior temporal area (BA 20), and occipitotemporal area (BA 37). The frontal eye field and the superior parietal lobule were chosen for their role in goal-directed visual attention [36,62,63]. On the other hand, the formation of objects visual representations is sustained by a ventral visual pathway, identified in an occipito-temporal network of regions lying between primary visual cortices and other specialised areas involved in memory and learning, forming representations comprising stable elements of visual information [64]. Key regions in this process include primary and associative visual cortices, occipito-temporal cortex, and inferior temporal areas [64,65].

GM volumes in these regions were extracted from each patient's smoothed, segmented, normalised, and modulated image by using the MarsBar toolbox for SPM (http://marsbar.sourceforge.net). Then, volumetric differences between hallucinating and non-hallucinating patients within each diagnostic group were, then, assessed performing ANCOVA analyses with TIV and age as covariates of no interest. Volumes were also correlated with the scores achieved on relevant cognitive tests using the same covariates (partial

correlations). Non-parametric correlations (Spearman's rho) were also performed to investigate the relationship with VH severity and frequency.

3.0 Results

3.1 Demographic and clinical features

Details and statistical tests on demographic, clinical, volumetric characteristics are reported in Table 1 and Table 2 for DLB and PD patients, respectively. The two subgroups of DLB patients did not significantly differ in age, gender, years of education, age of onset, duration of disease, presence of cognitive fluctuations, and UPDRS scores. Patients with DLB and VH presented higher percentage of RBD symptoms and had higher NPI scores. PD patients with and without VH and healthy controls did not differ significantly in age, gender and years of education. No differences were detected between PD subgroups in disease duration, H&Y scores, presence of sleep disturbances and LED. The most common sleep disturbance was repeated awakenings. Only one patient with VH presented RBD. PD patients with VH had higher NPI total scores; differences remained significant also after subtracting the NPI hallucination subscore.

- Insert Table 1 and Table 2 about here -

3.2 Neuropsychological findings

3.2.1 Dementia with Lewy bodies

A summary of scores on the screening tests is given in Table S1. Patients with VH had similar performance in global cognitive functioning, compared with patients without, as assessed with the MMSE (p=0.07).

To test the hypothesis of an involvement of visual attention and visual perception/construction in the development of VH, the following experimental tests were

taken into account: digit cancellation test, TMT-A, VOSP subtest silhouettes, copy of the Rey figure. The results from the comparison between patients with and without VH in these tests are reported in Table 3. Patients with VH had poorer performance in the digit cancellation test (p=0.01, Figure 1). Differences in the digit cancellation test were marginally significant when controlling for global cognitive functioning assessed with the MMSE (ANCOVA analysis, p=0.05). Even though statistically not significant, patients with VH presented worst performance on the copy of the Rey figure, with 4 patients out of 9 scoring 0 (as opposed to 1 patients out of 14 in the non-hallucinating group) (Fisher's Exact Test, p=0.06). Difference in the TMT-A showed a trend towards significance, even when controlling for MMSE (ANCOVA analysis, p=0.05).

- Insert Table 3 and Figure 1 about here -

Differences in the digit cancellation test persisted even when controlling for the VOSP subtest silhouettes (ANCOVA analysis, p=0.04), and the copy of the Rey figure (ANCOVA analysis, p=0.03). No differences were found in VOSP silhouettes (ANCOVA analysis, p=0.56) and copy of the Rey figure (ANCOVA analysis, p=0.71) when controlling for digit cancellation scores.

Non-parametric correlation analyses (Spearman's rho test) showed no significant association between severity and frequency of VH and performance on the digit cancellation, VOSP silhouettes, and copy of the Rey figure. Scores on the Rey figure copy was significantly correlated with VH frequency (p=0.03). When considering the NPI hallucination score (frequency x severity), performance on the TMT-A (p=0.003) and Rey figure copy (p=0.03) was found to correlate significantly, but not the digit cancellation test and the VOSP silhouettes.

Results for the other neuropsychological tests are reported in supplementary materials. Briefly, VH patients presented greater impairment compared with NVH only in the digit span backward (p=0.04), and delayed recall of Rey figure (p=0.03). None of these significant differences survived correction for multiple comparisons (p<0.003). Moreover, when

accounting for MMSE scores, differences in the digit span backward (ANCOVA analysis, p=0.23) and Rey figure delayed recall (ANCOVA analysis, p=0.16) were no longer significant. No significant differences were found in the following tests: digit span forward, prose memory (immediate and delayed recall), letter fluency, clock drawing, copy of the Rey figure, and all the VOSP subtests.

3.2.2 Parkinson's disease

A summary of scores on the screening tests is given in Table S2. PD patients with and without VH did not differ significantly in global cognitive performance (MMSE, Post-hoc Dunn's pairwise test, p=0.52), but MMSE scores were significantly lower than controls (Post-hoc Dunn's pairwise test, VH vs. controls: p=0.001; NVH vs. controls: p=0.03).

No differences between patients with and without VH were detected in the TMT-A and Rey figure copy. Results are reported in Table 4. ANCOVA analyses revealed no significant differences in the TMT-A controlling for the copy of the Rey figure (p=0.49); and no differences in the Rey figure copy controlling for the TMT-A (p=0.76). Non-parametric correlations (Spearman's rho) showed no significant association between TMT-A and copy of the Rey figure, and VH severity, frequency, and NPI hallucination score.

- Insert Table 4 about here -

Patients with VH presented greater impairment compared with those without in the RAVLT immediate recall (p=0.03), and FAB (p=0.006). Differences in scores on the letter fluency test were marginally significant (p=0.05) between VH and NVH groups. None of the differences survived correction for multiple comparisons (p<0.006). No significant differences were found in the following tests: digit span forward and backward, RAVLT delayed recall, Rey figure recall, Stroop tests (seconds and errors). In the comparison between patients with and without VH, differences in the FAB remained significant (ANCOVA analysis, p=0.02) after controlling for the

NPI total score minus the NPI hallucination subscore, but those in RAVLT immediate recall (ANCOVA analysis, p=0.08), and letter fluency (ANCOVA analysis, p=0.31) did not. *Post-hoc* correlation analyses on the tests where significant differences between VH and NVH patients were present revealed significant correlations (Spearman's rho) between the NPI hallucination score and performance on the FAB (p=0.001), and RAVLT immediate recall (p=0.03), but not on letter fluency (p=0.08). The total NPI score minus NPI hallucination also correlated with performance on the FAB (p=0.02), and letter fluency (p=0.03), but not on the RAVLT (p=0.15).

3.3 Whole brain VBM findings

3.3.1 Dementia with Lewy bodies

Reduced GM in DLB patients with VH in comparison with those without was found in three clusters located in frontal and subcortical areas. Specifically, peak coordinates were shown in the right superior frontal gyrus, putamen and medial frontal gyrus, with TIV and age included as covariate of no interest (Table 5 and Figure 2). All clusters were significant at a cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons. When the analysis was repeated including MMSE as covariate of no interest (in addition to TIV and age), only one cluster survived cluster-level correction for multiple comparisons. Peak coordinates were found in the right superior frontal gyrus, BA 10 (MNI coordinates: x=9, y=62, z=-12; cluster size: k=703 voxels; T score: 6.09; Z score: 4.65; p=0.01). Sub-peaks were located in the right superior frontal (BA 10; MNI coordinates: x=21, y=62, z=4; T score: 5.01; Z score: 4.08) and middle frontal gyri (MNI coordinates: x=34, y=54, z=-9; T score: 4.74; Z score: 3.92).

- Insert Table 5 and Figure 2 about here -

Whole brain analysis on WM revealed one cluster of reduced volume in the forceps minor/genu of corpus callosum (Table 5), which disappeared when adding MMSE scores in the model as covariate of no interest.

Whole brain correlation analyses showed positive associations between a) the digit cancellation test scores and the right putamen and left caudate nucleus volumes, and b) the VOSP silhouettes subtest scores and the right inferior temporal gyrus volume (Table 5 and Figure 3). No regions of GM volume were associated with scores on the copy of the Rey figure, VH severity and frequency.

- Insert Figure 3 about here -

3.3.2 Parkinson's disease

The same analyses in PD patients yielded no between group differences in regional GM and WM volumes using a cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons. No differences were found between each PD subgroup and a group of healthy controls. The analyses were repeated with no covariates of no interest, but no results reached statistical significance.

3.4 Post hoc region of interest analyses

3.4.1 Dementia with Lewy bodies

ROI analyses reported statistically significant differences in the left ($p=0.0004$) and right caudate nucleus ($p=0.002$), left putamen ($p=0.04$), left ($p=0.02$) and right hippocampus ($p=0.01$), using an ANCOVA design with TIV and age as covariates of no interest. Adding MMSE as covariate to the design, the left ($p=0.002$) and right caudate nucleus ($p=0.02$), the left putamen ($p=0.04$), the left hippocampus remained significant ($p=0.03$), while the right was only marginally significant ($p=0.05$). The only differences that survived correction for multiple comparisons ($p<0.004$) were in the left and right caudate nucleus. No significant differences were found in the other ROIs.

In order to investigate whether regions of reduced GM were associated with cognitive deficits, volumes within the clusters that were found to be significantly different between DLB subgroups were extracted and correlated with performance on the digit cancellation test and the TMT-A (assessing visual attention) within the whole DLB group. Partial correlational analyses (controlling for TIV and age) showed a statistically significant positive association between scores on the digit cancellation and the subcortical ROIs (within the putamen, insula and caudate nucleus; n=26, R=0.58, p=0.003; Figure 4). No other significant correlation was found with the ROIs based on the VBM results. Partial correlations were also run between the digit cancellation and TMT-A scores and the left and right pulvinar, in line with our hypothesis, which showed no significant results. None of the ROIs was associated with severity and frequency of VH (Spearman's rho correlations).

- Insert Figure 4 about here -

3.4.2 Parkinson's disease

ROI analyses were performed to investigate differences between patients with and without VH in PD, based on *a priori* hypotheses (covariates: TIV, age). Even though not surviving correction for multiple comparisons ($p<0.002$), significant differences were found in the left ($p=0.008$) and right caudate nucleus ($p=0.005$). These results remained significant even when adding MMSE to the model. As shown in Figure 5, these regions significantly correlated with scores on the FAB (n= 13) and the TMT-A (n=22). Specifically, partial correlations (TIV, age and MMSE as covariates) revealed significant positive associations between FAB scores and the left ($r=0.70$, $p=0.03$) and right ($r=0.68$, $p=0.03$) caudate nucleus, and negative associations between the TMT-A and the caudate nucleus, in the left ($r=-0.48$, $p=0.04$) and right ($r=-0.48$, $p=0.04$) hemispheres. Negative correlations, as assessed with the Spearman's rho test, were also reported with VH frequency (left caudate, $r=-0.46$, $p=0.03$; right caudate, $r=-0.46$, $p=0.03$) and VH severity (left caudate, $r=-0.48$, $p=0.02$; right caudate, $r=-0.47$, $p=0.02$).

- Insert Figure 5 about here -

Other differences were detected in the right putamen (p=0.03), left frontal eye field (p=0.03), while marginally significant in the right frontal eye field (p=0.05). None survived correction for multiple comparisons.

4.0 Discussion

The present pilot study provides evidence of the presence of frontal and subcortical GM loss, and visual attention deficits in DLB patients with VH compared with those without. Specifically, GM atrophy was found in the right superior, middle and medial frontal gyri, and in a subcortical cluster comprising the right putamen, caudate nucleus and insula. Interestingly, GM volumes in the putamen and caudate were significantly associated with performance on a visual attention test, as shown by whole brain correlational analyses. Even though no differences were detected between PD subgroups using whole brain VBM, GM loss in the caudate nucleus bilaterally was found when restricting the analyses to predefined ROIs, suggesting an involvement of this structure also in hallucinating PD patients without dementia. To our knowledge, this is the first whole brain VBM study investigating grey and white matter volumes, and cognitive impairments associated with VH in LBD that included both samples of patients with and without dementia, namely DLB and PD, in comparison with corresponding non-hallucinating patients.

Hallucinating DLB patients presented more severe deficits in visual attention, which remained significant even after accounting for visuoperceptive and visuoconstructive abilities. Studies have reported attention deficits in patients with both DLB and PD with VH [20,21]. The present pilot study adds additional insight about the interaction between attention and visual perception deficits in hallucinating patients. Specifically, the attention deficits shown by hallucinating DLB patients do not seem to rely on disrupted visual perception. Neuropsychological investigations reported evidence of deficits in visual perception in

hallucinating patients with LB dementia [18,19], and PD [10,12,15,16]. In the present study, however, we found no changes in visuoperceptive/visuoconstructive abilities in DLB and PD patients with VH. In spite of this, a non-significant trend indicating worst performance in hallucinating DLB was observed in the copy of the Rey figure. Since visuoperceptive and visuoconstructive deficits represent disease-specific symptoms of DLB [66], differences between VH and NVH patients in these cognitive functions may be subtle, due to the pronounced deficits presented also by non-hallucinating patients. We also found significant correlations between indices of VH and visual attention (TMT-A) and visuoconstructive performance (Rey figure copy), suggesting a contribution of both deficits to VH, as proposed by Collerton et al. [9].

In contrast, PD patients with and without VH presented comparable performance in both attention and visuoconstruction. These contrasting results may be due, at least in part, to slight differences in the neuropsychological tests used to assess attention and visual perception/construction abilities in the two clinical conditions. Some neuropsychological tests may be more sensitive than others in detecting such differences, which may be more subtle in LBD patients without dementia. Exploratory analyses on other cognitive tests revealed more severe executive dysfunction in PD with VH. The cognitive mechanisms underlying VH might be slightly different between DLB and PD, especially concerning top-down control mechanisms. They may be more related to attention deficits in DLB, and executive dysfunction in PD without dementia. Notably, a higher index of neuropsychiatric symptoms, different from VH, was observed in PD patients with VH compared to those without, but not in DLB, which may be linked to the greater executive dysfunctions observed in PD with hallucinations. In support of this view, a recent systematic review reported more severe executive deficits in PD patients with neuropsychiatric symptoms, including depression, apathy, impulse control disorders, and psychosis [67]. However, when controlling for neuropsychiatric symptoms, FAB scores in PD with VH patients were still significantly lower. Executive deficits have been previously

associated with VH in PD without dementia by using different neuropsychological tests, such as letter fluency, Stroop test, FAB, and go/no-go test [13,68-71]. Indeed, there is a notable lack of studies investigating this cognitive aspect in DLB. Executive dysfunction is typically observed in PD, regardless of the presence of dementia, and it has been shown to worsen as the disease progresses [72,73]. Further research is needed to understand better whether there are specific executive domains, and/or top-down attention mechanisms selectively impaired in hallucinating LBD patients with and without dementia. In this context, future studies would be very informative by including a sample of PDD patients, but also VH/NVH subgroups matched for other neuropsychiatric features. This would clarify whether the executive dysfunctions observed are related to the occurrence of VH, or represent disorder-specific features (PD vs. DLB), maybe exacerbated by the presence of comorbid neuropsychiatric symptoms.

DLB patients with and without VH presented GM volumetric differences in three big clusters located in the right hemisphere, specifically in the superior/middle and medial frontal gyri, and subcortical areas, including the putamen, caudate nucleus and insula. All clusters survived a cluster-level threshold of $p<0.05$ corrected for multiple comparisons. Similarly, Sanchez-Castaneda et al. [28] found GM loss in frontal areas in hallucinating patients with both DLB and PDD, which was strongly associated with VH severity in the DLB group. Superior frontal areas have been found to be involved in both spatial and object-based attention [74,75], which may explain the involvement of frontal regions in the development of VH in DLB. In contrast, frontal GM atrophy has not been consistently reported in hallucinating PD patients without dementia. Nevertheless, higher LB density in frontal areas, especially in the middle frontal gyrus, has been associated with VH in autopsy confirmed PD patients [8,34]. We speculate, therefore, that frontal LB accumulation in hallucinating patients may occur earlier in the progression of PD, which may result in macrostructural alterations and attention deficits only later, mainly in patients with concomitant dementia.

In addition to frontal atrophy, DLB patients with VH also showed GM loss in the striatum, both in the caudate and putamen. Due to the involvement of the striatum in attention processes [36], we propose that its macrostructural alterations may underlie dysfunctional pathophysiological mechanisms resulting in attention impairments, and ultimately VH. Interestingly, our whole brain correlation analyses showed an association between volumes in these regions and scores in a visual attention test, further corroborating this hypothesis.

No significant results were detected between PD patients with and without VH using whole brain VBM. However, when restricting the analyses to predefined ROIs, we observed GM loss in subcortical nuclei, especially in the caudate. In turn, regional volumes in the left and right caudate significantly correlated with executive dysfunction, attention deficits, and VH severity. Disrupted fronto-striatal circuits are among the mechanisms believed to underlie the executive dysfunction typical of PD [76,77]. Thus, the striatal atrophy observed in our cohort of PD patients may represent a macrostructural hallmark of dysfunctional brain mechanisms ultimately resulting in executive and attention deficits, as well as VH.

Contrary to our hypothesis, no pulvinar GM abnormalities were detected in association with VH, neither in PD, nor in DLB, suggesting that the visual attention deficits observed in DLB may rely more on other structures of a large-scale attention network, namely frontal and striatal areas. No significant differences were found not even in occipito-temporal regions, in contrast with other previous studies in PD with VH [25,27]. Reduced glucose metabolism/cerebral blood flow have been previously detected in occipito-temporal, occipital, and parietal regions in hallucinating LBD patients [22,23,30,31]. Therefore, it may be that occipito-temporal and parietal hypometabolism represents a functional hallmark of impaired visual processes underpinning VH [24], which may not necessarily result in GM atrophy.

The subcortical cluster found in the VBM analysis also included a sub-peak in the right insula. It has been hypothesised that the insula involvement in discriminating between internally

generated and external information may foster the development of hallucinations in schizophrenia [78]. Insular reduced GM volume has also been associated with hallucinations in other conditions, such as bipolar disorder [79] and AD [80]. The insula, along with the anterior cingulate cortex, represents a central hub of the salience network, involved in generating appropriate behaviour to salient stimuli by detecting and integrating internal and external events [81,82]. Therefore, the GM loss that we observed in the insula may underlie disrupted functional networks fostering the development of attention deficits and VH.

The present pilot study also provided evidence of macrostructural WM alterations in hallucinating DLB patients, mainly detected in the genu of the corpus callosum. As the corpus callosum interconnects corresponding cortical regions, such as the prefrontal and orbitofrontal cortices, it is implicated in different cognitive, sensory and motor functions [83]. Thus, in addition to GM abnormalities, corpus callosum alterations may partially contribute to the cognitive deficits outlined above.

A number of limitations should be taken into account when interpreting the results of the present study. Firstly, the sample size was reasonably small, and for this reason this can only be seen as a reference pilot study for future work. Future studies with larger sample sizes may elucidate further the role of specific cognitive functions and GM abnormalities linked to VH in LBD. Moreover, some clinical and neuropsychological data were not available, due to the retrospective nature of the study. Thus, analyses on cognitive measures included slightly different sample sizes, depending on the variables taken into account. Furthermore, cognitive results obtained for the DLB and PD groups were not fully comparable, due to differences in the neuropsychological testing. The tests used were not specifically designed to assess cognitive deficits related to VH. However, these tests are widely used in clinical settings, suggesting that the results from the present study may be, in the future, more easily transferable to clinical practice. Another limitation concerns the NPI, which is not specific for

the assessment of VH in LBD. Therefore, other tools may be more sensitive in detecting phenomenological characteristics that may clarify some of the differences detected between conditions.

5.0 Conclusion

The present study adds further knowledge about the presence of structural brain abnormalities, and cognitive deficits in LBD patients with VH, and the differences and similarities between clinical conditions experiencing this neuropsychiatric symptom. Our findings suggest that attention deficits, and their neural substrates, may play a significant role in the development of VH, in line with integrative models of VH. [9,84]. Specifically, Collerton et al. [9] proposed that VH might be the result of the combination of attentional and perceptual deficits. Our findings confirm the model only in part. Indeed, we found that DLB patients with VH had more severe deficits in visual attention, compared to patients without, which seemed to be independent from deficits in visual perception/construction. In turn, visuoconstructive deficits correlated with VH indices, but no between-group differences were detected. We suggest, therefore, that top-down attention mechanisms might have a predominant role in the development of VH, especially in patients with dementia. This is consistent with the pattern of GM atrophy we found in these patients, given the important role played by a network of fronto-parietal regions and the striatum in the top-down control of attention [35,36].

On the other hand, GM atrophy was identified in the striatum in PD without dementia only when restricting the analyses to predefined ROIs. We speculate that prefrontal macrostructural alterations might be more pronounced in hallucinating LBD patients with dementia. Cognitive changes, instead, may be detectable also in cognitively normal PD, and may be a behavioural hallmark of more severely disrupted fronto-striatal circuits. However,

the relationship between attention and executive deficits in PD, and their role in the development of VH still needs further clarification.

The presence of VH has a significant impact on the quality of life of patients and their caregivers, and they have been found to be a strong predictor of institutionalisation in PD [6,85]. However, there is currently no treatment specifically targeted to VH. Neuroimaging methods, and neuropsychological measures represent valuable tools that might provide a better understanding of the neural substrates, and cognitive deficits associated with the development of VH in LBD. In this context, the detection of symptom-specific biomarkers, and a wider knowledge of the underlying pathophysiology, may be helpful in the development of new targets to be used in the assessment of treatments efficacy in clinical trials.

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Figure captions

Figure 1. Significantly lower scores in the digit cancellation in DLB VH compared with NVH. ** $p<0.01$.

Figure 2. Regions of reduced GM volume in DLB patients with VH compared to those without: A) right medial orbitofrontal cortex, superior frontal, middle frontal and rectus gyri, and B) right putamen, insula and caudate nucleus; C) right gyrus rectus. The colour bar indicates the z scores with the cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons, with TIV and age as covariates of no interest. Images are shown in neurological orientation, i.e. L/L, R/R.

Figure 3. Results from whole brain voxel-based positive correlation between grey matter volumes and A) digit cancellation and B) VOSP silhouettes scores. The colour bar indicates the z scores with the cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons with TIV and age as covariates of no interest. Images are shown in neurological orientation, i.e. L/L, R/R.

Figure 4. A) Subcortical ROI of decreased grey matter volume as resulted from VBM analysis (ROI regions: right putamen, insula and caudate). B) Scatterplot showing the significant correlation between the digit cancellation test scores and the ROI volumes (MRI signal).

Figure 5. Top) ROIs: left (in red) and right (in blue) caudate nucleus. Bottom) Scatterplots showing the significant correlation between the ROIs volumes (MRI signal) and the FAB and TMT-A (seconds) scores.

Table 1. Demographic, clinical and volumetric characteristics of DLB patients with and without VH. Mean and SD values are reported for each variable unless otherwise specified.

Characteristic	**DLB VH (n=11)**	**DLB NVH (n=17)**	**p value**
Demographics			
Age	75.09 (5.03)	73.65 (6.47)	0.54 [a]
Gender M:F	4:7	9:8	0.46 [b]
Years of education	6.09 (3.24)	8 (4.90)	0.30 [c]
Clinical features			
Disease duration (years)	2.64 (1.21)	2.06 (1.30)	0.17 [c]
MMSE	22.45 (3.45)	25.00 (3.50)	0.07 [a]
UPDRS III	8.00 (11.86)	4.59 (5.92)	0.83 [c]
RBD [d]	91%	47%	0.04 [b]
Cognitive fluctuation	73%	88%	0.35 [b]
NPI total score	15.82 (9.64)	5.53 (3.7)	<0.01 [c]
NPI tot minus NPI hallucination	11.64 (9.51)	5.53 (3.71)	0.17 [c]
Brain volumes (ml)			
Total GM volume	479.20 (51.83)	493.39 (30.86)	0.37 [c]
Total WM volume	441.79 (65.81)	447.31 (59.50)	0.82 [c]
Total CSF volume	525.06 (81.66)	479.73 (82.30)	0.17 [c]
Total intracranial volume	1446.04 (134.09)	1420.43 (140.75)	0.64 [c]

CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; F: female; GM: grey matter; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no visual hallucinations; RBD: REM sleep behaviour disorder; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; VH: visual hallucinations; WM: white matter. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Mann-Whitney U test; [d] Missing data for a VH patient.

Table 2. Demographic, clinical and volumetric characteristics of PD patients with and without VH. Mean and SD values are reported for each variable unless otherwise specified.

Characteristic	**PD VH (n=9)**	**PD NVH (n=15)**	**Controls (n=15)**	**p value**
Demographics				
Age	67.00 (10.56)	67.33 (8.05)	67.27 (8.99)	1.00 [a]
Gender M:F	5:4	10:5	10:5	0.83 [b]
Years of education	11.33 (5.27)	11.33 (4.24)	11.47 (4.21)	0.97 [c]
Clinical features				
Disease duration (years)	9.89 (5.68)	10 (4.23)	–	0.76 [d]
MMSE	26.22 (2.05)	27.60 (1.68)	29.27 (0.88)	0.001 [c]
H&Y [f]	2 (1.00)	2.29 (0.95)	–	0.60 [d]
LED mg/d	608.33 (247.18)	546.27 (204.35)	–	0.51 [e]
Sleep disturbances	89%	67%	–	0.22 [b]
NPI total score	32.67 (25.45)	9.00 (9.89)	–	0.01 [d]
NPI tot minus NPI hallucination	28.00 (24.60)	9.00 (9.89)	–	0.03 [d]
Brain volumes (ml)				
Total GM volume	561.69 (71.52)	613.79 (64.86)	604.25 (59.94)	0.16 [a]
Total WM volume	458.48 (58.26)	498.09 (64.64)	460.21 (49.37)	0.14 [a]
Total CSF volume	393.29 (93.24)	376.86 (87.48)	378.03 (86.31)	0.89 [a]
Total intracranial volume	1413.46 (159.90)	1488.74 (146.13)	1442.48 (105.78)	0.40 [a]

CSF: cerebrospinal fluid; F: female; GM: grey matter; H&Y: Hoehn and Yahr scale; LED: Levodopa equivalent dose; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no visual hallucinations; PD: Parkinson's disease; SD: standard deviation; VH: visual hallucinations; WM: white matter. [a] One-way ANOVA; [b] Pearson Chi-Square; [c] Kruskal-Wallis Test; [d] Mann-Whitney Test; [e] Independent-sample t-test; [f] Missing data for 4 VH patients and 8 without VH.

Table 3. Differences in neuropsychological tests assessing visual attention and visual perception/visuoconstruction between DLB patients with and without VH.

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit cancellation	10	24.40 (8.90)	25.00 (12.00)	16	34.81 (9.90)	37.50 (16.00)	0.01 [a]
TMT-A (seconds)	8	184.00 (94.00)	139.50 (152)	14	123.64 (73.04)	96.50 (61.00)	0.05 [b]
Rey figure copy	9	11.94 (15.04)	2.00 (28.5)	14	20.68 (10.86)	22.00 (19.13)	0.16 [b]
VOSP Silhouettes	11	9.45 (5.37)	10.00 (7.00)	16	12.44 (3.76)	13.00 (5.25)	0.10 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; TMT-A: Trial Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

Table 4. Differences in neuropsychological tests assessing visual attention and visuoconstruction between PD patients with and without VH.

Test	PD VH			PD NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
TMT-A (seconds)	7	71.43 (23.75)	64.00 (38.00)	15	61.20 (31.01)	58.00 (39)	0.45 [a]
Rey figure copy	8	28.06 (2.47)	28.50 (4.30)	14	27.86 (7.15)	29.00 (12.90)	0.92 [a]

IQR: interquartile range; NVH: no visual hallucinations; PD: Parkinson's disease; SD: standard deviation; TMT-A: Trial Making Test A; VH: visual hallucinations. [a] Independent-sample t-test.

Table 5. Regions of reduced GM and WM volume in DLB patients with VH compared to NVH, and whole brain voxel-based correlations between GM volumes and digit cancellation and VOSP silhouette.

Structure	Side	Cluster size	MNI coordinates			T score	Z score	p value [a]
GM loss in DLB patients with VH								
Superior Frontal Gyrus (BA 10)	R	1328	9	62	-12	6.28	4.79	<0.001
Superior Frontal Gyrus (BA 10)	R		21	62	4	5.41	4.33	
Middle Frontal Gyrus	R		34	54	-9	5.06	4.14	
Putamen	R	625	26	20	-4	5.50	4.38	0.02
Insula (BA 13)	R		38	26	4	4.44	3.76	
Caudate Head	R		14	20	-2	3.83	3.35	
Medial Frontal Gyrus (BA 11)	R	576	3	45	-27	4.57	3.84	0.03
Medial Frontal Gyrus (BA 11)	R		6	32	-26	4.44	3.76	
WM loss in DLB patients with VH								
Forceps minor / Genu of corpus callosum	R	1043	9	30	0	4.55	3.83	<0.001
Body of corpus callosum	R		16	15	24	4.38	3.72	
Right Anterior thalamic radiation / Genu of corpus callosum	R		20	24	21	4.36	3.71	
GM volumes and digit cancellation positive correlation								
Putamen	R	599	22	14	3	5.59	4.37	0.02
Caudate Body	R		15	-3	20	4.51	3.76	
Caudate Body	R		18	-12	21	4.32	3.63	
Caudate Body	L	482	-15	-4	24	5.47	4.30	0.05
Caudate Body	L		-20	10	18	5.18	4.14	
Caudate Body	L		-9	-2	14	3.67	3.21	
GM volumes and VOSP silhouettes positive correlation								
Inferior Temporal Gyrus (BA 20)	R	1059	60	-36	-20	5.32	4.25	0.002
Middle Temporal Gyrus (BA 21)	R		66	-28	-14	5.29	4.23	
Middle Temporal Gyrus (BA 21)	R		64	-22	-20	4.87	4.00	

BA: Brodmann area; DLB: dementia with Lewy bodies; FWE: family-wise error; GM: grey matter; NVH: no VH; TIV: total intracranial volume; VH: visual hallucinations; WM: white matter. [a] Cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons with TIV and age as covariates of no interest.

Figure 1

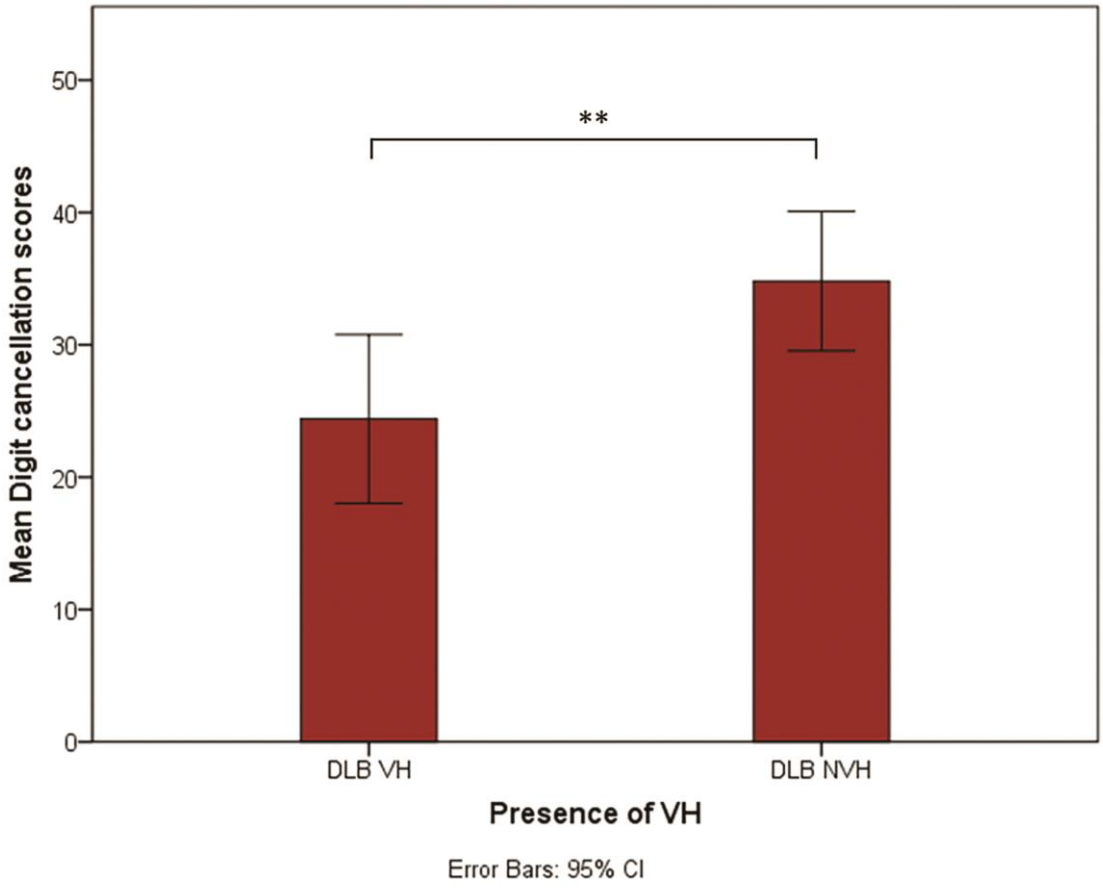

50
40
30
20
10
0
**
Mean Digit cancellation scores
DLB VH
DLB NVH
Presence of VH
Error Bars: 95% CI

Figure 2

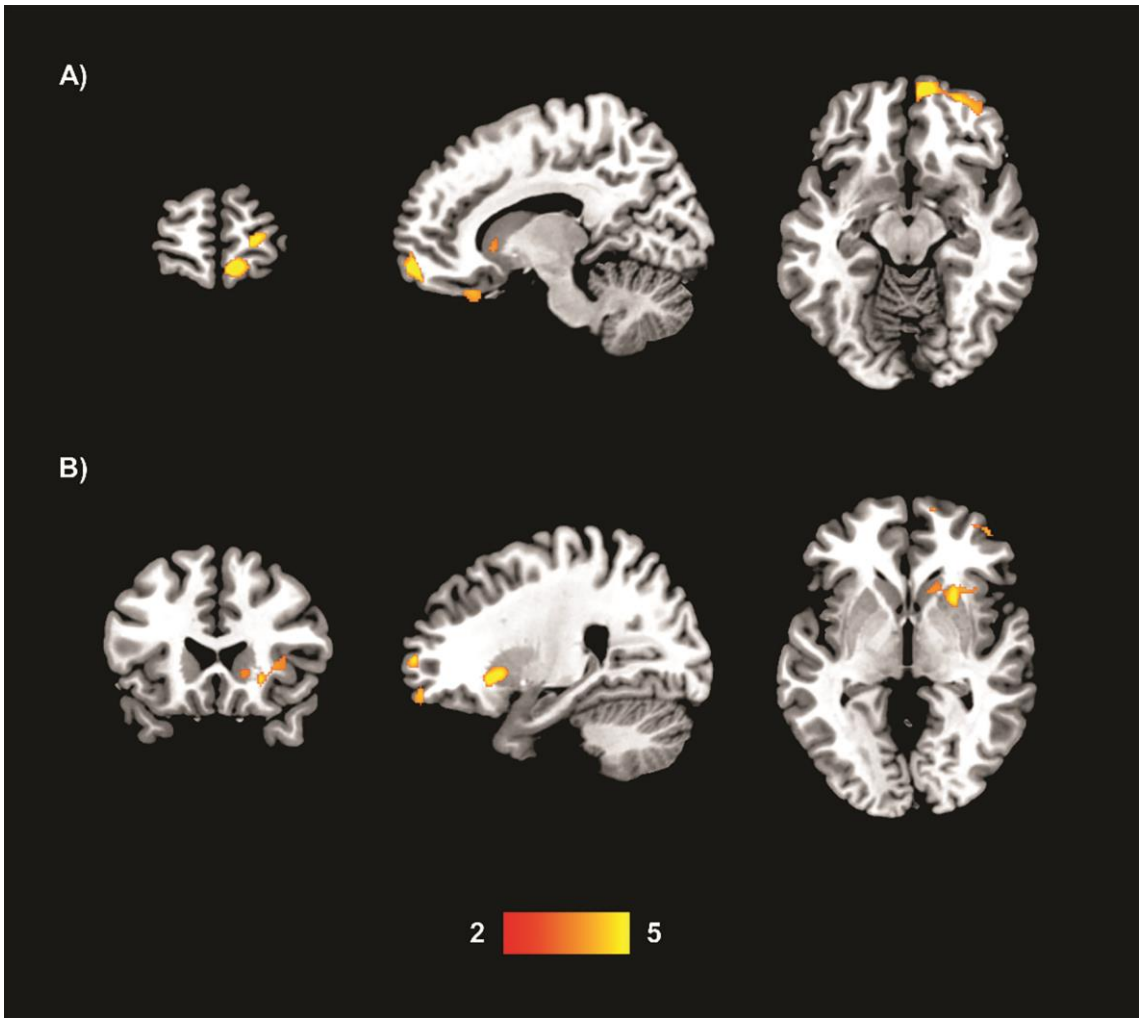


Figure 3

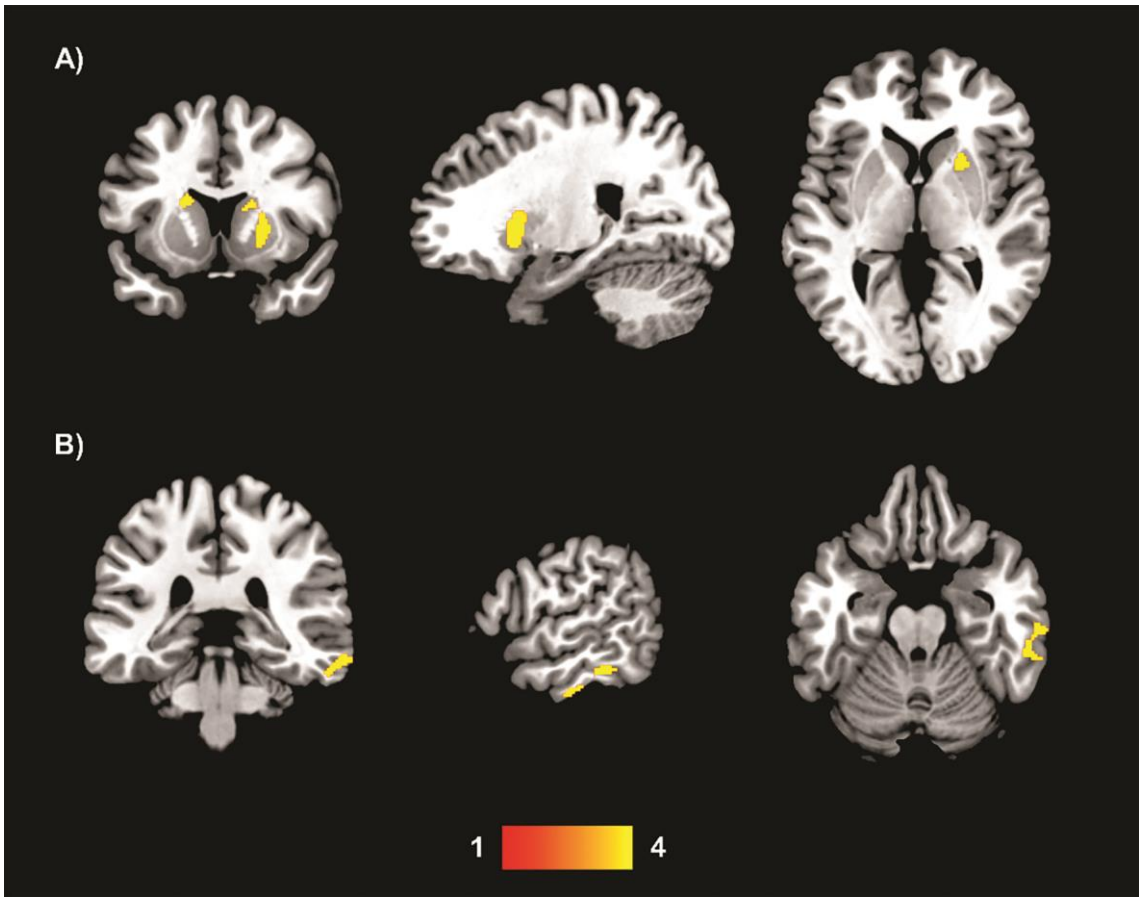


Figure 4

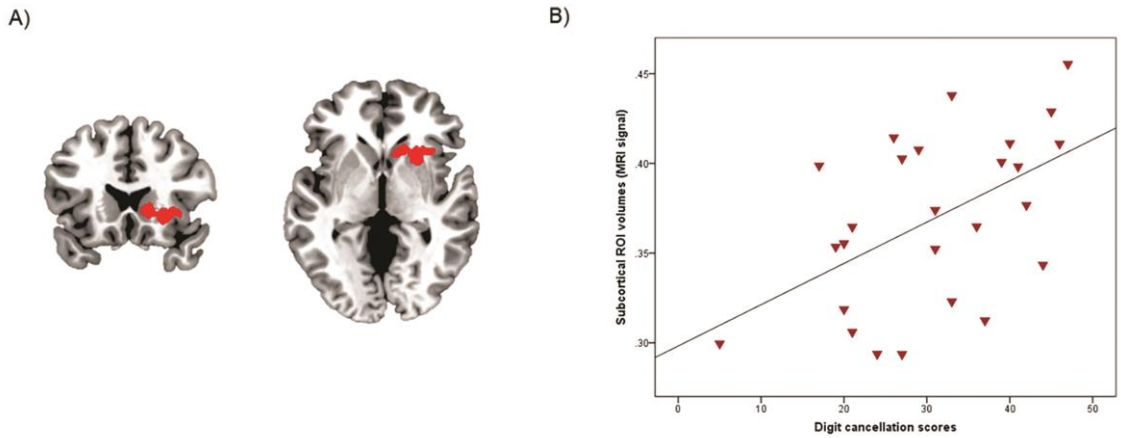
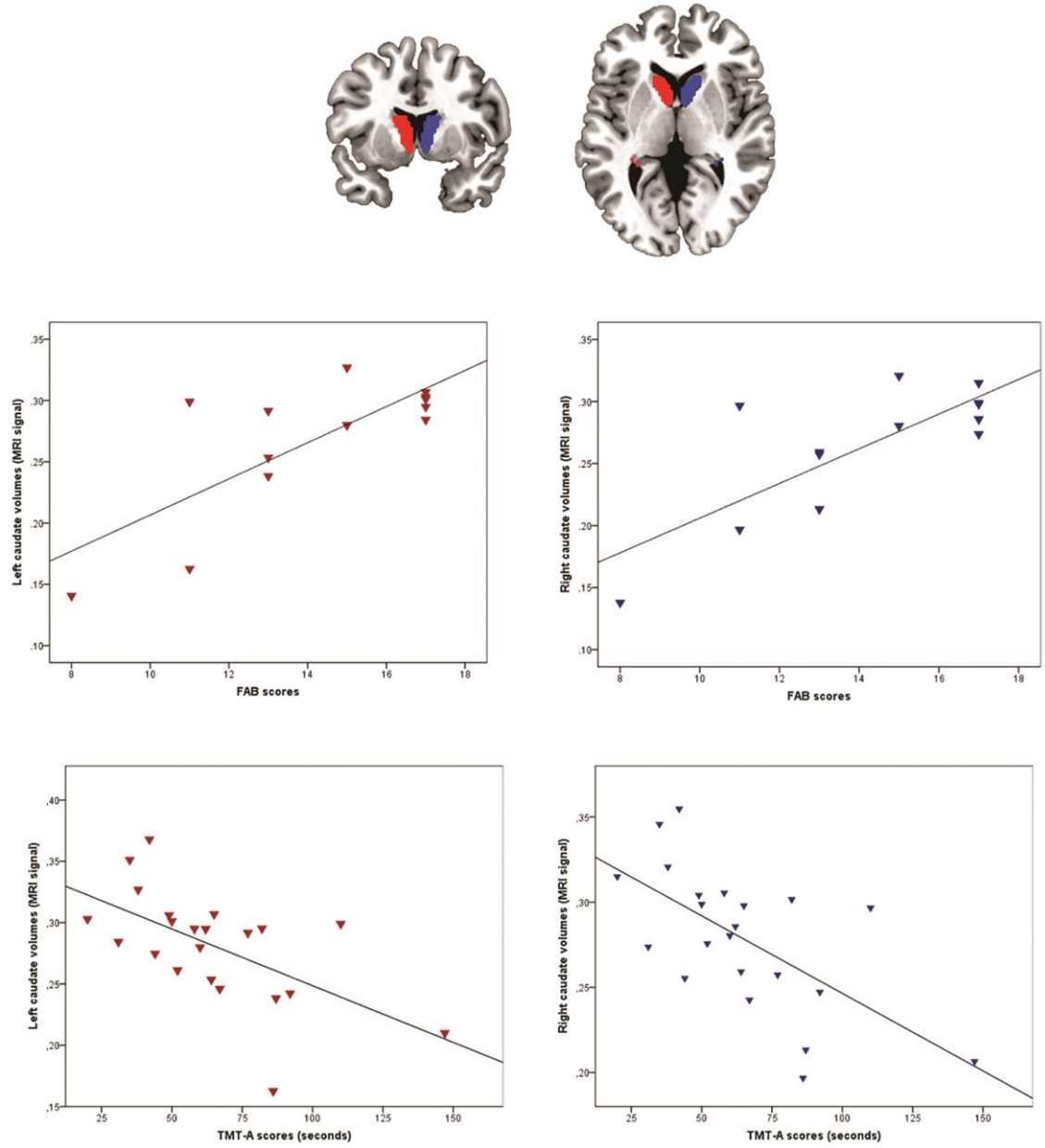

A)
B)
Subcortical ROI volumes (MRI signal)
.45
.40
.35
.30
0
10
20
30
40
50
Digit cancellation scores

Figure 5


Left caudate volumes (MRI signal)
FAB scores
Right caudate volumes (MRI signal)
FAB scores
Left caudate volumes (MRI signal)
TMT-A scores (seconds)
Right caudate volumes (MRI signal)
TMT-A scores (seconds)

Supplementary materials

Table S1. Differences in screening neuropsychological tests between DLB patients with and without VH.

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit span:							
Forward	10	3.70 (1.57)	4.0 (1.25)	16	4.75 (1.06)	4.50 (1.75)	0.07 [b]
Backward	9	2.00 (0.82)	2.0 (0.25)	15	2.81 (1.17)	3.00 (1.75)	0.04 [b]
Prose memory:							
Immediate recall	11	7.36 (5.57)	6.0 (5.00)	17	7.24 (3.98)	6.00 (3.50)	0.87 [b]
Delayed recall	11	8.09 (4.97)	7.0 (7.00)	17	7.94 (5.06)	7.00 (6.50)	0.89 [b]
Phonemic fluency	10	14.5 (10.5)	11.50 (8.50)	14	17.07 (11.6)	14.0 (19.25)	0.84 [b]
Clock drawing	10	3.80 (3.22)	4.0 (5.50)	17	4.80 (3.46)	6.00 (6.25)	0.47 [a]
Rey figure recall	9	2.94 (4.35)	0.0 (6.25)	14	8.00 (5.97)	7.75 (10.00)	0.03 [b]
VOSP:							
Screening test	11	18.73 (2.2)	20.0 (1.0)	16	19.38 (0.72)	19.50 (1.00)	0.96 [b]
Incomplete letters	11	9.27 (6.25)	8.0 (10.0)	16	12.38 (7.32)	15.0 (12.25)	0.24 [b]
Object decision	11	8.90 (4.97)	11.0 (7.0)	15	11.07 (3.82)	12.00 (6.00)	0.28 [b]
Progressive silhouettes	11	9.55 (6.88)	13.0 (16.0)	15	11.60 (3.85)	11.00 (4.00)	0.74 [b]
Dot counting	11	8.45 (2.30)	9.0 (2.0)	16	9.44 (1.50)	10.00 (0.75)	0.10 [b]
Position discrimination	11	15.18 (7.4)	19.0 (5.0)	16	17.44 (3.67)	19.50 (6.75)	0.37 [b]
Number location	11	6.09 (4.25)	7.0 (7.0)	16	6.06 (2.46)	7.00 (4.00)	0.98 [a]
Cube analysis	11	4.09 (3.08)	5.0 (6.0)	16	5.69 (3.24)	5.00 (5.50)	0.21 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

Table S2. Differences in screening neuropsychological tests between PD patients with and without VH.

Test	PD VH			PD NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit span:							
Forward	5	6.00 (1.23)	6.0 (2.0)	8	6.38 (0.92)	6.0 (1.0)	0.54 [a]
Backward	5	3.60 (0.89)	3.0 (2.0)	8	3.63 (0.74)	3.50 (1.0)	0.87 [b]
RAVLT							
Immediate recall	6	26.33 (6.47)	26.0 (11.0)	11	38.73 (11.33)	34.0 (21.0)	0.03 [a]
Delayed recall	6	5.17 (2.32)	5.50 (5.0)	11	7.73 (3.50)	9.0 (7.0)	0.17 [b]
Phonemic fluency	8	24.25 (4.92)	25.0 (8.0)	15	31.6 (9.47)	31.0 (16.0)	0.05 [a]
Rey figure recall	8	11.31 (4.87)	12.25 (9.10)	14	12.73 (5.85)	13.50 (5.30)	0.57 [a]
Stroop test (s)	6	64.67 (77.5)	36.50 (56.0)	15	32.83 (17.82)	28.50 (29.0)	0.48 [b]
Stroop test (errors)	6	5.00 (5.97)	3.0 (6.0)	15	3.30 (5.11)	2.0 (5.0)	0.31 [b]
FAB	6	11.83 (2.40)	12.0 (3.0)	7	16.14 (1.57)	17.0 (2.0)	0.01 [b]

FAB: Frontal Assessment Battery; IQR: interquartile range; RAVLT: Rey Auditory Verbal Learning Test; NVH: no visual hallucinations; PD: Parkinson's disease; s: seconds; SD: standard deviation; VH: visual hallucinations. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.