Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2008;25:531–538
DOI: 10.1159/000132084

Accepted: March 23, 2008
Published online: May 14, 2008

Cerebral Metabolic Dysfunction in Patients with Dementia with Lewy Bodies and Visual Hallucinations

Robert Perneczky[a] Alexander Drzezga[b] Henning Boecker[b, d] Hans Förstl[a]
Alexander Kurz[a] Peter Häussermann[c, e]

Departments of [a]Psychiatry and Psychotherapy, [b]Nuclear Medicine and [c]Neurology, Technical University Munich, Munich, [d]Department of Radiology, Rheinische Friedrich Wilhelms University Bonn, Bonn, and [e]Centre for Integrative Psychiatry, Kiel, Germany

Key Words
Dementia with Lewy bodies · Metabolic dysfunction · Psychosis · Visual hallucinations

Abstract
Aims: To identify the pattern of cerebral hypometabolism in patients with dementia with Lewy bodies (DLB) and visual hallucinations (VH). ***Methods:*** Fourteen patients with DLB and VH, 7 with DLB without VH and 16 healthy controls underwent clinical and ^{18}F-FDG PET evaluations. The 2 patient groups did not significantly differ in their clinical characteristics, except in the occurrence of VH. A voxel-wise comparison of ^{18}F-FDG PET scans was conducted between each of the 2 patient groups and the control group, and the patient groups among each other. ***Results:*** Compared with the control group, hypometabolic regions were more extensive and confluent in the patient group with VH than in the group without VH. The direct comparison between the 2 patient groups revealed a significant metabolic deficit in the group with VH at the right occipito-temporal junction and the right middle frontal gyrus. ***Conclusions:*** These results suggest that hypometabolism in visual association areas rather than the primary visual cortex is involved in VH in DLB.

Introduction

We recently reported that brain metabolic abnormalities in patients with Parkinson's disease (PD) suffering from visual hallucinations (VH) were clustered in the dorsal and ventral visual streams rather than within the primary visual cortex [1]. We furthermore suggested that the metabolic correlates matched quite well with the clinical phenomenology of VH in PD, which are often described as complex animated scenarios involving people, animals, buildings or scenery [2]. Similar complex VH have also been repeatedly reported by individuals with isolated lesions of the temporo-occipital and parieto-occipital cortex [3, 4], and they are also a core clinical feature of dementia with Lewy bodies (DLB) [5], in which posterior cortical areas are predominantly affected by neurodegeneration [6]. Furthermore, VH are amongst the strongest predictors of DLB at autopsy; Harding et al. [7], for example, described a close correlation between temporal Lewy bodies and well-formed VH in an autopsy series. Taking into account these findings and the clinical and neurobiological similarities between PD and DLB [8], we hypothesized that brain function correlates of VH should also be localized in downstream visual areas rather than within the primary visual cortex in DLB.

The aim of the present study was therefore twofold. First, we used ^{18}F-fluoro-2-deoxy-glucose positron emis-

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Dr. Robert Perneczky, MD
Psychiatrische Klinik der Technischen Universität München
Ismaninger Strasse 22
DE–81675 München (Germany)
Tel. +49 89 4140 4279, Fax +49 89 4140 4923, E-Mail robert.perneczky@lrz.tum.de

sion tomography (^{18}F-FDG PET) to explore the pattern of relative glucose hypometabolism in hallucinating and non-hallucinating patients with DLB in contrast to a group of normal control subjects (NL). Second, we directly compared the relative cerebral metabolic rate of glucose (rCMRglc) of the 2 patient groups in order to detect statistically significant differences, hypothesizing a stronger decrease of glucose metabolism in visual association areas rather than the primary visual cortex in the DLB group suffering from VH (DLB + VH).

Materials and Methods

Sample

The study included 21 patients with mild to moderate DLB, who were all recruited between 2001 and 2003 from the Departments of Psychiatry and Neurology of the Technical University of Munich. The diagnosis of DLB was established by consensus of 2 experienced clinicians according to current diagnostic guidelines [9]. All patients fulfilled diagnostic criteria for probable DLB. The patients' thorough diagnostic evaluation included neuropsychological testing, routine blood sampling, physical examination, and structural (MRI or CT) and functional (^{18}F-FDG PET) imaging of the brain. The neuropsychological set-up was based on the Consortium to Establish a Registry for Alzheimer's Disease (AD) Neuropsychological Assessment Battery (CERAD-NAB) [9, 10], which incorporates the Mini-Mental State Examination (MMSE) [11]. In addition, a total score of the CERAD-NAB was calculated for each patient according to recently published criteria (subtest addition method) [12], because this score allows for a more comprehensive rating of global cognitive function than the MMSE. Briefly, total scores were obtained by summing scores from the individual subtests (excluding the MMSE score) into a total composite score (maximum score for verbal fluency set at 24 points, maximum total score 100 points). Neuropsychiatric symptoms, including frequency and severity of hallucinations within the past 4 weeks prior to the examination, were rated on the Neuropsychiatric Inventory (NPI) [13]. The severity of parkinsonian signs was rated on the Unified PD Rating Scale (UPDRS) motor section [14]. The clinical documentation also included information on age, gender and years of school education (defined as years attending school plus years of apprenticeship, technical school, college and university), and a standardized assessment of recurrent falls, and fluctuations in consciousness. Patients were excluded who fulfilled diagnostic criteria for neurodegenerative causes of dementia other than DLB, such as AD [15], frontotemporal lobar degeneration [16], PD [17], or PD dementia [18]. Patients were also excluded if they had significant cerebrovascular lesions on their structural brain scans, relevant functional psychiatric disorders such as major depression, or a history of traumatic brain injury, stroke, cerebral tumors, epilepsy or alcohol abuse. All patients who fulfilled the inclusion and exclusion criteria were entered into the study. Written informed consents were available for all patients. In the case of patients with moderate dementia, informed consents by proxy were also obtained. The ethics committee of the Technical University of Munich approved the study procedures.

Acquisition and Pre-Processing of ^{18}F-FDG PET Scans

Each patient fasted for at least 6 h prior to PET scanning. All patients with DLB were scanned in the medical 'off condition', i.e. dopaminergic medication was ceased at least 12 h prior to scanning. ^{18}F-FDG PET images were acquired in 3D mode using a Siemens ECAT EXACT HR+ scanner (CTI, Knoxville, Tenn., USA). Injection of 185 MBq ^{18}F-FDG and consecutive PET imaging was done under standard resting conditions (eyes closed, dimmed ambient light, no movement). We used a 20-min static acquisition protocol beginning 30 min after the injection. Transmission scans were obtained for attenuation correction purposes using a rotating ^{68}Ge/^{68}Ga source. After corrections for random, dead time and scatter effects, images were reconstructed with filtered back-projection (Hamm filter, cut-off frequency 0.5 cycles/projection element) resulting in 47 slices in a 128 × 128 matrix (pixel size 2.0 mm) and interplane separation of 3.447 mm. Images were realigned, transformed into standard stereotactic space, and smoothed (12 mm full-width at half maximum) in the statistical parametric mapping software package SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2), based on Matlab v6.5 (The Mathworks, Natwick, Mass., USA). Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

Statistical Evaluation

Patient characteristics were analyzed in the Statistical Package for the Social Sciences v11.5 (SPSS, Chicago, Ill., USA). The analyses of the ^{18}F-FDG PET data were performed in SPM2. The statistical analysis of the functional imaging data included 2 independent steps. First, a voxel-wise comparison was conducted between each of the 2 patient groups and an NL group in order to visually compare their hypometabolic pattern, controlling for each individual's MMSE score using an analysis of covariance (ANCOVA). A pre-existing dataset of 16 healthy volunteers was used that had been previously collected for diagnostic and research purposes [19]. This group consisted of outpatients' spouses recruited at the same departments as the DLB group. The control subjects were not related to patients with dementia. The PET data of these NL had been acquired following the identical criteria as for the patients, and the population was approximately age matched to the patient group (7 men, 9 women; age 65 ± 8 years; MMSE 30 ± 0 points; schooling 12 ± 4 years). The scans for all NL were acquired on the same scanner using the same acquisition protocol, reconstruction software and image processing procedures as for the patients. All normal subjects had undergone MRI of the brain and neuropsychological evaluation without detection of abnormalities. Their PET scanning was approved by the radiation protection authorities. A significance threshold of $p < 0.05$, corrected for multiple comparisons according to the false discovery rate procedure (FDR), was applied in this analytic step in order to minimize the chance of false-positive findings.

Second, a direct voxel-based comparison was conducted between the DLB + VH and the non-hallucinating (DLB – VH) groups in order to identify brain regions with significant reductions of the rCMRglc in the group of patients with VH. Again, a statistical correction for each individual's MMSE and UPDRS III scores was performed (ANCOVA) in order to control for differences in cognitive and motor functions. Significant findings were only expected in the predefined hypometabolic network identified in the comparison between the 2 patient groups and the NL group.

Table 1. Patient characteristics

Characteristic	Entire sample (n = 21)	DLB – VH (n = 7)	DLB + VH (n = 14)	p
Age, years	69.52 ± 5.71	68.86 ± 3.02	69.86 ± 6.76	0.71
Men/women	11/10	6/8	5/2	0.21
Schooling, years	10.43 ± 2.82	9.14 ± 2.61	11.07 ± 2.79	0.14
Duration of disease, years	5.82 ± 5.63	5.71 ± 2.67	5.85 ± 4.88	0.96
MMSE score	20.76 ± 4.80	23.14 ± 2.55	19.57 ± 5.27	0.11
CERAD-NAB sum score	46.55 ± 14.35	46.64 ± 13.52	46.50 ± 15.24	0.98
UPDRS III score	30.43 ± 15.59	26.6 ± 14.44	34.6 ± 16.53	0.34
NPI VH score	5.29 ± 4.44	0 ± 0.00	7.93 ± 2.79	<0.001
Fluctuations in consciousness, yes/no	20/1	7/0	13/1	0.47
Recurrent falls, yes/no	9/12	2/5	7/7	0.35
L-dopa equivalent dose, mg	254.8 ± 107.35	246.4 ± 114.11	271.4 ± 98.27	0.91

Therefore, a significance threshold of $p < 0.001$, uncorrected for multiple comparisons, was applied, based on our a priori hypothesis of involved brain regions, which is consistent with other studies using comparable approaches [20]. Based on previous FDG PET studies in DLB, we defined the occipital, temporo-parietal and frontal cortices as predominant candidate areas for possible metabolic reductions in patients with DLB [21]. For metabolic differences between groups, voxels exceeding the p value threshold within this set of cortical areas were regarded as significant. All statistical approaches were selected in correspondence with previously published studies on similar questions. Coordinates were converted from MNI (Montreal Neurological Institute; http://www.bic.mni.mcgill.ca) to Talairach space [22] with the Matlab function 'mni2tal' (http://www.mrc-cbu.cam.ac.uk/Imaging). Anatomical regions were identified with the Talairach Demon Client v2.0 (http://ric.uthscsa.edu/recources/body.html).

Results

Clinical Data

The characteristics of the study sample are displayed in table 1. The MMSE score range of 11–26 supported the diagnosis of mild to moderate dementia [23]. Years of school education ranged from 8 to 15 years. Men and women were almost equally represented in the sample. The onset of cognitive symptoms was prior to or within 12 months of the onset of parkinsonian symptoms in all of the patients. Parkinsonian symptoms were present and of mild severity in all patients at the point of the diagnostic assessment. VH were present in 67%, recurrent falls in 57% and fluctuations in cognition in 95% of the patients. The 2 patient groups did not differ significantly in their clinical characteristics, except in the occurrence of VH. The DLB + VH group scored lower on the MMSE score and higher on the UPDRS III score than the DLB – VH group; however, the difference did not reach statistical significance at a level of $p < 0.05$, and both patient groups scored almost equally on the CERAD-NAB sum score.

Functional Imaging Data

Both patient groups were compared with the NL group to identify differences in the pattern of relative hypometabolism. In these group comparisons, regions located in the frontal, parietal and occipital cortices and the basal ganglia, typically affected in DLB, were identified in both patient groups. The pattern of metabolic abnormalities was similar in both groups; however, in the visual comparisons the reductions of the rCMRglc were more extensive and confluent in the DLB + VH group than in the DLB – VH group. Consequently, less independent clusters could be distinguished by the SPM2 routine at the conservative significance threshold of $p < 0.05$, FDR-corrected for multiple comparisons, in the DLB + VH group than in the DLB – VH group (table 2; fig. 1).

A direct comparison between the 2 patient groups was conducted to investigate if the visually detected differences between the 2 patient groups were also statistically significant. In the voxel-wise group comparison of the 2 patient groups, significant hypometabolic areas were detected in the DLB + VH group compared with the DLB – VH group in 2 extensive clusters located in right hemispheric areas including the temporo-occipital junction at Brodmann area (BA) 39 (maximum in Talairach space at x/y/z 47/–71/10, right middle temporal gyrus, cluster of 312 contiguous voxels, $p < 0.001$ uncorrected for multiple comparisons) and the middle frontal gyrus (BA 6, maximum in Talairach space at x/y/z 36/2/45, cluster of

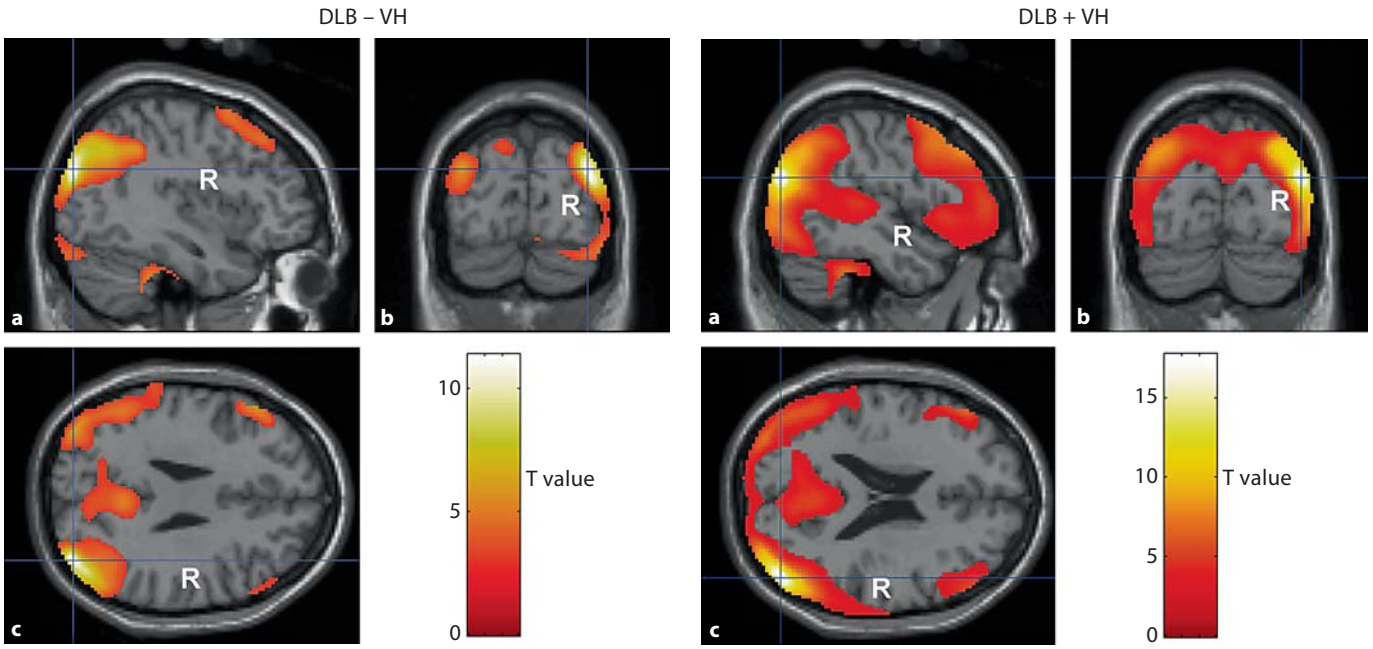

Fig. 1. Brain regions with significant reductions of rCMRglc levels in the DLB – VH and DLB + VH groups compared with the NL group. Anatomical localization as projected on sagittal (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized into the MNI template ($p < 0.05$ FDR-corrected for multiple comparisons; DLB – VH: maximum at x/y/z 40/–80/30 in Talairach space, right superior occipital gyrus, Brodmann area 19; DLB + VH: maximum at x/y/z 50/–75/24 in Talairach space, right middle temporal gyrus, Brodmann area 39). R = Right side.

Table 2. Peak metabolic reductions in both patient groups compared with the NL group

DLB + VH							DLB – VH						
region	BA	x	y	z	Z-score	cluster	region	BA	x	y	z	Z-score	cluster
rMTG	**39**	**50**	**–75**	**24**	**7.31**	**37,913**	**rSOG**	**19**	**40**	**–80**	**30**	**6.44**	**10,845**
rPC	19	32	–68	42	6.77		rMTG	39	50	–71	24	6.04	
rPC	19	–36	–76	37	5.93		rPC	19	30	–64	40	5.93	
rCN		**12**	**8**	**3**	**6.82**	**17,362**	**rIFG**	**47**	**61**	**31**	**0**	**5.61**	**5,067**
rMFG	6	36	16	56	5.96		lSFG	8	–10	43	48	5.04	
rMFG	8	44	31	41	5.95		lIFG	45	–57	26	6	4.89	
							rCN		**12**	**6**	**5**	**5.37**	**1,184**
							rMFG	25	12	7	–17	4.50	
							rOG	11	6	34	–27	2.91	
							lIPL	**40**	**–59**	**–41**	**39**	**5.05**	**4,180**
							lAG	39	–40	–76	33	4.61	
							lMTG	39	–48	–69	24	3.96	
							lCN		**–10**	**2**	**9**	**4.31**	**191**
							rUC	**20**	**30**	**–19**	**–29**	**4.13**	**462**

Bold markings delineate a cluster, subsequent non-bold markings identify further peaks within the same cluster; brain regions are indicated by Talairach and Tournoux coordinates, x, y and z. x = The medial to lateral distance relative to midline (positive: right hemisphere); y = the anterior to posterior distance relative to the anterior commissure (positive: anterior); z = superior to inferior distance relative to the anterior commissure–posterior commissure line (positive: superior). BA = Brodmann area; cluster = extension of contiguous voxels within the cluster; r = right; l = left; MTG = middle temporal gyrus; PC = precuneus; CN = caudate nucleus; MFG = middle frontal gyrus; SOG = superior occipital gyrus; IFG = inferior frontal gyrus; SFG = superior frontal gyrus; OG = orbital gyrus; IPL = inferior parietal lobule; AG = angular gyrus; UC = uncus.

332 contiguous voxels, $p < 0.001$ uncorrected for multiple comparisons). These results did not survive the statistical correction for multiple comparisons (FDR-corrected values; BA 39: $p = 0.118$; BA 6: $p = 0.141$); however, results were only regarded as significant in a predefined network, which is consistent with previous similar approaches [20]. The results are displayed in figure 2.

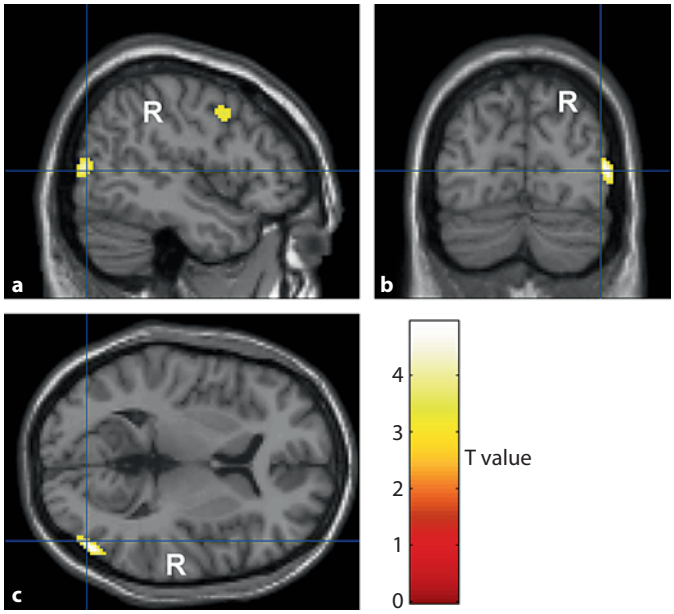

Fig. 2. Brain regions with significant reductions of the rCMRglc in the DLB + VH group compared with the DLB – VH group. Anatomical localization as projected on sagittal (**a**), coronal (**b**) and axial (**c**) sections of a normal MRI, spatially normalized into the MNI template ($p < 0.001$ uncorrected for multiple comparisons; maximum at x/y/z 47/–71/10 in Talairach space, right middle temporal gyrus, Brodmann area 39). R = Right side.

Discussion

VH are common amongst patients with DLB and similar to those experienced by individuals with PD. They typically are of an animated nature and often cause a feeling of unease. VH are moreover frequently accompanied by other neuropsychiatric symptoms such as anxiety, apathy or sleep disturbances, which further impair the individual's quality of life. The phenomenology of VH suggests an involvement of visual association areas rather than the primary visual cortex [24]. These higher order visual association areas are generally divided into 2 interlinked streams: (1) the ventral stream for the recognition of objects, colours and people, which extends to the inferior temporal cortex; (2) the dorsal stream for motion and overview vision [25], which runs to the posterior parietal cortex. Our results provide a further piece of evidence that might help to understand the functional pathology of VH in neurodegenerative disorders.

In the present study, relative metabolic reductions in hallucinating patients with DLB as compared with non-hallucinating patients were found at the right temporo-occipital junction and the right middle frontal gyrus. It is important to note that although our patients had had a history of VH in the 4 weeks before the PET scan, none of them had actually experienced hallucinations during the scan. Our finding therefore represents trait-related rather than state-related metabolic changes. The right temporo-occipital junction and the right middle frontal gyrus are both known to participate in the processing of visual stimuli, and they have been linked to VH in other neurodegenerative conditions such as PD before. In addition to our own previous ^{18}F-FDG PET study on VH in PD [1], in which we reported a significant hypometabolism of brain regions of the 2 visual streams. Matsui et al. [26] also described significant functional damage to these visual pathways in hallucinating patients with PD. This finding is also mirrored in a study by Nagano-Saito et al. [27], who also reported a relative metabolic deficit in posterior cortical areas in a hallucinating PD group. However, they also found a relative hypermetabolism in frontal brain regions. This up-regulation of frontal areas could be considered as an equivalent of executive control over internally created images, according to the authors. In contrast, Okada et al. [28] reported that the blood flow deficit of patients with PD and medication-induced VH was located in the left temporal cortex. In addition, Oishi et al. [29] found a decreased flow in the right fusiform gyrus and an increased flow in the right superior and middle temporal gyri in a group of non-psychotic, hallucinating patients with PD. Despite the relative heterogeneity of the findings, which can partly be explained by differences in patient characteristics and study procedures including imaging modalities, all reports imply that downstream visual areas, rather than the primary visual cortex, are involved in the occurrence of VH in PD and DLB.

Lance [30] hypothesized that complex VH due to temporo-parieto-occipital brain damage are linked to spontaneous discharges of neurons in visual association areas rather than to an input deficiency from the primary visual cortex. In the particular case of our DLB group, exstrastriate neurodegeneration or complex neurotransmitter abnormalities are most likely involved. Traditionally, disturbances in dopaminergic transmission have

been considered to underlie psychotic phenomena, including VH, in individuals with dementia. There is, however, only limited evidence that L-dopa can exacerbate VH [31], and an increased L-dopa dose does not implicate an increased frequency of VH [32]. There is little specific evidence regarding the impact of L-dopa upon VH in DLB, but more extensive reductions of presynaptic cholinergic activity have been identified in DLB than in AD [33]. Furthermore, greater cholinergic deficits have been found in hallucinating than in non-hallucinating patients with DLB [34], indicating that although other factors such as L-dopa administration could possibly play an adjunctive role, acetylcholine is probably more important than dopamine as a substrate of hallucinations in these patients. O'Brien et al. [35] reported that the perfusion of the left posterior cingulate cortex and precuneus decreased with worsening VH in a mixed PD dementia and DLB group. In contrast, in a study by Imamura et al. [36], VH were associated with hypometabolism in the primary visual cortex and a relatively preserved metabolism of right temporo-parietal association areas. However, in line with most findings VH in DLB are particularly responsive to cholinergic treatment. In a study by Mori et al. [37] not only VH but also blood flow deficits in the visual association cortex improved after application of donepezil. In an effort to provide an integrative psychological model of recurrent complex VH, Collerton et al. [38] suggested that both executive and perceptual dysfunctions are needed for a patient to be prone to experiencing recurrent complex VH (perception and attention deficit model); either impaired attention or impaired sensory activation alone would seldom cause VH.

The limitations of our study include patient recruitment at university-based departments, which limits the generalization of the results. Furthermore, no pathological verification of the clinical diagnoses were performed. However, current clinical diagnostic criteria were applied that yield a variable sensitivity (mean 54%) but a high specificity (mean 94%). The accuracy of the clinical diagnosis of DLB is therefore comparable to the diagnosis of AD or PD [39]. The hypometabolic pattern and the frequency of typical clinical symptoms were comparable to previous reports on this particular condition. Tiraboschi et al. [40] recently reported that recurrent VH were the best positive predictor of DLB at autopsy (positive predictive value of 83%). However, this finding was not replicated in another autopsy-confirmed study [41]. Due to the exclusion of patients who developed dementia more than 12 months after the initial motor symptoms, not only patients with AD but also those with PD dementia were reliably excluded. However, an inclusion of patients with AD cannot be entirely ruled out without a histopathological examination. Patients with DLB can have concomitant AD neuropathology even if clinical diagnostic criteria for DLB are strictly applied. Therefore, the contribution of AD pathology cannot be totally separated out in a clinical study. However, Merdes et al. [42] demonstrated that the degree of concomitant AD pathology, staged by a modification of the method of Braak and Braak, has an important influence on the clinical characteristics of DLB and, therefore, the clinical diagnostic accuracy of DLB. Consistent with previous studies, they report a higher prevalence of core symptoms in patients with 'pure' DLB than in those with superimposed AD pathology. Furthermore, Del Ser et al. [43] reported that the early onset of core symptoms was crucial for a highly accurate clinical diagnosis of 'pure' DLB. In our study, approximately 70% of the included patients had dementia of a mild degree and the remaining 30% were moderately demented. Almost all of them had parkinsonian symptoms and fluctuations in cognition, and approximately two thirds had VH and/or recurrent falls, but, again, an autopsy would have been necessary to definitely exclude all patients with mixed AD neuropathology. A further limitation of the study is the assessment of VH using the NPI, which does not separate between hallucinations of different modalities. Semi-structured interviews will be used in future studies to improve the accuracy of the assessment [44]. However, no patient suffered from hallucinations other than visual ones in the present study; therefore, the severity/frequency rating was not diluted by other modalities of hallucinations. It also has to be acknowledged that the presence or absence of fluctuating consciousness, a key diagnostic feature of DLB, was assessed by consensus of 2 experienced clinicians as part of a routine clinical protocol. The use of a standardized interview might have improved the accuracy of the assessment [45].

To conclude, our results stress the involvement of visual association cortices rather than the primary visual cortex in the occurrence of VH in DLB. This finding provides evidence for the neurobiological mechanisms underlying psychotic symptoms in DLB and it should also be considered in the planning of future treatment studies.

Acknowledgement

The study was co-financed by grants of the Technical University of Munich and the German Parkinson's Disease Foundation.

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