J Neurol (2012) 259:147–154
DOI 10.1007/s00415-011-6149-z

ORIGINAL COMMUNICATION

The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study

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Received: 8 April 2011 / Accepted: 14 June 2011 / Published online: 30 June 2011

Abstract Visual hallucinations (VH) are common in Parkinson's disease (PD) and lead to a poor quality of life. For a long time, dopaminergic therapy was considered to be the most important risk factor for the development of VH in PD. Recently, the cholinergic system, including the pedunculopontine nucleus (PPN), has been implicated in the pathophysiology of VH. The aim of the present study was to investigate grey matter density of the PPN region and one of its projection areas, the thalamus. Thirteen non-demented PD patients with VH were compared to 16 non-demented PD patients without VH, 13 demented PD patients (PDD) with VH and 11 patients with dementia with Lewy bodies (DLB). Isotropic 3-D T1-weighted MRI images (3T) were analysed using voxel-based morphometry (VBM) with the PPN region and thalamus as ROIs. PD and PDD patients with VH showed grey matter reductions of the PPN region and the thalamus compared to PD patients without VH. VH in PD(D) patients are associated with atrophy of the PPN region and its thalamic target area, suggesting that a cholinergic deficit may be involved in the development of VH in PD(D).

Keywords Voxel-based morphometry · Visual hallucinations · Parkinson's disease · Neuroimaging

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Introduction

Visual hallucinations (VH) in Parkinson's disease (PD) are a common non-motor symptom and constitute a major source of distress to patients and caregivers. They lead to increased disability, poor quality of life, and are a risk factor for later dementia and nursing home placement [1–3]. Conversely, cognitive impairment is an independent risk factor for VH leading to a higher prevalence of VH in demented PD patients (PDD) [2]. Furthermore, VH are also a core feature of dementia with Lewy bodies (DLB) and, therefore, may be associated with Lewy body pathology in a broader sense [5].

In cross-sectional studies prevalence rates for major VH in PD range from 22 to 38% while longitudinal studies have shown that the prevalence of VH increases over time reaching a life-time prevalence of up to 70% [2, 4]. Importantly, only a minority of PD patients report VH spontaneously, probably leading to an underestimation of the actual prevalence [2]. VH are also prevalent in DLB, occurring in about 60% of patients [5].

Historically, dopaminergic therapy was considered to be the most important risk factor for the development of VH in PD. The mechanism of action was thought to be dopaminergic overstimulation of mesolimbic dopamine receptors [6]. This hypothesis was supported by the powerful effect of antipsychotics on VH by way of their antagonistic activity on dopamine receptors [7]. Recently, changes in

other neurotransmitter systems, in particular the cholinergic system, are considered as a possible cause of VH. The cholinergic system plays a role in various cognitive functions including attention, memory, cognitive shifting, and sensory perception [8]. Disturbances in the cortical processing of visual perception due to degeneration of cholinergic brain structures including the pedunculopontine nucleus (PPN) are now believed to be involved in the development of VH in PD [8, 9]. This is supported by similarities in the phenomenology of VH in PD and those occurring in peduncular hallucinosis, known to result from damage to the midbrain and/or the thalamus [10].

Neuropathological studies in humans have reported that at least 50% of the large cholinergic neurons of the lateral part of the PPN, pars compacta, degenerate in PD [11]. The PPN has also been implicated in the regulation of sleep and REM-sleep behaviour disorder (RBD) [12]. Interestingly, PD patients with VH have vivid dreams and nightmares which may precede the onset of VH. Moreover, an association between RBD and VH has been suggested, linking the PPN and VH in PD [13]. In contrast, the pathophysiology of VH in DLB is considered to be related to Lewy body pathology in cortical brain areas, especially in the primary and secondary visual cortices [14].

So far, structural and functional studies addressing VH in PD, PDD and DLB focused mainly on grey matter loss in cortical areas, especially the primary visual system, the visual association areas and frontal areas [15–19]. Several voxel-based morphometry (VBM) MRI studies showed involvement of these visual cortical areas in non-demented and demented PD patients with VH [15, 16]. In addition, VH in DLB and PDD were associated with decrease of volume in frontal and associative visual areas in a recently published study by Sanchez-Castañeda et al. [17]. Functional imaging studies, including regional cerebral blood flow studies and functional MRI studies, reported hypermetabolism or increased cortical activation in the superior and inferior frontal gyrus in combination with hypometabolism or decreased cortical activation in the more posterior located cortical visual areas in PD patients with VH [18, 19].

To our knowledge, no structural or functional studies have addressed the involvement of the cholinergic output structures of the midbrain in hallucinating demented and non-demented PD patients [PD(D)] and DLB patients. Therefore, the aim of the present retrospective study was to investigate the PPN region and one of its projection areas, the thalamus, by means of voxel-based morphometry in these patients. We expected to find more pronounced grey matter reductions of the PPN region and the thalamus in PD(D) patients with VH compared to PD patients without VH. Secondly, since cortical involvement by Lewy body pathology is considered to occur early in DLB patients, we predicted more pronounced decrease in cortical grey matter areas in DLB patients with VH compared to PD(D) patients with VH.

Methods

Sample

Data were obtained in a retrospective manner from patients who were referred to the outpatient clinic for Movement Disorders at the VU University Medical Center, Amsterdam, the Netherlands (PD and PDD patients) and from the Alzheimer Center at the VU University Medical Center (DLB patients). The MRI scans and neuropsychological examinations used for this study, were part of the regular diagnostic work-up. All patients gave a written informed consent to store their medical information in a database and to use these data for scientific research. Patients were diagnosed by a movement disorder specialist (EF or HB) according to the UK PD Brain Bank criteria [20] for idiopathic PD, and the Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease [21] for PDD. The diagnosis of DLB was made by the multidisciplinary team of the Alzheimer Center according to the Consensus criteria for dementia with Lewy bodies [22] for probable DLB.

The Mini-Mental State Examination (MMSE) [23] with a cut-off value of <24 for dementia was used in cases where an extensive neuropsychological examination was missing (6 out of 13 patients). The severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale-motor part (UPDRS-III) in the "on" state [24]. The stage of the disease was determined using the Hoehn and Yahr scale [25]. Patients were considered hallucinating if they had experienced well-formed visual hallucinations of people or animals for at least 4 weeks determined by means of the Scales for Outcomes in Parkinson's disease—Psychiatric Complications (SCOPA-PC) [26] or by inquiry. The levodopa equivalent dose was calculated as described previously [27]. One (7.7%) PD + VH patient, four (30.8%) PDD + VH patients, one (9.1%) DLB patient and none of the PD–VH patients were taking antipsychotics (clozapine or quetiapine). Five (38.5%) PDD + VH patients and four (36.4%) DLB patients were taking a cholinesterase-inhibitor (rivastigmine).

Statistical analysis of the demographic and clinical characteristics was carried out by the Statistical Package for Social Sciences 15.0 (SPSS Inc, Chicago, Illinois, USA). For normally distributed variables with homogeneity of variance, we performed one-way analysis of variance (ANOVA) and post-hoc Tukey tests. For those variables that did not meet normality, we used a non-parametric Kruskal–Wallis test and a post-hoc Mann–Whitney *U* test

with a Hochberg correction for multiple testing. Differences between groups were considered to be statistically significant at $P < 0.05$.

MRI acquisition and voxel-based morphometry analysis

All MRI data were acquired on a 3.0 T GE Signa HDxt scanner (General Electric, Milwaukee, Wisconsin, USA). Prior to the volumetric analysis, the MRI scans were visually checked. Scans with severe vascular white matter lesions (Fazekas III) or extensive global cortical atrophy were excluded. A 3-D structural MRI was obtained using a T1-weighted FSPGR sequence with the following parameters: TR (Repetition Time) = 7.8 ms; TI (Inversion Time) = 450 ms; TE (Echo Time) = 3.0 ms; 1 mm slice thickness; FoV (field of view) = 25 cm; FA (flip angle) = 12°; matrix = 256 × 256; voxel size = 1 × 0.94 × 0.94 mm.

Regional differences in grey matter volume were assessed using VBM. The VBM analysis was performed with SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for NeuroImaging, Institute of Neurology, University College London, London, UK) running on Matlab 7 (Mathworks, Natick, Massachusetts, USA). The processing included the following steps: images were reoriented by placing the centre point on the anterior commissure and were then segmented into grey matter, white matter and cerebrospinal fluid (CSF). After automatic brain segmentation the global volumes of grey matter, white matter and CSF were calculated and an estimation of the total intracranial volume (TIV) was made. A study-specific T1 MR template was created from all participants using non-linear registration and DARTEL [28] and the segmented images were spatially normalised to this template. Subsequently, the images were normalised to MNI (Montreal Neurological Institute) space. A modulation step was added to maintain the total amount of grey matter in each voxel after spatial normalisation. The obtained modulated segmented images were smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel.

To address our specific hypothesis and have sufficient statistical power, we restricted our initial analysis to grey matter regions of interest (ROIs) that were defined in the thalamus and the PPN region. The ROI of the thalamus was derived from the WFU Pick Atlas tool version 2.4 for SPM [29]. The ROIs of the PPN region consisted of two 5 mm spheres at MNI coordinates [±6.4 −27 −15]. These coordinates are midpoints of the PPN derived from a stereotactic localization study [30].

Regional differences in grey matter volume were assessed from the smoothed and modulated grey matter images using an ANOVA design as implemented in SPM8, including age and TIV as covariates. Individual voxel and cluster significance thresholds were set at $P < 0.05$ corrected for multiple comparisons (Family Wise Error).

After the masked VBM analysis with the PPN region and thalamus, we also performed a whole brain VBM study to determine the specificity of our findings. For whole brain comparisons the threshold was set at an uncorrected $P < 0.001$ level.

Results

Clinical and demographical characteristics

We included 13 non-demented PD patients with VH (PD + VH), 16 non-demented PD patients without VH (PD − VH), 13 demented PD patients with VH (PDD + VH), and 11 patients with dementia with Lewy bodies (DLB). Demographic and clinical characteristics are shown in Table 1. The four groups, PD patients with and without VH, demented PD patients with VH and DLB patients, did not differ in age at time of study or age at disease onset. There were significant differences in disease duration between PD patients without VH and PD(D) patients with VH but no significant differences between PD patients with VH and PDD patients with VH. PDD patients with VH were more severely affected than PD patients with and without VH, as reflected by a higher UPDRS-III score and H&Y stage which was expected due to the natural disease progression. The MMSE-score ranged from 16 to 22 for PDD patients without neuropsychological examination.

VBM results

The masked analysis revealed differences in grey matter volume of the PPN region and the thalamus after covarying for age and TIV as demonstrated in Table 2 for the different groups.

Hallucinating PD(D) patients versus non-hallucinating PD patients

Hallucinating PD (PD + VH and PDD + VH) patients showed significant clusters of reduced grey matter volume compared to non-hallucinating PD (PD–VH) patients, both in the PPN region and in the thalamus (Fig. 1). A restricted comparison including only non-demented PD patients with and without VH confirmed significant grey matter reduction related to VH in the PPN region, but not in the thalamus. However, using a lower statistical threshold of uncorrected $P < 0.01$ we did see an apparent trend of volume reduction in the right thalamus in PD patients with VH compared to PD patients without VH. Furthermore, grey matter volume reductions in both the PPN region and

Table 1 Demographical and clinical characteristics

	PD − VH $N = 16$	PD + VH $N = 13$	PDD + VH $N = 13$	DLB $N = 11$	F/χ^2	P value
Sex (m/f)	9/7	6/7	7/6	11/0	9.90*	0.016[a,b]
Age (years)	64.3 ± 8.0	66.0 ± 6.9	67.7 ± 7.1	62.6 ± 6.5	1.42**	0.248 ns
Age at onset (years)	61.3 ± 7.4	54.5 ± 8.2	56.8 ± 9.4	58.0 ± 7.5	1.77**	0.165 ns
Disease duration (years)	3.1 ± 3.6	11.5 ± 5.2	10.9 ± 5.5	4.6 ± 4.5	23.7***	<0.001[a,b,c,d]
MMSE	28.9 ± 1.6	28.0 ± 1.7	21.2 ± 2.7	24.5 ± 1.4	26.8***	<0.001[d,e,f]
UPDRS-III	23.6 ± 11.5	29.1 ± 8.4	45.7 ± 15.9	na	13.7***	0.001[d,e]
Hoehn & Yahr	2.1 ± 0.5	2.5 ± 0.3	3.5 ± 1.0	na	23.0***	<0.001[c,d,e]
Levodopa equivalent dose (mg)	170.2 ± 359.4	712.2 ± 380.8	68.4 ± 343.5	0.0 ± 0.0	29.8***	<0.001[a,b,c,d]

Results are expressed as mean ± standard deviation

* Chi-square

** One-way ANOVA

*** Kruskal–Wallis

[a] Significant differences between PD + VH and DLB after Hochberg correction for multiple testing

[b] Significant differences between PDD + VH and DLB after Hochberg correction for multiple testing

[c] Significant differences between PD − VH and PD + VH after Hochberg correction for multiple testing

[d] Significant differences between PD − VH and PDD + VH after Hochberg correction for multiple testing

[e] Significant differences between PD + VH and PDD + VH after Hochberg correction for multiple testing

[f] Significant differences between PD − VH and DLB after Hochberg correction for multiple testing

Table 2 Group comparisons: ROI analysis

	Regions	Cluster level		Voxel level			T value
		Cluster size	P corrected	MNI coordinates			
				x	y	z	
VH < non-VH	Left PPN region	99	0.015	−4	−24	−12	4.55*
	Right PPN region	121	0.013	6	−24	−15	4.06*
	Left thalamus	31	0.019	−8	−13	0	4.15*
	Right thalamus	9	0.033	9	−12	0	3.90*
PD + VH < PD–VH	Left PPN region	53	0.020	−3	−25	−14	4.28*
	Right PPN region	45	0.022	2	−25	−14	3.60*
	Right thalamus	391	0.070	6	−13	1	3.24**
PDD + VH < PD–VH	Left PPN region	74	0.017	−3	−25	−15	4.16*
	Right PPN region	62	0.019	2	−25	−15	3.81*
	Left thalamus	76	0.007	−9	−10	0	6.43*
PDD + VH < DLB	Left PPN region	40	0.073	−4	−25	−9	2.94**
	Right PPN region	28	0.081	8	−30	−14	2.82**

MNI coordinates refer to the location of the most statistically significant voxel in the cluster

* Significance threshold of $P < 0.05$ corrected voxel-level for multiple comparisons (FWE)

** Significance threshold of $P < 0.01$ uncorrected voxel-level

thalamus were also present when comparing PDD patients with VH to PD patients without VH (Table 2).

Hallucinating PD(D) patients versus DLB patients

No significant differences in grey matter volume of the PPN region or thalamus were found between hallucinating PD patients (PD + VH or PDD + VH) and DLB patients using a FWE corrected threshold. However, a trend for grey matter reduction of the PPN region was visible in PD patients with VH compared with DLB patients and in PDD patients with VH compared with DLB patients, when using a lower threshold of uncorrected $P < 0.01$ (Table 2).

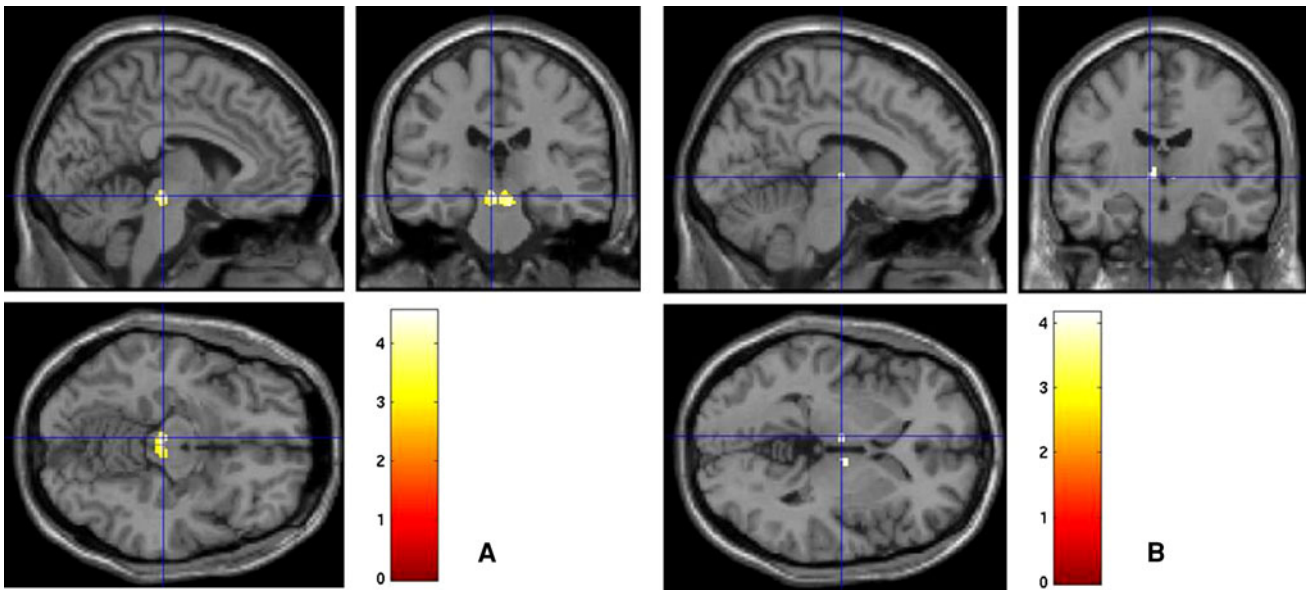

Fig. 1 Grey matter volume reductions in hallucinating PD patients (PD + VH and PDD + VH) compared to non-hallucinating patients (PD–VH) obtained from a VBM analysis with selected regions of interest. Results are overlapped in a normal TI-weighted image. Clusters in **a** PPN and **b** thalamus reach significance at a corrected cluster level ($P < 0.05$ FWE)

Whole brain analysis

Grey matter reductions of the PPN region and thalamus were also visible in the whole brain comparisons of hallucinating PD patients (PD + VH and PDD + VH) with the non-hallucinating PD patients and not in other brain areas. In addition, whole brain analysis of demented hallucinating patients (DLB and PDD + VH) compared with hallucinating PD patients (PD + VH) showed reduced grey matter volume of the right middle frontal cortex (BA 10) (Fig. 2).

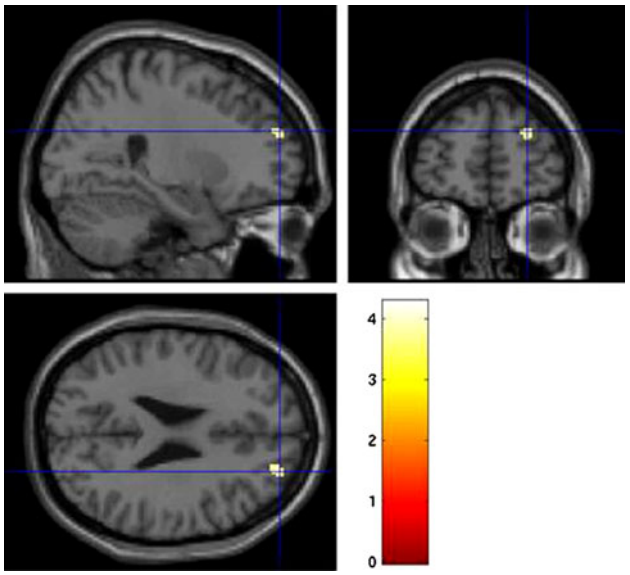

Fig. 2 Grey matter volume reductions in demented hallucinating patients (PDD + VH and DLB + VH) compared to non-demented hallucinating PD patients (PD + VH) obtained from a whole brain analysis. Results are overlapped in a normal TI-weighted image. Threshold was set at uncorrected level of $P < 0.001$. Cluster of grey matter volume reductions in demented patients is observed in right middle frontal gyrus (BA 10)

Discussion

The present study aimed to identify grey matter alterations associated with VH in PD(D) and DLB. To our knowledge, this is the first study which focused on brainstem and thalamic regions rather than cortical areas. Our findings support the hypothesis that the PPN region and thalamic nuclei are involved in the pathophysiology of VH in Parkinson's disease.

Recently, different models have been postulated to explain the mechanisms of VH in PD. In the Perception and Attention (PAD) model, which relates attention and object perception deficits to VH, cholinergic inhibition gives a greater chance to misperception of objects and allows the intrusion of incorrect representations [31]. Dopamine is also considered to mediate a net increase in signal-to-noise ratio to maintain attention focus. However, given that dopamine receptors are not prevalent in visual processing areas, cholinergic dysfunction seems necessary to induce VH [31]. In the early 1990s, Perry and co-workers [8] reported the hallucinogenic character of anticholinergic drugs. They mentioned that this was not necessarily a cortical phenomenon but suggested instead a potential role for the thalamic targets of the pedunculopontine-lateral dorsal tegmental cholinergic nuclei [8]. This is particularly

interesting when considering the cholinergic deficit hypothesis for VH in PD. It is known that the PPN degenerates in PD which may lead to impaired cholinergic brainstem control of the cortex [10, 11]. Subsequently, reduced cortical acetylcholine may lead to an inability to suppress intrinsic cortical activity, which comes to conscious awareness in the form of VH [8].

Our results showed that hallucinating PD patients (both demented and non-demented) had grey matter reductions in the PPN and its thalamic targets compared to non-hallucinating PD patients. The comparison restricted to non-demented PD patients with and without VH revealed grey matter reduction of the PPN region but not of the thalamus. One could interpret this as if volume loss of the thalamus is the result of dementia rather than VH. However, we did find a trend of grey matter reduction in the right thalamus of PD patients with VH compared to PD patients without VH. Furthermore, no significant differences were found in thalamic grey matter volume between PDD and PD patients with VH. These findings support the concept that atrophy of both the PPN region and its thalamic projection area related more strongly to VH than to concomitant cognitive decline. However, although covariation for disease duration revealed comparable results, the large difference in disease duration between the hallucinating groups and the non-hallucinating PD patients might influence the observed results and therefore only reflect natural disease progression.

Compared to DLB patients, hallucinating PD(D) patients showed a trend of grey matter reductions of the PPN region. Conversely, whole brain analysis showed reduced grey matter volume of the right middle frontal cortex (BA 10) in hallucinating DLB and PDD patients compared to hallucinating PD patients. This is line with the study of Sánchez-Castañeda et al. [17] in which frontal involvement in demented hallucinating patients (PDD and DLB) was observed. However, because the hallucinating patients in this study were also more demented compared to the non-hallucinating control patients, it remains unclear whether the differences in frontal cortex volume were not confounded by the concomitant dementia and not related to VH per se. Nevertheless, one may consider that the PPN region plays an important role in provoking VH in PD(D) while in DLB, VH are primarily the result of other cholinergic output structures.

The previously reported grey matter loss of visual cortical areas (gyrus lingualis and superior parietal lobe) in hallucinating non-demented PD patients were not observed in the present study [15]. This may be due to differences in general cognitive status as reflected by a difference in mean MMSE score between our non-demented PD patients and the PD patients in the study of Ramirez-Ruiz et al., reflecting a more advanced disease stage. This is supported by the absence of cortical grey matter volume changes in hallucinating non-demented PD patients in the recently published study by Meppelink et al. [32].

Based on our results, we hypothesize that degeneration of the PPN in PD influences thalamocortical activity hereby decreasing the arousal state and hence leading to VH. The decrease in volume of visual association areas and frontal areas described in other VBM studies may be interpreted as being secondary to the PPN degeneration. However, neuropathological confirmation is necessary to establish this hypothesis. Until now, neuropathological studies did not consider brainstem structures to be a potential neural substrate of VH in PD but focussed on cortical structures. More Lewy body (LB) pathology was observed in the amygdala and parahippocampus in PD patients with VH compared to those without VH [33]. One study reported that cases presenting with VH early in the disease course have more LB pathology within the temporal cortex [34]. However, these cortical changes may be related to dementia because most of the patients included were also demented. In addition, VH early in the disease course are suspect for the diagnosis of DLB. As previously suggested, VH in DLB patients may result from degeneration of other cholinergic brain structures. In this respect, one may consider the basal forebrain structure nucleus basalis of Meynert (nBM) [35]. This is supported by a neuropathological study showing a relationship between neuronal loss and LB formation in the nBM and inverse decrease in neocortical choline acetyltransferase activity [36]. In addition, one study addressed the degeneration of the PPN in DLB. Loss of cholinergic neurons in DLB patients was less severe than in MSA patients, the latter patients being cognitive intact and not suffering from VH [37]. Although speculative, this may suggest that VH in DLB patients are more related to degeneration of the nBM than to degeneration of the PPN compared to PDD patients with VH.

Limitations of the study

Firstly, the relatively small sample size and the unmatched patient characteristics of the different groups in the present retrospective study limits the generalization of the results and, therefore, the results should be interpreted as preliminary. However, whole brain analysis performed as post-hoc analysis showed comparable significant clusters of grey matter reduction of the PPN region and thalamus and not in other brain areas, indicating the specificity of the obtained results. Secondly, due to the dichotomous measure of VH, we could not correlate the degree of grey matter reduction with the severity of VH. Another limitation is the small volume and the not-well defined boundaries of the PPN. Because the brainstem has a high density

of nuclei at this level, we could not be absolutely sure about interference of neighbouring nuclei of the PPN region including the more medial located laterodorsal tegmental nuclei (LDTN). This is of particular interest because the LDTN mainly consists of cholinergic neurons and immunohistochemical studies have shown that 85–95% of brainstem afferents to most thalamic nuclei originate from cholinergic neurons in the rostral brainstem where the PPN and the LDTN are maximally developed [38]. However, using two small 5 mm spheres at the midpoint of the PPN derived from a stereotactic localization study makes it unlikely that the LDTN has been included in the ROI.

In conclusion, we found reduced grey matter in the PPN region and the thalamus in hallucinating PD(D) patients, which suggests that degeneration of the PPN may contribute to VH in PD(D). This supports that the cholinergic system may be important when considering new treatment strategies for VH in PD. Further studies combining structural and functional imaging with special focus on the cholinergic system in larger patient groups are needed.

Conflict of interest The authors report no conflicts of interest.

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