

**THE RELATIONSHIP OF PLAQUES, TANGLES, AND LEWY-TYPE ALPHA-SYNUCLEINOPATHY
TO VISUAL HALLUCINATIONS IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE**

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Trisha Morshed
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Mentor: Sandra Jacobson, MD

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Abstract

Objective: Formed visual hallucinations are a common phenomenon in neurodegenerative disorders such as Parkinson's Disease (PD), Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB). While Lewy-type alpha-synucleinopathy (LTS) is the hallmark neuropathological finding in PD and DLB, amyloid plaques and neurofibrillary tangles are the pathological finding in AD. Previous research has linked complex or formed visual hallucinations (VH) to LTS in neocortical and limbic areas in patients with PD and DLB. As VH also occur in Alzheimer's disease, and AD pathology often co-occurs with LTS, we questioned whether this pathology might also be linked to VH.

Methods: We performed a semi-quantitative neuropathological study across brainstem, limbic, and cortical structures in subjects with a documented clinical history of VH and a clinicopathological diagnosis of Parkinson's disease (PD), Alzheimer's disease (AD), or dementia with Lewy bodies (DLB). 173 subjects – including 50 with VH and 123 without VH – were selected from the Arizona Study of Aging and Neurodegenerative Disorders. Clinical variables examined included the Mini-mental State Exam, Hoehn & Yahr stage, and total dopaminergic medication dose. Neuropathological variables examined included total and regional LTS and plaque and tangle densities.

Results: A significant relationship was found between the density of LTS and the presence of VH in all diagnostic groups. Plaque and tangle densities also were associated with VH in PD ($p=.003$ for plaque and $p=.004$ for tangles), but not in AD, where densities were high regardless of the presence of hallucinations..

Conclusion: Plaques and tangles as well as LTS may contribute to the pathogenesis of VH. Incident VH may be a clinical indicator of underlying pathological events: the development of plaques and tangles in patients with PD, and LTS in patients with AD.

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Introduction

Formed visual hallucinations (fVH), of people, animals, or objects, are a common symptom of various neurodegenerative diseases. Prior studies have noted the presence of fVH in 8-40% of patients with Parkinson's disease {Barnes, 2001}, 20% of patients with Alzheimer's disease {Holroyd, 2000}, and 60-80% of patients with dementia with Lewy bodies {Mosimann, 2006}. VH in PD and DLB frequently are reported as non-threatening images of people, animals, or objects that persist for seconds to minutes {Barnes, 2001}. The images may be highly detailed; for example, the people may be dressed in colorful costumes although only a few inches tall ("Lilliputian"). The hallucinations are experienced in a clear sensorium with eyes open. In the absence of dementia, insight into the hallucinatory nature of the images usually is retained {Fénelon, 2000}. The phenomenology of hallucinations in AD is somewhat different, in that images tend to be less well elaborated and less persistent, and insight generally is not retained {Ballard, 1997}. Even so, VH in these different conditions may have a common pathological substrate.

It is of interest that these phenomena are observed in diseases involving differing pathogenetic mechanisms. AD is believed to result from a cascade of events involving first the abnormal cortical deposition of amyloid- β protein, followed by a series of inflammatory events, and resulting in the formation of neurofibrillary tangles, which are associated with brain atrophy, cognitive impairment, and neurotransmitter derangements. The process first involves the hippocampus, and then spreads gradually to involve the frontal lobes in later stages. In PD, Lewy-type synucleinopathy (LTS), which refers to alpha-synuclein cytoplasmic inclusions, are the major correlated neuropathology. The LTS in Parkinson's disease is thought to begin in the brainstem, and to progress through the raphe nucleus and locus coeruleus to the substantia nigra, amygdala, and nucleus basalis; only in later stages is the cortex involved. In dementia with Lewy bodies, the progression of disease is from brainstem to limbic system to cortex, with the hallmark lesion being the Lewy body, but with a variable association with plaque and tangle pathology

Given the frequent occurrence of VH in DLB and PD, it is not surprising that clinicopathological studies have implicated Lewy-type alpha-synucleinopathy (LTS) as the pathological culprit, both in neocortex {Harding, 2002; Papapetropoulos, 2006; Gallagher, 2011} and limbic structures {Harding, 2002; Kalaitzakis, 2009; Gallagher, 2011}. Less well investigated has been the contribution of plaque and tangle pathology to VH in PD, DLB, or AD. In one study, tangle density in frontal cortex was found to correlate with *psychosis* in patients with AD, but that study included patients with delusions as well as hallucinations {Zubenko, 1991}. Another study found that, even in AD, VH were associated with cortical LTS, although neuropathology was evaluated only qualitatively (present or absent), and regional differences were not studied {McShane, 1995}.

Just as LTS can be present in neuropathologically-confirmed AD {Jellinger, 2003; Beach, 2009}, plaque and tangle pathology often are present in neuropathologically-confirmed PD {Braak, 1990}. The presence of LTS in AD does not necessarily warrant a concomitant diagnosis of DLB or PD; the diagnosis depends upon the amount and location of LTS {Uchikado, 2006; Frigerio, 2011}.

The question arises whether AD and LTS pathologies might both contribute to the genesis of VH, or whether in fact only LTS is implicated. To address this question, we performed a semi-quantitative neuropathological study across brainstem, limbic, and cortical structures in patients with a documented clinical history of VH and a clinicopathological diagnosis of AD, PD, or DLB. Overlapping diagnoses of AD+PD and AD+DLB also were included.

Research Materials and Methods

Subjects and Methods

The research was in full compliance with the ethical rules for human experimentation stated in the Declaration of Helsinki. All subjects were enrolled in an ongoing longitudinal clinicopathological study, the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) within the Banner Sun Health Research Institute Brain and Body Donation Program

(BBDP){Beach 2008}. All subjects or their legally authorized representatives signed an Institutional Review Board-approved informed consent form at the time of enrollment for clinical assessments as well as for brain and/or body donation after death. For this study, data from all subjects with a pathologically-confirmed clinical diagnosis of AD, PD, or DLB were identified from the AZSAND database. Subjects with potentially confounding conditions were excluded (Figure 1) to maintain homogeneity of pathology related to disease. Also excluded were subjects with unclear documentation regarding VH and those without documentation of VH who had used antipsychotic medication, in most cases for delusions. The latter were excluded because antipsychotic medication effectively treats VH, so that group assignment (VH versus no VH) for treated patients would be uncertain.

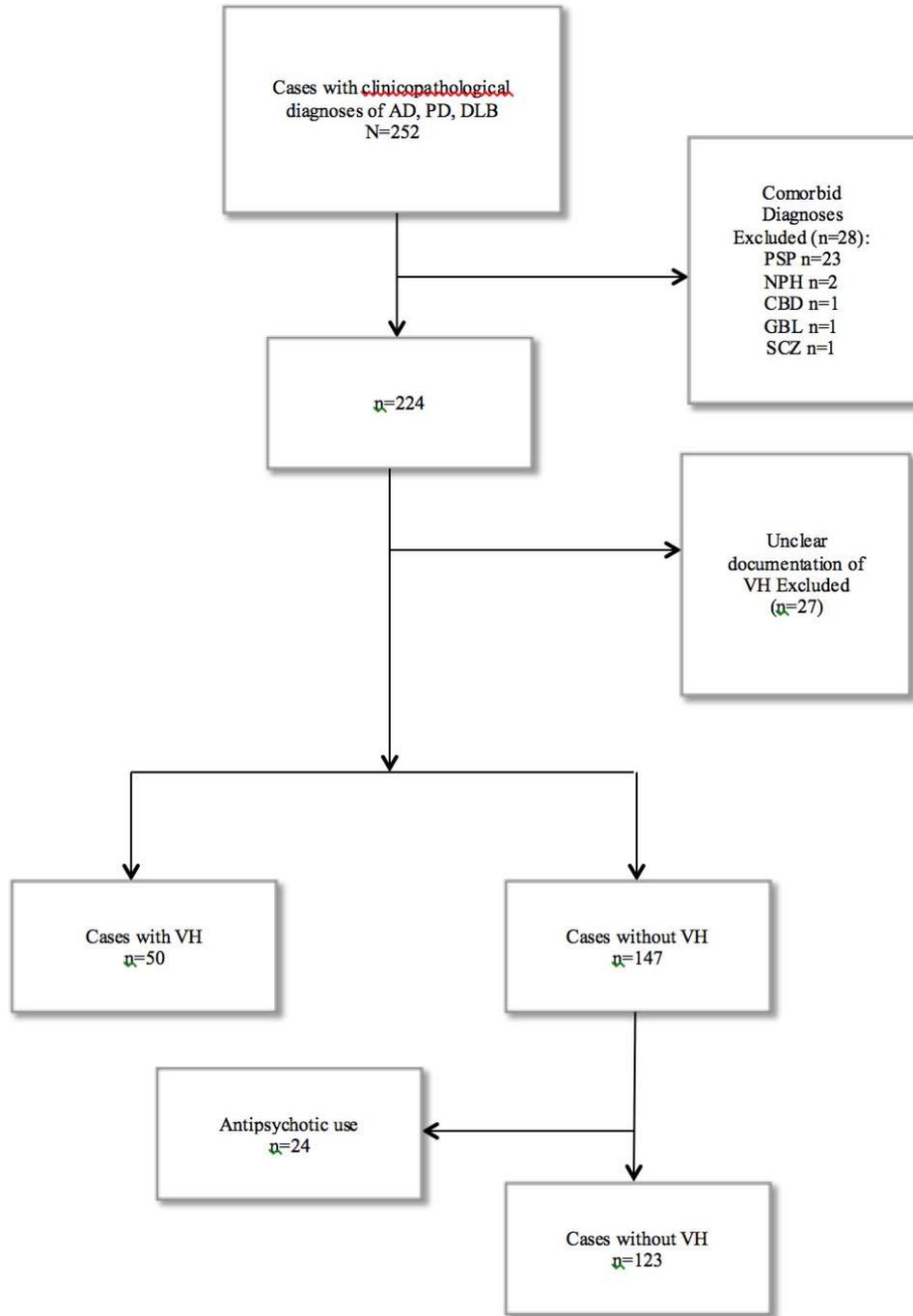


Figure 1. Flow diagram showing case exclusions. AD=Alzheimer's disease, PD=Parkinson's disease, DLB=dementia with Lewy bodies, PSP=progressive supranuclear palsy, NPH=normal pressure hydrocephalus, CBD=corticobasal degeneration, GBL=glioblastoma, SCZ=schizophrenia, VH=visual hallucinations

Clinical Evaluation.

Annually, each subject underwent a standardized physical, neurological, and movement disorder examination, as well as neuropsychological testing, performed in accordance with National Alzheimer's Coordinating Center Uniform Data Set guidelines (NACC UDS). Clinical scales completed at each visit included the Clinical Dementia Rating Scale {Morris, 1993} and the Neuropsychiatric Inventory-Q {Cummings, 1994}. Specific neuropathological diagnostic criteria were used for AD {Mira, 1991} PD {Gelb, 1999}, and DLB {McKeith, 2005}.

For the purpose of this study, visual hallucinations were defined as recognizable images –usually people, animals, or objects – reported at one or more evaluations {Fenelon, 2000}. The presence of VH was ascertained using the caregiver-based structured interview of the Neuropsychiatric Inventory (presence of hallucinations established) and the Clinician Summary Form (NACC UDS Form B9), which documents whether hallucinations were visual and formed. Clinical variables examined included the Mini-mental State Exam (MMSE) {Folstein, 1975} and Hoehn & Yahr stage {Hoehn, 1967} at the index visit, when VH were noted. Total dopaminergic medication dose at the index visit was calculated {Tomlinson, 2010}.

Neuropathological examination.

Neuropathological assessment was performed blinded to clinical categorization, and diagnosis was assigned by an experienced neuropathologist (TGB). Neuropathological variables examined for all subjects included total and regional Lewy body/neurite scores, plaque and tangle density scores, and Braak neurofibrillary stages. Tissue processing methods have been described in detail elsewhere {Beach, 2008}. In brief, the cerebrum was cut in the coronal plane at the time of brain removal into 1-cm thick slices and then divided into right and left halves. Slices from the right half were frozen between slabs of dry ice, and slices from the left half were fixed by immersion in neutral-buffered 4% formaldehyde for 48 hours at 4° C. Following cryoprotection in ethylene glycol and glycerol with 0.1 M pH 7.4 phosphate buffer, selected 3 x 4 cm blocks were sectioned at 40 or 80 µm thickness on a sliding freezing microtome. Sections were stained with Hematoxylin and Eosin, Thioflavin S,

and enhanced Silver methods. For detection of amyloid plaques and neurofibrillary tangles, Campbell-Switzer and Gallyas methods were used, respectively; these are the original methods used to develop Thal-Braak amyloid staging [25] and Braak neurofibrillary staging [26]. Thioflavin S is one of two methods recommended and validated for neuritic plaque density grading by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) {Mirra, 1991}.

To detect LTS, formalin-fixed, 5µm paraffin-embedded sections were used for immunohistochemistry with an antibody against phosphorylated α-synuclein peptide (1:10,000; rabbit polyclonal anti-human phosphoserine 129, gift of Dr. Akiyama) {Obi, 2008}. Density of LTS was graded according to the criteria of McKeith and colleagues {McKeith, 2005} on a scale of 0-4, with 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. This grading system includes intra-cytoplasmic inclusions as well as those contained in neuritic processes. LTS density scores in the middle frontal gyrus, middle temporal gyrus, inferior parietal gyrus, cingulate cortex, transentorhinal region including the hippocampus, amygdala, substantia nigra, anterior medulla including the nuclei of the IX and X cranial nerves, and the olfactory bulb and tract were determined. In addition, each case was classified according to the Unified Staging System for Lewy Body Disorders, with scores ranging from 1 (olfactory bulb only) to 4 (cortical) {Beach 2009}.

Amyloid plaque and neurofibrillary tangle (NFT) density were graded and staged using large-format, 40-80 µm-thick formaldehyde-fixed sections of the superior frontal gyrus at the level of the genu, parietal cortex at the level of the splenium, two temporal cortex sections - one at the level of the anterior amygdala including the body of the hippocampus and substantia nigra, and the other at the level of the posterior half of the amygdala including the anterior thalamus and lenticular nucleus - and occipital lobe including the line of Gennari. Neurofibrillary tangles were detected with Gallyas silver stains and Campbell-Switzer silver stains were used to detect amyloid plaques. Thioflavin-S was used as a secondary stain to detect LTS, neurofibrillary tangles and amyloid plaques. Plaque and

tangle density scores were assigned according to the published CERAD templates {Mirra, 1991} and tangle distribution also was staged according to the original Braak protocol {Braak, 1991}. Scores for plaque density were derived from a consideration of all types of plaques - cored, neuritic and diffuse - together, while cored and neuritic plaques also were estimated separately to obtain a CERAD neuritic plaque density score. Plaque and tangle density scores were obtained separately by assigning values of none, sparse, moderate, and frequent, according to the published CERAD templates {Mirra, 1991}. Conversion of the descriptive terms to numerical values resulted in scores of 0-3 (0=none, 1=sparse, 2=moderate, 3=frequent) for each area (frontal, temporal, and parietal cortex as well as entorhinal cortex and CA1 area of hippocampus), with a maximum total score of 15 for all five cortical areas combined ("total plaque score" and "total tangle score"). A neuropathological diagnosis of AD was made on the basis of the NIA-Reagan criteria indicating "intermediate" or "high" probability that the dementia was due to AD; for this determination, any combination of Braak NFT stages III-VI and moderate or frequent CERAD neuritic plaque density was used. A neuropathological diagnosis of PD was made on the basis of Lewy bodies and pigmented neuron loss in the substantia nigra {Gelb, 1999}. Subjects received a diagnosis of AD if they had a clinical history of dementia and were classified as "intermediate" or "high" probability that dementia was due to AD according to the NIA-Reagan criteria {Mirra, 1991}. DLB was diagnosed according to consensus criteria published by the Dementia with Lewy Bodies Consortium {McKeith 2005}. Cases were classified as AD/DLB or PD/AD if criteria were met for both diagnoses. The diagnoses of PD and DLB are mutually exclusive.

Data Analysis and Statistics.

For the first analysis, the sample was divided into two groups for comparison: those with VH and those without VH. For the second analysis, AD and PD groups each were divided into two sets for comparison: those with VH and those without VH. Data were analyzed using SAS software Version 9.2. Mean values were compared using the two-sample *t* test. Frequencies of dichotomous characteristics were compared using the Pearson Chi-square test. The Fisher exact

test was used instead if the minimum expected cell count was less than five. The Bonferroni correction was made to adjust for nine primary multiple comparisons (p -value of $.05/9=.006$): LTS, tangle, and plaque totals in the PD, AD, and combined groups. Regions were tested if the total score was significant.

There were 252 cases identified with a clinicopathological diagnosis of PD, AD, and/or DLB. A flow diagram of cases excluded is shown in Figure 1. Fifty cases with VH (+VH) and 147 cases without visual hallucinations (–VH) were culled. In 20 +VH cases and 24 –VH cases, subjects had used atypical antipsychotics; the 24 –VH cases were excluded, as noted above. The final study group comprised 173 cases: 50 with VH and 123 without VH. Demographic, clinical, and neuropathological data are shown in Table 1. In the sample as a whole, subjects +VH expired at a significantly younger age than subjects –VH, were more likely to have neuropathologically-confirmed PD, had a higher Hoehn & Yahr stage, and were more likely treated and at a higher mean dose of dopaminergic medication (Table 1).

Table 1 All Subjects (N=173)			
	Hallucinators (n=50)	Non-hallucinators (n=123)	<i>p</i> -value
Expired age	80.8 (5.9)	85.0 (7.3)	<.001
Sex (% male)	36/50 (72%)	65/123 (53%)	.02
Years of education	15.3 (2.3)	14.9 (2.3)	.37
Alzheimer's disease	34/50 (68%)	97/123 (79%)	.13
Parkinson's disease	38/50 (76%)	33/123 (27%)	<.001
Alzheimer's disease + Parkinson's disease	22/50 (44%)	7/123 (6%)	<.001
Dementia with Lewy bodies	6/50 (12%)	13/123 (11%)	.79
Alzheimer's disease + dementia with Lewy bodies	6/50 (12%)	13/123 (11%)	.79
Alzheimer's disease with Lewy bodies	3/50 (6%)	28/123 (23%)	.009
Dementia or mild cognitive impairment	47/50 (94%)	108/123 (88%)	.23
MMSE	18.6 (8.7)	20.0 (7.8)	.48
Hoehn & Yahr Stage	3.5 (1.2)	2.0 (1.9)	<.001

Duration of Parkinson's disease	16.4 ± 7.3	11.9 ± 6.6	.009
Levodopa equivalents	506 (486)	256 (550)	0.001
Lewy-type alpha-synucleinopathy (range 0-4): (LTS: includes Lewy bodies and Lewy neurites)			
Total (max 40)	24 (11)	9 (11)	<.001
olfactory bulb/tract	2.8 (1.4)	1.4 (1.5)	<.001
IX, X	2.8 (1.4)	1.3 (1.6)	<.001
locus coeruleus	2.7 (1.3)	1.2 (1.5)	<.001
substantia nigra	2.4 (1.3)	1.0 (1.4)	<.001
amygdala	3.3 (1.2)	1.6 (1.7)	<.001
transentorhinal cortex	2.7 (1.3)	1.2 (1.5)	<.001

cingulate cortex	2.5 (1.3)	0.9 (1.3)	<.001
temporal cortex	1.7 (1.2)	0.6 (0.99)	<.001
frontal cortex	1.4 (1.2)	0.4 (0.68)	<.001
parietal cortex	1.4 (1.1)	0.42 (0.76)	<.001
Unified Lewy Body Stage	3.2 (1.1)	1.6 (1.5)	<.001
Plaque (range 0-3)			
Total (max 15)	9.3 (5.4)	10.4 (4.8)	.19
frontal	2.1 (1.2)	2.3 (1.1)	.38
temporal	2.0 (1.2)	2.3 (0.99)	.13
parietal	2.1 (1.2)	2.3 (1.0)	.21

hippocampus	1.2 (0.96)	1.46 (1.1)	.10
transentorhinal	1.9 (1.2)	2.0 (1.0)	.33
Plaque density (neuritic)	2.0 (1.1)	2.3 (1.0)	.10
Tangles (range 0-3)			
Total (max 15)	6.8 (4.1)	8.5 (4.7)	.03
frontal	0.6 (0.97)	1.1 (1.2)	.01
temporal	1.1 (1.1)	1.6 (1.2)	.01
parietal	0.7 (1.0)	1.0 (1.2)	.08
hippocampus	1.9 (1.0)	2.3 (0.99)	.04
transentorhinal	2.5 (0.69)	2.5 (0.75)	.43

Braak Tangle Stage	3.7 (1.2)	4.1 (1.4)	.06
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Results

	AD Hallucinators (n=34)	AD Non- Hallucinators (n=97)	<i>p</i> -value	PD Hallucinators (n=38)	PD Non-Hallucinators (n=33)	<i>p</i> -value
Expired age	81.8 (5.7)	86.4 (6.7)	<.001	80.2 (6.1)	80.5 (6.6)	.82
MMSE	15.6 (8.8)	18.9 (7.5)	.11	22.0 (6.4)	26.3 (3.8)	.03
Hoehn & Yahr	3.4 (1.2)	1.7 (2.0)	<.001	3.62 (0.92)	3.03 (1.15)	.02
Levodopa equivalents	411 (376)	101 (334)	<.001	665 (468)	884 (766)	.21
Pathologically Confirmed AD*	34/34 (100%)	97/97 (100%)	>.99	22/38 (58%)	7/33 (21%)	.002

Pathologically Confirmed PD*	22/34 (65%)	7/97 (7%)	<.001	38/38 (100%)	33/33 (100%)	>.99
Pathologically Confirmed DLB	6/34 (18%)	13/97 (13%)	.58	--	--	--
Lewy-type alpha-synucleinopathy (LTS) (Lewy bodies + Lewy neurites)						
Total	25 (13)	6 (10)	<.001	26.8 (7.3)	19.9 (7.3)	.001
olfactory bulb/tract	3.1 (1.4)	1.3 (1.6)	<.001	2.9 (1.2)	2.0 (1.1)	.002
IX, X	2.7 (1.6)	0.9 (1.4)	<.001	3.22 (0.80)	2.87 (1.02)	.12
locus coeruleus	2.5 (1.5)	0.7 (1.4)	<.001	3.03 (0.83)	2.88 (0.91)	.47
substantia nigra	2.4 (1.5)	0.6 (1.2)	<.001	2.67 (0.99)	2.41 (1.13)	.31
amygdala	3.3 (1.4)	1.2 (1.7)	<.001	3.61 (0.55)	3.03 (1.12)	.007
transentorhinal cortex	2.7 (1.5)	0.9 (1.5)	<.001	3.03 (0.94)	2.34 (1.17)	.01
cingulate cortex	2.6 (1.5)	0.7 (1.2)	<.001	2.8 (1.0)	2.0 (1.1)	.002

temporal cortex	1.9 (1.4)	0.5 (1.0)	<.001	1.9 (1.1)	1.1 (1.1)	.003
frontal cortex	1.71 (1.29)	0.33 (0.68)	<.001	1.50 (1.08)	0.97 (0.64)	.02
parietal cortex	1.62 (1.26)	0.37 (0.78)	<.001	1.45 (1.03)	0.81 (0.74)	.005
Unified Lewy Body Stage	3.2 (1.3)	1.3 (1.5)	<.001	3.50 (0.56)	2.97 (0.65)	<.001
Plaque:						
Total	12.1 (2.4)	12.5 (2.5)	.44	8.0 (5.6)	4.2 (4.5)	.003
frontal	2.75 (0.44)	2.73 (0.54)	.85	1.9 (1.2)	1.0 (1.1)	.003
temporal	2.65 (0.53)	2.72 (0.45)	.48	1.8 (1.2)	1.1 (1.1)	.01
parietal	2.69 (0.51)	2.76 (0.45)	.45	1.9 (1.2)	1.0 (1.1)	.004
hippocampus	1.55 (0.84)	1.82 (0.95)	.15	0.91 (0.92)	0.29 (0.54)	.001
transentorhinal	2.46 (0.64)	2.43 (0.67)	.83	1.6 (1.2)	0.9 (1.0)	.008

Plaque density (neuritic plaque)	2.62 (0.55)	2.71 (0.46)	.33	1.8 (1.1)	1.0 (1.0)	.003
Tangles:						
Total	7.9 (4.3)	10.0 (4.1)	.01	5.3 (2.7)	3.6 (2.0)	.004
frontal	0.8 (1.1)	1.4 (1.2)	.01	0.24 (0.39)	0.06 (0.15)	.02
temporal	1.4 (1.1)	2.0 (1.1)	.01	0.68 (0.71)	0.29 (0.41)	.008
parietal	0.9 (1.1)	1.3 (1.2)	.11	0.30 (0.53)	0.03 (0.12)	.005
hippocampus	2.18 (0.98)	2.56 (0.81)	.03	1.75 (0.02)	1.41 (0.93)	.15
transentorhinal	2.57 (0.66)	2.80 (0.50)	.04	2.36 (0.68)	1.80 (0.87)	.004

*The diagnoses of AD and PD are not mutually exclusive. Patients with AD + PD would have a clinical diagnosis of AD with parkinsonism, and would meet neuropathological criteria for both conditions.

On neuropathological examination, all brain areas examined had significantly more LTS in +VH subjects compared to -VH subjects. In contrast, neither plaque nor tangle densities distinguished the groups when AD, PD, and DLB were considered as a whole (using $p < .006$ for determining significance, as noted above).

AD and PD data are shown separately in Table 2. Among subjects with AD, +VH subjects expired at a younger age and were more likely to have comorbid PD. Consistent with this comorbidity,

AD subjects +VH had a higher Hoehn & Yahr stage score, were more likely treated with dopaminergic medications, and were treated with a higher average dose of dopaminergic medications than –VH subjects. AD subjects +VH also had significantly more LTS in all brain areas examined (Table 2). Neither plaque nor tangle densities distinguished the AD subjects +VH from –VH; *values were high for both groups*.

Among subjects with PD, +VH subjects were more cognitively impaired and were more likely to have comorbid AD than –VH subjects (Table 2). Some degree of AD pathology was present in most PD subjects +VH, even those who did not meet neuropathological criteria for AD or clinical/neuropathological criteria for DLB. PD subjects +VH as a group had significantly greater total plaque density, neuritic plaque density, and plaque density in frontal, parietal, and hippocampal areas; and significantly greater total tangle density and tangle density in parietal and transentorhinal areas than PD subjects –VH. Finally, significantly more LTS was found for PD subjects +VH than PD subjects –VH in several areas, including olfactory bulb/tract and cingulate, temporal, and parietal cortex.

We examined neuropathological findings and selected clinical characteristics of 173 cases with clinicopathological diagnoses of Parkinson’s disease (PD), Alzheimer’s disease (AD), and/or dementia with Lewy bodies (DLB), and compared the findings of those with visual hallucinations (+VH) to those without VH (–VH). In accord with previously published work {Harding, 2002; Papapetropoulos, 2006; Gallagher, 2007; Kalaitzakis, 2009} significant relationship was found between the extent of Lewy-type alpha-synucleinopathy (LTS) and the presence of VH in both PD and AD. A novel finding was the relationship between plaque and neurofibrillary tangle burden and the presence of VH in patients with PD. In addition, with DLB cases excluded, comorbidity of PD and AD was significantly more prevalent among subjects with VH than subjects without VH. These findings suggest that both AD and PD neuropathology may contribute to the pathogenesis of VH.

For LTS, findings in some cases were localized to olfactory bulb and tract, while in others had spread to involve the brainstem, cingulate cortex, temporal cortex, and parietal cortex. For plaques, findings were localized to hippocampus, frontal cortex, and parietal cortex. For tangles, findings were localized to transentorhinal and parietal cortex. In previous studies of patients with PD with VH, higher Lewy body densities were found in neocortex work {Harding, 2002; Papapetropoulos, 2006; Gallagher, 2007} but also in limbic structures work {Harding, 2002; Papapetropoulos, 2006; Gallagher, 2007; Kalaitzakis, 2009}.

Discussion

This is the first study using semi-quantitative neuropathological methods to confirm the observation that LTS is implicated when VH arise in AD subjects, as suggested by McShane and colleagues {McShane, 1995}. Although it is known that limbic Lewy body pathology often is found at autopsy in patients with sporadic AD {Jellinger, 2003; Uchikado, 2006} past studies of VH generally have not included subjects with AD. This is also the first study to demonstrate that AD pathology is associated with VH in PD subjects, possibly consistent with an additive pathological effect analogous to that proposed for dementia in this population {Kempster, 2010}.

With respect to clinical findings, the presence of VH was associated with more advanced PD (as reflected by higher Hoehn & Yahr stages) and with higher levodopa equivalent medication dosages. These findings confirm those of earlier investigations Papapetropoulos, 2006 #36}. It has previously been noted that, although these factors are *associated* with VH, they are not sufficient to explain their occurrence {Holroyd, 2001}.

One clinical implication of our findings is that incident VH may be an indicator of underlying pathological milestones. For example, when a patient with AD develops VH, it may be that LTS has developed, and when a patient with PD develops VH, it may be that plaques and/or neurofibrillary tangles have developed. Thus, the occurrence of VH could be predictive of concomitant AD/PD pathology even when criteria are not met for a second diagnosis.

The findings also help to address the question of why it would be that VH become *more* prevalent as PD progresses. This observation has been difficult to reconcile with the dopamine excess hypothesis of hallucinations – if indeed it applies to hallucinations in neurodegenerative disease – because dopamine is progressively *depleted* in the course of PD. As noted above, it is now understood that increasing doses of dopaminergic medications do not fully explain this observation{Holroyd, 2001}. Supervening AD pathology could provide the explanation.

Future Directions

Strengths of this study include the large sample size, the comprehensive and standardized protocol for clinical and neuropathological evaluation, and the fact that only subjects with clearly documented visual hallucinations were included. Both delusions and other types of visual hallucinations – *presence* or *passage* hallucinations, for example – might arise from different pathological substrates. Weaknesses of the study included the small sample of subjects with DLB and of hallucinators with AD-only for adequate investigation. In addition, information was not available to examine temporal aspects of VH in the context of PD or AD, which could be an area of further research. Lastly, while our study demonstrated the correlation of increased LTS and plaque/tangle pathology being associated with VH, we did not find a relationship between VH and the spatial location of pathology in the brain. Prior studies have demonstrated a correlation between VH and increased burden of pathology in specific regions of the brain, such as the occipital lobe, and is a topic of interest for future studies.

Conclusions

In summary, our findings suggest that both LTS and AD pathology - plaques and tangles – may contribute to the pathogenesis of VH. Incident VH may be an indicator of particular neuropathological milestones: the development of LTS in the AD patient, and of plaques and/or tangles in the PD patient. With continued investigation, this may have clinical implications in directing medical therapy for patients with AD or PD and new onset visual hallucinations.

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