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Author: Prabitha Urwyler, Tobias Nef, René Müri, Neil Archibald, Selina Margaret Makin, Daniel Collerton, John-Paul Taylor, David Burn, Ian McKeith, Urs Peter Mosimann

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Visual Hallucinations in Eye Disease and Lewy Body Disease

Prabitha Urwyler, Ph.D.[1], Tobias Nef, Ph.D.[1,2], René Müri, M.D.[1,3], Neil Archibald, Ph.D.[4,5], Selina Margaret Makin, Ph.D.[5,6], Daniel Collerton, M.Sc.[5,7], John-Paul Taylor, M.D.[5], David Burn, M.D.[5], Ian McKeith, M.D.[5], Urs Peter Mosimann, M.D.[1,5,8]*

[1] Gerontechnology & Rehabilitation Group, University of Bern, Bern, Switzerland

[2] ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland

[3] Perception and Eye Movement Laboratory, Departments of Neurology and Clinical Research, University Hospital Inselspital, University of Bern, Bern, Switzerland

[4] The James Cook University Hospital, Middlesbrough, United Kingdom

[5] Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom

[6] The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom

[7] Northumberland, Tyne & Wear NHS Foundation Trust, Bensham Hospital, Gateshead, United Kingdom

[8] University Hospital of Old Age Psychiatry, University of Bern, Switzerland

***Corresponding author:** Urs P. Mosimann, MD; PhD

Professor of Old Age Psychiatry, Murtenstrasse 50, CH-3008 Bern, Switzerland

Email: urs.mosimann@artorg.unibe.ch / Telephone: +41 31 632 7478 / Fax: +41 31 632 7576

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Visual hallucinations, phenomenology, Lewy body diseases, eye disease

ABSTRACT

Objective: Visual hallucinations (VH) most commonly occur in eye disease (ED), Parkinson's disease (PD), and Lewy body dementia (LBD). The phenomenology of VH is likely to carry important information about the brain areas within the visual system generating them. **Methods:** Data from five controlled cross-sectional VH studies (164 controls, 135 ED, 156 PD, 79 (PDD 48 + DLB 31) LBD) were combined and analysed. The prevalence, phenomenology, frequency, duration, and contents of VH were compared across diseases and gender. **Results:** Simple VH were most common in ED patients (ED 65% vs. LBD 22% vs. PD 9%, Chi-square [χ^2] test: χ^2=31.43, df=2, p<0.001), whilst complex VH were more common in LBD (LBD 76% vs. ED 38%, vs PD 28%, Chi-square test: χ^2=96.80, df=2, p<0.001). The phenomenology of complex VH was different across diseases and gender. ED patients reported more "flowers" (ED 21% vs. LBD 6% vs. PD 0%, Chi-square test: χ^2=10.04, df=2, p=0.005) and "body parts" (ED 40% vs. LBD 17% vs. PD 13%, Chi-square test: χ^2=11.14, df=2, p=0.004); in contrast LBD patients reported "people" (LBD 85% vs. ED 67% vs. PD 63%, Chi-square test: χ^2=6.20, df=2, p=0.045) and "animals/insects" (LBD 50% vs. PD 42% vs. ED 21%, Chi-square test: χ^2=9.76, df=2, p=0.008). Males reported more "machines" (13 % vs. 2%, Chi-square test: χ^2=6.94, df=1, p=0.008), whilst females reported more "family members/children" (48% vs. 29%, Chi-square test: χ^2=5.10, df=1, p=0.024). **Conclusions:** The phenomenology of VH is likely related to disease specific dysfunctions within the visual system and to past, personal experiences.

Keywords: Visual hallucinations, phenomenology, Lewy body dementia, Parkinson's disease, eye disease

Recurrent visual hallucinations (VH) are visual perceptions in the absence of an appropriate external visual stimulus. In later life, they occur mainly in the context of eye disease (ED)(1-3) and Lewy body diseases such as Parkinson's disease (PD)(4, 5) and Lewy body dementia (LBD) including Parkinson's disease dementia (PDD)(5-7) and dementia with Lewy bodies (DLB).(2, 7, 8) There are numerous studies examining VH in these specific diseases; however, there has been very little direct comparison of phenomenology across diseases.(9)

The phenomenology of VH is commonly classified into simple VH,(10) passage hallucinations / the feeling of presence,(11) visual illusions,(12) and complex VH.(7) Simple VH lack recognizable form and refer to dots, lines, shapes, patterns, and flashes.(10, 13) Complex VH are well-formed and include faces, people, animals, objects or landscapes.(7, 13, 14) The feeling of presence involves the sense of a person being present but not clearly visible in the room or house.(11) Illusions refer to experiences where it is clear that one object is distorted into another – for example, see a person in a curtain or perceive blobs on the wall as faces.(12)

The phenomenology of VH likely refers to underlying dysfunction within the visual system.(13, 15, 16) Imaging of higher visual processing areas within the ventral and dorsal visual pathways in ED,(15) PD,(17-19) and DLB(8, 20) has indicated that specific content may be related to particular patterns of neural activity. For example, a case report in ED suggested that VH consisting of letters or words are related to the left posterior fusiform gyrus, the visual word form area(21) whilst VH involving colour, faces, textures, and objects are due to increased activity in the ventral occipital lobe.(15) Functional magnetic resonance imaging studies show increased activation in the visual association cortex with deficits in the primary visual cortex(17) and hyper-activation in the frontal lobes in PD patients with VH.(19) In DLB, abnormalities in the occipitoparietal visual area have been related to VH(20) with

complex VH of images of people associated with hypoperfusion in the bilateral parietal areas and left ventral occipital gyrus.(22)

VH is mostly assessed using questionnaires relying on informant or patient information. Existing questionnaires tend to underestimate the characteristics of VH.(11) Very few are designed to be used across diseases. The North East Visual Hallucination Inventory (NEVHI)(3) is an exception and has been developed for patients with visual and/or cognitive impairments and screens for different phenomenology and characteristics including frequency and severity. The aim of the present study was to compare the phenomenology and characteristics of VH in ED, PD, LBD patients using the NEVHI(3) interview based on patient information.(23) We hypothesized that the phenomenology and characteristics of VH would be different across diseases. We further explored the effects of gender on hallucinatory content.

METHODS

Study Selection and Data Collection

There have been several studies(2-5, 8, 24) using NEVHI(3) since its original publication in 2008. Only controlled cross-sectional NEVHI studies with ED, PD, PDD, and DLB samples using similar methodology were included in this study. Three(3, 4, 8) of them had two sample groups (patients, controls), while the other two had three sample groups (controls, ED, DLB;(2) controls, PD, PDD(5)). The control groups which included friends/relatives(2, 8) or spouses of patients,(2, 3, 5, 8) volunteers recruited via advertisement in the Newcastle Elders magazine(4) and in a local church(3, 4) and healthy controls from the research database held at the Institute for Ageing, Newcastle University(3, 5) comprise the comparison group in this study. Diagnostic criteria were met using the revised International Consensus Guidelines from the third report of the DLB consortium for DLB, the Movement Disorder Society consensus criteria for dementia associated with PD for PDD, and the UK PD Society Brain Bank Clinical Diagnostic Criteria for PD. The principal investigators of these studies agreed to contribute their original data for the present study. Data were collected in accordance with the latest version of the Declaration of Helsinki and was approved by the National Health Service (NHS) Research Ethics

Committee, United Kingdom. All procedures related to the study were explained to the participants and a written informed consent was obtained prior to participation. All data were merged into a single database including 164 individuals in the comparison group and 383 patients (135 ED, 156 PD, 48 PDD, 31 DLB, 13 with combination of ED/PD/PDD/DLB). The latter 13 patients were excluded from further analysis. A sub-analysis of VH phenomenology did not reveal any differences between DLB and PDD patients, which were subsequently considered as one LBD group. PD and LBD patients were only included if they had no visual field defects on neurological examination.

Assessments

An interview was used to gather demographic data in all studies. Best near visual acuity was examined using Landolt broken rings or Snellen Charts at a test distance of 40 cm.(25) The Mini Mental State Examination (MMSE)(26) was used as screening instrument for global cognition. The maximal score was 29 in the ED (omission of overlapping pentagon drawing)(24) and 30 for all other groups. The verbal fluency test (FAS)(27) and category (animal) fluency test(27) assessed the executive and language skills. The verbal fluency scores were averaged across three one-minute trials. The Unified Parkinson's Disease Rating Scale (UPDRS III)(28) served as a measure to quantify extrapyramidal motor features. The Mayo sleep questionnaire(29) screened for the presence of rapid eye movement sleep behaviour disorder (RBD) and the Epworth Sleepiness scale (ESS)(30) was the screening measure for excessive daytime somnolence. The accepted cut-off for excessive daytime somnolence using the ESS was set to a score of 10. Clinical parameters specific to Lewy body diseases (UPDRS, RBD, ESS) were assessed in PD, PDD, and DLB patients only. The NEVHI(3) screens for the presence and phenomenology of VH, and establishes the duration and frequency of hallucinations. Section 1 of the NEVHI assesses the presence and phenomenology of VH (simple VH and complex VH, visual illusions, passage of shadows, feeling of presence), section 2 the frequency, duration of VH and section 3 assesses perceived severity (i.e. the emotions, cognitions associated with VH). A detailed description of the questionnaire can be found elsewhere.(3) Complex VH were grouped into the categories: "people" (anonymous or family

members/children), “body parts”, “animals/insects”, “machines”, and “letters/numbers/musical notes”.(7, 13, 15) Prevalence, phenomenology, frequency, duration and severity of VH were compared between the (i) comparison group and patients and (ii) different patient groups (ED, PD, LBD). The phenomenology of Complex VH was also compared between gender.

Statistical analysis

Statistical analysis was undertaken using the Statistical Package for Social Sciences (SPSS Version 20). Normal distribution of data was examined using the Shapiro-Wilk test. Means and standard deviations (SD) were calculated. Data were analysed using parametric tests (one-way analysis of variance (ANOVA)). Multiple comparisons were assessed with Post-hoc Bonferroni tests. Frequencies were compared using the chi-square (χ^2) test and Fisher’s exact test when expected frequency in either group was < 5. The effect of gender, disease and interaction of gender × disease on contents of complex VH was tested using a two-way ANOVA (Effect sizes are reported using partial η^2), whilst logistic regression was used to ascertain whether the VH phenomenology could significantly predict the disease. The homogeneity of variance of the interaction model was tested using Levene’s test, while goodness-of-fit of the regression model was tested using Hosmer and Lemeshow test. All reported p-values are two-tailed and a p-value < 0.05 was considered significant.

RESULTS

Demographics

The demographics and clinical characteristics are summarised in Table 1. The groups did not differ in education, but females were overrepresented in the ED group and the ED and LBD groups tended to be older than the other groups. The ED group had, as expected, the lowest visual acuity score and the LBD group performed poorest in all cognitive measures (MMSE, verbal and categorical fluency) compared to all other groups. When the PD and LBD groups were compared disease duration was not different, but the

LBD group had higher UPDRS III scores. PD and LBD had also higher ESS and more RBD than the ED or comparison groups.

-Table 1 about here-

Visual hallucination phenomenology

The 1-year prevalence of any type of VH was not different between ED and LBD (84% vs. 86%; Chi-square test: $\chi^2 = 0.22$, df = 1, p = 1.000), but the ED and LBD groups had more VH than the PD patients (PD vs. ED: 66% vs. 84%, Chi-square test: $\chi^2 = 11.82$, df = 1, p = 0.002; PD vs. LBD: 66% vs. 86%, Chi-square test: $\chi^2 = 10.64$, df = 1, p = 0.004). The phenomenology of VH across diseases is summarised in Table 2. Complex VH were exclusively found in patients and not in the comparison group, although some in the comparison group reported visual illusions. Complex VH were most commonly observed in LBD patients and the observed 1-year prevalence was two or three times higher than in PD or in ED. In addition, the passage of shadow and feeling of presence were more common in LBD than in the other groups, but the group differences were less distinct. The simple VH were the most common hallucination in ED, while they are rarely observed in PD or in the comparison group.

-Table 2 about here-

Frequency, duration and distress of visual hallucinations

The VH of patients occurred more frequently (weekly or daily) compared to those in the comparison group (monthly) as shown in Table 3. Daily hallucinations were most commonly reported by the ED patients, whereas LBD and PD patients experienced them on a weekly or monthly basis. The VH occurred for minutes to maximal 2 hours with no major difference between the groups. Long-lasting hallucinations (> 2 hours) were rare and commonly reported by LBD patients. A tendency to more irritating and

frightening hallucinations was found in LBD whilst only a minority of the ED and PD patients found their hallucinations distressing.

- *Table 3 about here* -

Phenomenology of complex visual hallucinations across diseases

The details of the phenomenology of complex VH in patients are summarized in Table 4. The most common complex VH experienced was of "people", followed by "animals/insects". ED patients reported more "flowers" and "body parts" than the other groups and LBD patients more often reported hallucinations containing "people".

- *Table 4 about here* -

Phenomenology of complex visual hallucinations across gender

The differences in the phenomenology of complex VH across gender irrespective of the diseases are summarized in Table 5. Both male and female patients reported "people" equally frequently. However, "family members/children" were more commonly reported by females and "anonymous people" were more common in males. In addition, VH containing "body parts" were more often reported by female patients, whilst male patients reported more VH containing "machines".

- *Table 5 about here* -

Effect of gender, disease and interaction of gender × disease on complex visual hallucination phenomenology

There was a main effect of gender on "anonymous people" (two-way ANOVA: F (df 1,134) = 5.109, p = 0.025, partial η^2 = 0.037), "family members/children" (two-way ANOVA: F (df 1,136) = 8.172, p =

0.005, partial $\eta^2 = 0.057$), and "machines" (two-way ANOVA: F (df 1,136) = 9.531, p = 0.002, partial η^2 = 0.065), whilst disease had a main effect on "people" (two-way ANOVA: F (df 2,136) = 3.331, p = 0.039, partial $\eta^2 = 0.047$), "family members/children" (two-way ANOVA: F (df 2,136) = 3.994, p = 0.021, partial $\eta^2 = 0.055$), "body parts" (two-way ANOVA: F (df 2,136) = 3.328, p = 0.039, partial η^2 = 0.047), "animals/insects" (two-way ANOVA: F (df 2,136) = 5.042, p = 0.008, partial $\eta^2 = 0.069$), and "flowers" (two-way ANOVA: F (df 2,126) = 7.163, p = 0.001, partial $\eta^2 = 0.102$). Two of the above main effects were qualified by a significant gender × disease interaction which was only present in ED with a female gender effect on "family members/children" (two-way ANOVA: F (df 1,136) = 5.093, p = 0.026, partial $\eta^2 = 0.036$) and a male gender effect on "machines" (two-way ANOVA: F (df 1,136) = 7.973, p = 0.005, partial $\eta^2 = 0.055$).

Association between the visual hallucination phenomenology and diseases:

The significant disease predictors were simple VH for ED (Logistic regression: Odds ratio [OR] = 12.1, 95% confidence interval [CI] = 6.653 – 21.939, Wald $\chi^2 = 67.004$, df = 1, $p < 0.001$, Nagelkerke R^2 = 0.396), feeling of presence/passage for PD (Logistic regression: OR = 1.910, 95% CI = 1.065 – 3.425, Wald $\chi^2 = 4.719$, df = 1, p = 0.030, Nagelkerke $R^2 = 0.160$) and complex VH for LBD (Logistic regression: OR = 13.126, 95% CI = 5·928 – 29·063, Wald $\chi^2 = 40.303$, df = 1, $p < 0{\cdot}001$, Nagelkerke R^2 = 0·310).

DISCUSSION

This study assessed the prevalence and phenomenology of VH in the comparison group, ED, PD and LBD using the same standardised and validated assessment. As hypothesised, the phenomenology of VH was different across diseases: (i) simple VH were most commonly experienced in ED whilst complex VH was the most common form of hallucination in LBD, (ii) VH occurred more frequently in ED (daily basis) than in PD and LBD, (iii) longer, irritating and frightening episodes of VH were common in LBD,

(iv) complex VH features like "people", "family members/children" were reported more frequently in LBD, whilst "flowers" and "body parts" were reported more commonly in ED. In addition, female patients reported more hallucinations of "family members/children", while male patients reported more "machines". The predictors for diseases were simple VH for ED, feeling of presence/passage for PD and complex VH for LBD.

This is the first time that VH phenomenology and characteristics were compared across diseases in which VH are common using the same methodology and a largest ever published sample size for these diseases. The 1-year prevalence of VH in our combined study are in line with the individual ED, PD and LBD studies reported before.(3, 5, 13) However, the 1-year prevalence of complex VH in PD in our study is lower owing to the clear differential diagnosis of PD and PDD, which before the year 2004 were studied as a single group. Our results confirm the highest prevalence of simple VH in ED(13, 31) and highest prevalence of complex VH in LBD.(7) This supports the assumption that simple VH are related to pathology within the primary retino-cortical visual system,(31) whereas complex VH are likely tied to higher cortical dysfunction in the context of LB pathology;(13, 14, 16, 31) for example, LB pathology within the temporal and ventral visual stream has been linked to a higher prevalence of complex VH in LBD.(16) In addition, the well-formed quality of complex VH suggests involvement of regions outside the primary visual areas. In our study, both complex VH and irritating, frightening episodes of VH were common in LBD, whereas increased visual excitability has been previously reported as a marker for frequency × severity of complex VH in LBD.(8) The two different predictors, simple VH for ED and complex VH for LBD also support assumptions that VH are clinically useful disease-specific predictors.(6)

Comparing our results with previous studies,(7, 10, 11, 13) features like "inverse hats" reported previously in ED patients(13) were rarely reported by our patients, but overall our results are in line with studies that have reported features like "people" and "animals" as the most common categories of images

in complex VH.(7, 10, 11) As with earlier studies where VH content tends to be familiar in PD,(11) our study found that the complex VH content were well-formed and familiar in LBD. High densities of LB in the amygdala and the parahippocampus, areas upon which judgements of familiarity depend, are in fact associated with well-formed CVH in LBD.(16) However it is not clear that recognition of VH content as familiar is necessarily reliable.

The so-called "continuity hypothesis"(32) contends that dream images are often an extension of waking day thoughts, feelings and behaviours that can possibly be extended to hallucinations. Accordingly, VH may refer to real life experiences of which family members and friends can be the most common phenomenology. Females reporting more about "family members/children" and males more on "machines" suggest that the content of complex VH is presumably influenced by personal experience.(33)

The strength of this study lies in its large sample size and its focus on the phenomenology of VH. The pooling of data and the use of similar methodology to characterise patients or VH allowed a more thorough analysis of sub-groups than in previous studies. However, since data was combined across studies, findings will need to be confirmed within a single group comparison.

CONCLUSIONS

Our main findings, namely that the phenomenology and characteristics of VH are different across diseases and are related to past personal experiences, provide mounting evidence and may inform models of mechanisms underpinning this link. There is further a clear need for future studies that link the pathophysiology within the visual system to the phenomenology of VH.

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References

1. Teunisse RJ, Cruysberg JR, Hoefnagels WH, et al: Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome. Lancet 1996; 347:794-797
2. Makin SM, Redman J, Mosimann UP, et al: Complex visual hallucinations and attentional performance in eye disease and dementia: a test of the Perception and Attention Deficit model. Int J Geriatr Psychiatry 2013; 28:1232-1238
3. Mosimann UP, Collerton D, Dudley R, et al: A semi-structured interview to assess visual hallucinations in older people. Int J Geriatr Psychiatry 2008; 23:712-718
4. Urwyler P, Nef T, Killen A, et al: Visual complaints and visual hallucinations in Parkinson's disease. Parkinsonism Relat Disord 2014; 20:318-322
5. Archibald NK, Clarke MP, Mosimann UP, et al: Visual symptoms in Parkinson's disease and Parkinson's disease dementia. Mov Disord 2011; 26:2387-2395
6. Galvin JE, Pollack J,Morris JC: Clinical phenotype of Parkinson disease dementia. Neurology 2006; 67:1605-1611
7. Mosimann UP, Rowan EN, Partington CE, et al: Characteristics of visual hallucinations in Parkinson disease dementia and dementia with lewy bodies. Am J Geriatr Psychiatry 2006; 14:153-160
8. Taylor JP, Firbank M, Barnett N, et al: Visual hallucinations in dementia with Lewy bodies: transcranial magnetic stimulation study. Br J Psychiatry 2011; 199:492-500
9. Diederich NJ, Pieri V,Goetz CG: Visual hallucinations in Parkinson and Charles Bonnet Syndrome patients. A phenomenological and pathogenetic comparison. Fortschritte der Neurologie-Psychiatrie 2000; 68:129-136
10. Barnes J,David AS: Visual hallucinations in Parkinson's disease: a review and phenomenological survey. J Neurol Neurosurg Psychiatry 2001; 70:727-733

11. Fénelon G, Mahieux F, Huon R, et al: Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000; 123:733-745

12. Uchiyama M, Nishio Y, Yokoi K, et al: Pareidolias: complex visual illusions in dementia with Lewy bodies. Brain 2012; 135:2458-2469

13. Santhouse AM, Howard RJ,ffytche DH: Visual hallucinatory syndromes and the anatomy of the visual brain. Brain 2000; 123:2055-2064

14. Collerton D, Perry E,McKeith I: Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. Behav Brain Sci 2005; 28:737-757; discussion 757-794

15. ffytche DH, Howard RJ, Brammer MJ, et al: The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1998; 1:738-742

16. Harding AJ, Broe GA,Halliday GM: Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain 2002; 125:391-403

17. Holroyd S,Wooten GF: Preliminary fMRI evidence of visual system dysfunction in Parkinson's disease patients with visual hallucinations. The Journal of neuropsychiatry and clinical neurosciences 2006; 18:402-404

18. Meppelink AM, de Jong BM, Renken R, et al: Impaired visual processing preceding image recognition in Parkinson's disease patients with visual hallucinations. Brain 2009; 132:2980-2993

19. Stebbins GT, Goetz CG, Carrillo MC, et al: Altered cortical visual processing in PD with hallucinations: an fMRI study. Neurology 2004; 63:1409-1416

20. Taylor JP, Firbank MJ, He J, et al: Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study. Br J Psychiatry 2012; 200:491-498

21. ffytche DH, Lappin JM,Philpot M: Visual command hallucinations in a patient with pure alexia. J Neurol Neurosurg Psychiatry 2004; 75:80-86

22. Nagahama Y, Okina T, Suzuki N, et al: Neural correlates of psychotic symptoms in dementia with Lewy bodies. Brain 2010; 133:557-567

23. Urwyler P, Nef T, Müri R, et al: Patients' and Informants' views on visual hallucinations in Parkinson's disease. Am J Geriatr Psychiatry 2015; 23:970-976

24. Graham G, Dean J, Mosimann UP, et al: Specific attentional impairments and complex visual hallucinations in eye disease. Int J Geriatr Psychiatry 2011; 26:263-267

25. Hohmann A,Haase W: Development of visual line acuity in humans. Ophthalmic research 1982; 14:107-112

26. Folstein MF, Folstein SE,McHugh PR: Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198

27. Lezak MD, Howieson DB,Loring DW: Neuropsychological assessment, Oxford, Oxford University Press, 2004

28. Fahn S,Elton R: Unified Parkinson's Disease Rating Scale - UPDRS, in Recent Developments in Parkinson's Disease. Edited by Fahn S, Marsden CD, Calne DB, et al. Florham Park, NJ, Macmillan Health Care Information, 1987, pp 153-163

29. Boeve BF, Silber MH, Ferman TJ, et al: Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. Neurology 2002; 58:A509

30. Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14:540-545

31. ffytche DH: The hodology of hallucinations. Cortex 2008; 44:1067-1083

32. Schredl M,Hofmann F: Continuity between waking activities and dream activities. Consciousness and cognition 2003; 12:298-308

33. Scott IU, Schein OD, Feuer WJ, et al: Visual hallucinations in patients with retinal disease. Am J Ophthalmol 2001; 131:590-598

TABLE 1. Clinical and demographic characteristics (*n* = 534)

	Comparison group *n* = 164	Patients			Statistics	*p*
		ED *n* = 135	PD *n* = 156	LBD *n* = 79		
Age (years)	72.9 (8.2)	79.8 (8.3)	70.9 (9.4)	74.8 (7.4)	F=28.59^{Z}, 5.62^{A}, 71.89^{B},19.98^{C}, 9.91^{D}	<0.001^{Z,B,C}, 0.018^{A}, 0.007^{D}
Female (%)	92 (56)	93 (69)	64 (41)	23 (29)	χ^2=40.34^{Z}, 2.52^{A}, 22·61^{B}, 31.76^{C}, 3.19^{D}	<0.001^{Z,B,C}, 0.449^{A} , 0.296^{D}
Education (years)	11.5 (3.2)	10.7 (2.2)	10.9 (3.2)	10.8 (2.2)	F =2.61^{Z}, 7.37^{A}, 0.53^{B}, 0.09^{C}, 0.07^{D}	0.051^{Z}, 0.007^{A}, 1.000^{B}, 1.000^{C}, 1.000^{D}
Visual acuity (decimals)	0.48 (0.22)	0.19 (0.18)	0.42 (0.20)	0.35 (0.15)	F =52.71^{Z}, 71.06^{A}, 75.81^{B}, 17.27^{C}, 2.93^{D}	<0.001^{Z,A,B}, 0.001^{C}, 0.574^{D}
MMSE [max = 30]	28.5 (1.7)	27.1 (1.9)	28.2 (2.3)	21.6 (4.5)	F =152.18^{Z}, 43.87^{A}, 20.50^{B}, 149.86^{C}, 223.67^{D}	<0.001^{Z,A,C,D}, 0.001^{B}
Verbal fluency (words per minute)	13.2 (5.3)	11.5 (5.0)	12.3 (5.7)	5.9 (4.1)	F =5.15^{Z}, 6.02^{A}, 1.06^{B}, 7.97^{C}, 8.07^{D}	0.002^{Z}, 0.015^{A}, 1.000^{B,} 0·052^{C} ,0.017^{D}
Categorical fluency (animals per minute)	21.3 (6.8)	14.2 (3.6)	16.5 (5.9)	8.9 (3.5)	F =34.79^{Z}, 60.14^{A}, 4.66^{B}, 35.76^{C}, 37.65^{D}	<0.001^{Z,A,D}, 0.265^{B}, 0.002^{C}
Parkinsonism duration (years)	n.a	n.a	8.4 (5.6)	8.5 (6.3)	F =0.003^{D}	0.959^{D}
UPDRS III [max = 67]	n.a	n.a	22.5 (10.3)	31.7 (15.3)	F =22.7^{D}	<0.001^{D}
ESS [max = 24]	4.4 (3.4)	5.5 (0.7)	8.2 (5.5)	11.8 (4.4)	F =23.91^{Z}, 54.94^{A}, 0.487^{B}, 3.97^{C}, 10.47^{D}	<0.001^{Z,A}, 1.000^{B}, 0.408^{C}, 0.002^{D}

RBD likely (%)	4 (3)	1 (1)	58 (37)	35 (44)	χ^2=88.99^{Z}, 73.86^{A}, 12.69^{D}	<0.001^{Z,A,D}, °1.000^{B}, °1.000^{C}

Data are mean and (SD) unless specified otherwise; Statistics are one-way ANOVA (F) or chi-square (χ^2) tests or °Fisher's Exact; MMSE = Mini-Mental State Examination, UPDRS = Unified Parkinson's Disease Rating Scale – motor evaluation, ESS = Epworth Sleeping Scale; RBD = Rapid eye movement sleep behavior disorder; ED = Eye disease; PD = Parkinson's disease; LBD = Lewy body dementia; n.a = not available; ^{Z} comparison across all groups, df =3; ^{A} comparison group vs. patients, df =1; ^{B} ED vs. PD, df =1; ^{C} ED vs. LBD , df =1; ^{D} PD vs. LBD, df =1;

TABLE 2. The phenomenology of visual hallucinations across diseases

	Comparison group ***n* = 164**	**Patients**			**Statistics (χ^2)**	***p***
		ED ***n* = 135**	**PD** ***n* = 156**	**LBD** ***n* = 79**		
Complex visual hallucinations	0 (0)	52 (38)	43 (28)	60 (76)	157.57^{Z}, 96.80^{A}, 3.95^{B}, 27.99^{C}, 49.87^{D}	<0.001^{Z,A,C,D}, 0.188^{B}
Illusion	15 (9)	22 (16)	42 (27)	34 (43)	41.87^{Z}, 20.48^{A}, 4.76^{B}, 18.45^{C}, 6.22^{D}	<0.001^{Z,A,C}, 0.116^{B}, 0.050^{D}
Passage of shadow / Feeling of presence	34 (21)	57 (42)	82 (53)	52 (66)	55.96^{Z}, 44.47^{A}, 3.10^{B}, 11.11^{C}, 3.76^{D}	<0.001^{Z,A}, 0.313^{B}, 0.003^{C}, 0.210^{D}
Simple visual hallucinations	15 (9)	88 (65)	13 (8)	17 (22)	162.28^{Z}, 31.43^{A}, 103.22^{B}, 38.02^{C}, 8.19^{D}	<0.001^{Z,A,B,C}, 0.017^{D}

Data are n (%);Statistics are chi-square (χ^2) or Fisher's exact tests; ED = Eye disease; PD = Parkinson's disease; LBD = Lewy body dementia; ^{Z} comparison across all groups: df = 3; ^{A} comparison group vs. patients: df = 1; ^{B} ED vs. PD: df = 1; ^{C} ED vs. LBD: df = 1; ^{D} PD vs. LBD: df = 1;

TABLE 3. Frequency, duration and distress of visual hallucinations across diseases

	Comparison group	ED	PD	LBD	Statistics (χ^2)	*p*
Frequency	***n* = 24**[#]	***n* = 101**[#]	***n* = 79**[#]	***n* = 55**[#]		
Less than once a week	17 (71)	14 (14)	33 (42)	16 (30)	36.12^{Z}, 19.77^{A}, 17.89^{B}, 5.32^{C}, 2.25^{D}	$<0.001^{Z,A,B}$, 0.084^{C}, 0.535^{D}
1-6 times a week	3 (3)	38 (38)	32 (41)	29 (53)	11.54^{Z}, 8.01^{A}, 0.16^{B}, 3.31^{C}, 1.95^{D}	0.009^{Z}, 0.019^{A}, 1.000^{B}, 0.275^{C}, 0.649^{D}
Daily	1 (2)	34 (34)	14 (18)	10 (18)	13.34^{Z}, 5.21^{A}, 5.76^{B}, 4.22^{C}, 0.01^{D}	0.004^{Z}, 0.022^{A}, 0.066^{B}, 0.160^{C}, 1.000^{D}
Duration	***n* = 13**[§]	***n* = 101**[§]	***n* = 74**[§]	***n* = 49**[§]		
Less than 5 min	3 (23)	50 (50)	32 (43)	18 (37)	4.60^{Z}	0.203^{Z}
5 min to 2 hrs	10 (77)	44 (44)	40 (54)	25 (51)	5.95^{Z}	0.114^{Z}
Longer than 2 hrs	0 (0)	3 (3)	2 (3)	6 (12)	8.29^{Z}, 0.63^{A}, 0.01^{B}, 5.03^{C}, 4.41^{D}	0.040^{Z}, $1.000^{A,B}$, 0.1^{C}, 0.143^{D}
Distress	***n* = 10**[¥]	***n* = 91**[¥]	***n* = 74**[¥]	***n* = 49**[¥]		
Irritating	0 (0)	28 (30)	13 (18)	31 (62)	32.77^{Z}, 4.86^{A}, 3.49^{B}, 13.65^{C}, 25.73^{D}	$<0{\cdot}001^{Z,C,D}$, $0{\cdot}110^{A}$, 0.246^{B}
Frightening	0 (0)	27 (30)	11 (15)	25 (51)	23.16^{Z}, 4.09^{A}, 5.05^{B}, 6.22^{C}, 18.62^{D}	$<0.001^{Z,D}$, 0.172^{A}, 0.099^{B}, 0.051^{C}

Data are n (%); Statistics are chi-square (χ^2) or Fisher's exact tests; ED = Eye disease; PD = Parkinson's disease; LBD: Lewy body dementia; # = number of answers to sections corresponding to frequency of visual hallucination; § = number of answers the duration of visual hallucination section;¥ = number of answers to emotions associated with visual hallucination section;

^{Z} comparison across all groups: df = 3; ^{A} comparison group vs. patients: df = 1; ^{B} ED vs. PD: df = 1; ^{C} ED vs. LBD: df = 1; ^{D} PD vs. LBD: df = 1;

TABLE 4. Phenomenology of complex visual hallucinations (complex VH) across diseases

Contents of complex VH	ED with complex VH *n* = 52	PD with complex VH *n* = 38	LBD with complex VH *n* = 52	Statistics (χ^2)	*p*
People	35 (67.3)	24 (63.2)	44 (84.6)	6.20^{Z}, 0.17^{B}, 4.27^{C}, 5.47^{D}	0.045^{Z}, 1.000^{B}, 0.078^{C}, 0.039^{D}
anonymous people e.g.: soldiers, people	24 (48.0)	14 (36.8)	27 (51.9)	2.09^{Z}, 1.10^{B}, 0.16^{C}, 2.02^{D}	0.353^{Z}, 0.886^{B}, 1.000^{C}, 0.467^{D}
family members, children	18 (34.6)	10 (26.3)	26 (50.0)	5.63^{Z}, 0.71^{B}, 2.52^{C}, 5.13^{D}	0.060^{Z}, 1.000^{B}, 0.337^{C}, 0.047^{D}
Body parts	21 (40.4)	5 (13.2)	9 (17.3)	11.14^{Z}, 7.92^{B}, 6.75^{C}, 0.29^{D}	0.004^{Z}, 0.015^{B}, 0.028^{C}, 1.000^{D}
Animals & Insects	11 (21.2)	16 (42.1)	26 (50.0)	9.76^{Z}, 4.59^{B}, 9.44^{C}, 0.55^{D}	0.008^{Z}, 0.097^{B}, 0.006^{C}, 1.000^{D}
Machines	5 (9.6)	3 (7.9)	3 (5.8)	0.54^{Z}, 0.08^{B}, 0.54^{C}, 0.16^{D}	0.763^{Z}, 1.000^{B}, 1.000^{C}, 1.000^{D}
Flowers	11 (21.2)	0 (0)	3 (5.9)	10.74^{Z}, 7.09^{B}, 5.11^{C}, 1.77^{D}	0.005^{Z}, 0.023^{B}, 0.071^{C}, 0.549^{D}
Letters, Numbers, Musical Notes	2 (3.8)	0 (0)	1 (1.9)	1.59^{Z}, 1.49^{B}, 0.34^{C}, 0.74^{D}	0.453^{Z}, 0.664^{B}, 1.000^{C}, 1.000^{D}

Data are n (%);Statistics are chi-square (χ^2) or Fisher's exact tests; ED = Eye disease; PD = Parkinson's disease; LBD = Lewy body dementia;
^{Z} comparison across all groups: df = 2; ^{B} ED vs. PD: df = 1; ^{C} ED vs. LBD: df = 1; ^{D} PD vs. LBD: df = 1;

TABLE 5. Phenomenology of complex visual hallucinations (complex VH) across gender

Contents of complex VH	Males with complex VH *n* = 75	Females with complex VH *n* = 67	Statistic [df], *p*
People	53 (70.7)	50 (74.6)	$\chi^2_{[1]} = 0.28$, $p = 0.598$
anonymous people e.g.: soldiers, people	40 (54.8)	25 (37.3)	$\chi^2_{[1]} = 4.29$, $p = 0.038$
family members, children	22 (29.3)	32 (47.8)	$\chi^2_{[1]} = 5.10$, $p = 0.024$
Body parts	12 (16.0)	23 (34.3)	$\chi^2_{[1]} = 6.40$, $p = 0.011$
Animals & Insects	29 (38.7)	24 (35.8)	$\chi^2_{[1]} = 0.12$, $p = 0.726$
Machines	10 (13.3)	1 (1.5)	$\chi^2_{[1]} = 6.94$, $p = 0.008$
Flowers	8 (11.4)	6 (9.7)	$\chi^2_{[1]} = 0.11$, $p = 0.744$
Letters, Numbers, Musical Notes	3 (4.0)	0 (0.0)	$\chi^2_{[1]} = 2.74$, $p = 0.247$

Data are n (%); Statistics are chi-square (χ^2) or Fisher's exact tests with df =1.