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Motion discrimination in dementia with Lewy bodies and Alzheimer disease

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ABSTRACT

Objective: Visual processing abilities of patients with dementia with Lewy bodies (DLB) or Alzheimer disease (AD) dementia were assessed psychophysically using a simple horizontal motion discrimination task that engages the dorsal visual processing stream.

Methods: Participants included patients with mild dementia with DLB, AD dementia or Parkinson disease (PD) with dementia (PDD), without dementia with PD, and normal controls. Participants indicated the left or right direction of coherently moving dots that were embedded within dynamic visual noise provided by randomly moving dots. The proportion of coherently moving dots was increased or decreased across trials to determine a threshold at which participants could correctly indicate their direction with greater than 80% accuracy.

Results: Motion discrimination thresholds of patients with DLB and PDD were comparable and significantly higher (i.e., worse) than those of patients with AD dementia. The thresholds of patients with AD dementia and patients with PD were normal. These results were confirmed in subgroups of patients with DLB/PDD and AD dementia with autopsy-confirmed disease. A motion discrimination threshold greater than 0.23 distinguished between DLB/PDD and AD dementia with 67% sensitivity and 85% specificity.

Conclusions: Differential deficits in detecting direction of simple horizontal motion suggest that dorsal processing stream dysfunction is greater in DLB and PDD than in AD dementia. Therefore, impaired performance on simple visual motion discrimination tasks that specifically engage occipitoparietal brain regions suggests the presence of Lewy body pathology. *Neurology*® 2015;85:1376–1382

GLOSSARY

AD = Alzheimer disease; **ADRC** = Alzheimer's Disease Research Center; **DLB** = dementia with Lewy bodies; **MMSE** = Mini-Mental State Examination; **NC** = normal control; **PD** = Parkinson disease; **PDD** = Parkinson disease dementia; $_{p}\eta^{2}$ = partial η^{2}; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Structural and functional abnormalities within occipitoparietal regions in patients with dementia with Lewy bodies (DLB) suggest that dorsal stream visual processes may be vulnerable to the disease.[1–11] Since an important function of the dorsal stream is to process motion stimuli,[12] patients with DLB should have difficulty processing motion direction or speed. Consistent with this possibility, patients with DLB demonstrated reduced fMRI activation in the dorsal processing stream during motion perception.[13] It is not known if this reduced activity was associated with a perceptual deficit since behavioral measures of motion perception were not obtained.

Because occipitoparietal dysfunction is greater in DLB than in Alzheimer disease (AD) dementia,[4,7,8,10] differences in motion feature discrimination ability might distinguish between the 2 disorders.[14,15] While simple horizontal motion discrimination is preserved in AD dementia,[16–19] discriminating simple motion in an outward or inward radial flow[13,18–23] is impaired. Simple horizontal motion discrimination has not been examined in patients with DLB. We therefore compared the ability of patients with DLB or AD dementia to identify horizontal global coherent motion direction embedded within dynamic visual noise.[17] We predicted that patients with DLB would require greater than normal coherence to identify motion direction

Supplemental data at Neurology.org

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and would be more impaired than patients with AD dementia. We also examined the performance of cognitively normal patients with Parkinson disease (PD) or with PD and dementia (PDD) to determine if motion processing is affected across the spectrum of Lewy body disorders or only in those with prominent cortical involvement due to Lewy body or combined Lewy body and AD pathology.

METHODS

Participants. A total of 108 individuals participated in the study: 21 patients with DLB, 14 patients with PDD, 19 patients with PD without dementia, 29 patients with AD dementia, and 25 cognitively normal controls (NC). The patient groups consisted of clinically diagnosed individuals and those who died subsequent to testing and received a definite diagnosis of disease at autopsy. Neuropathologic confirmation at autopsy was obtained in 5 patients with DLB, 1 with PD, 3 with PDD, and 8 with AD. The DLB, AD dementia, and NC participants were recruited from the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). The patients with PDD and PD were recruited from the ADRC, UCSD Movement Disorders Clinics, or from community neurologists. Clinical diagnoses were based on published criteria and made by board-certified neurologists with expertise in dementia and movement disorders. Neuropathologic diagnoses were made by a board-certified neuropathologist with expertise in AD, DLB, and PD. Detailed neuropathologic methods and diagnostic procedures are described in appendix e-1 on the *Neurology*® Web site at Neurology.org.

Probable DLB was diagnosed clinically using established criteria[24,25] based on the presence of dementia and at least 2 of 3 additional core features of mild parkinsonism, well-formed visual hallucinations, and fluctuations in consciousness or attention. In all cases, cognitive decline was the presenting symptom and preceded parkinsonism by more than 1 year. Idiopathic PD was clinically diagnosed by the presence of at least 2 of the cardinal motor signs of resting tremor, rigidity, and bradykinesia in accordance with established criteria.[26] Patients with atypical findings or secondary causes of PD were excluded. Patients with PD did not have sufficient cognitive or functional decline to warrant a diagnosis of dementia. In accordance with established criteria,[27] the clinical diagnosis of PDD was based on the presence of at least 2 of the cardinal motor signs of PD, as well as objective cognitive deficits on neuropsychological tests and functional decline due to cognitive problems. In all cases, motor signs preceded cognitive decline by more than 1 year. Probable AD (i.e., AD dementia) was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[28] Elderly NC participants were judged to be cognitively normal following extensive assessment through the ADRC.

Standard protocol approvals, registrations, and patient consents. The research protocol was reviewed and approved by the human participants review board at UCSD. Written informed consent to participate in the study was obtained prior to testing from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

Procedure. Participants were tested individually in a quiet, well-lit room. Motor functioning was assessed with procedures outlined in part III of the Unified Parkinson's Disease Rating Scale (UPDRS) by a board-certified neurologist. The Mini-Mental State Examination (MMSE) and the apparent motion discrimination task were administered by a trained examiner. Corrected near visual acuity was screened with a hand-held chart and patients with poor acuity (i.e., >20/100) were not recruited for the study.

Motion discrimination task. This psychophysical task was presented on a 12-inch Macintosh iBook. Detailed methods are presented in appendix e-2. Briefly, the stimulus consisted of a dynamic array of 200 dots of 0.18° diameter presented within a circular aperture of 12° diameter. The apparent motion stimulus was a percept of a subset of dots streaming across the circular aperture (at ~8.24°/s) amidst randomly moving noise dots. Each motion stimulus lasted 1.01 seconds. On any given trial, the signal and noise dots were identical in cue value (i.e., all black or all white presented on a gray background) and could be distinguished only on the basis of motion information. The luminance value of the dots was randomly assigned across trials. The participant was seated at a viewing distance of approximately 75 cm in front of the computer. The angle of the screen was adjusted to eliminate glare and otherwise provide maximal visibility of the stimuli. The task was described while the participant viewed sample displays. The participant was told that the dots would be in motion and that a portion of the dots would be moving in a consistent direction, either left or right. Their task was to identify the motion direction, guessing if necessary. When the participant indicated a direction verbally or nonverbally (by pointing), their response was recorded by the examiner. They were told that across trials the number of dots moving in a consistent direction would be adjusted according to their performance, and the participant's response accuracy (not reaction time) was then used to determine signal strength thresholds. Practice trials were administered until the participant was comfortable with the task.

Signal strength thresholds were obtained using a QUEST staircase procedure[29] in which the number of signal dots necessary to accurately discriminate direction of motion was adjusted across trials to an estimated threshold value that would yield 82% correct performance. Forty-three test trials were administered to obtain a threshold value. Signal strength remained constant in the first 3 trials (to allow participants to get into set) and then adjusted according to the staircase procedure in the remaining 40 trials. The starting value of the staircase for the first threshold determination was 0.25 signal strength (i.e., 50 signal dots, 150 noise dots). Subsequent threshold determinations started at the participant's previous threshold. Two separate runs of 43 test trials each were used to calculate 2 threshold values. If the 2 threshold values differed by more than 0.10 signal strength, another run of 43 test trials was used to calculate a third threshold value. The 2 best threshold values were averaged for the measure of motion discrimination ability.

Data analysis. Statistical analyses were completed using SPSSv20. Group differences in demographic characteristics, clinical test scores, and motion discrimination thresholds were tested using one-way analysis of variance. Partial η^2 ($_p\eta^2$) was used to measure effect sizes. Post hoc pairwise group comparisons were made with Tukey least significant difference test (α for significance set at $p < 0.05$). Correlations between MMSE scores and motion discrimination thresholds were examined with Pearson product-moment (r) tests. Comparisons of motion discrimination thresholds between groups of patients with or without visual hallucinations or fluctuations were made with Student t tests. The effectiveness of the motion discrimination threshold in differentiating between DLB and

AD dementia was examined using receiver operating characteristic analyses to determine the area under the curve (for overall effectiveness) and the sensitivity and specificity for differentiating between the 2 patient groups at an optimal cut-off threshold score.

RESULTS **Participant characteristics.** Of the 108 participants who attempted the motion discrimination task, 17 (DLB = 6, PDD = 4, PD = 3, AD dementia = 3, and NC = 1) could not attain a reliable threshold (i.e., 2 of 3 thresholds were greater than 0.40, a point above which the QUEST procedure may be unreliable with 40 trials) and were dropped from further analyses. The final sample included 24 NC participants and 15 patients with DLB, 10 with PDD, 16 with PD, and 26 with AD dementia. The final groups did not differ in age ($F_{4,86} = 1.60$; $p > 0.1$; ${}_p\eta^2 = 0.07$) or years of education ($F_{4,86} = 0.50$; $p > 0.7$; ${}_p\eta^2 = 0.02$) (table). The DLB, PDD, and PD groups, but not the AD dementia or NC groups, included a greater proportion of men than women ($\chi^2[4] = 9.64$; $p < 0.05$). As expected, groups differed in MMSE scores ($F_{4,85} = 17.24$; $p < 0.001$; ${}_p\eta^2 = 0.45$). The MMSE scores of patients with DLB, PDD, and AD dementia did not differ, but were lower than those of the PD and NC groups. The MMSE scores of the PD and NC groups did not differ. Patients with DLB, PDD, or PD scored higher than patients with AD dementia or NC participants (the latter 2 did not differ) on the UPDRS ($F_{4,89} = 34.2$; $p < 0.001$; ${}_p\eta^2 = 0.62$). Patients with PDD, DLB, and PD did not differ from each other.

Motion discrimination thresholds. The mean motion discrimination thresholds achieved by the DLB, PDD, PD, AD dementia, and NC groups are shown in figure 1. There were differences in motion discrimination thresholds among the groups ($F_{4,86} = 5.98$; $p < 0.001$; ${}_p\eta^2 = 0.22$). Post hoc pairwise comparisons showed that patients with DLB and patients with PDD had higher thresholds than patients with AD dementia, patients with PD, or NC. There was no difference in the thresholds of patients with DLB and patients with PDD. Motion discrimination thresholds of patients with AD dementia, patients with PD, and NC were not different. The same pattern of significant group differences was obtained when the analyses were repeated but limited to men to avoid sex effects ($F_{4,56} = 10.19$; $p < 0.001$; ${}_p\eta^2 = 0.42$).

Analyses of motion discrimination thresholds were repeated with only autopsy-confirmed cases. The 5 patients with autopsy-confirmed DLB and the 3 with autopsy-confirmed PDD were combined into a single group (i.e., a Lewy body dementia group) and compared to the 8 patients with autopsy-confirmed AD (figure 2). Patients with Lewy body dementia had higher motion discrimination thresholds than patients with AD ($t[14] = 2.40$; $p < 0.05$).

There were no appreciable correlations between motion discrimination thresholds and MMSE scores for a combined DLB/PDD group ($r = -0.07$; $p = 0.73$) or for the AD dementia group ($r = -0.10$; $p = 0.63$). Patients with DLB/PDD with visual hallucinations had marginally higher motion discrimination thresholds (mean = 0.30, SD = 0.08) than those without hallucinations (mean = 0.23, SD = 0.09) ($t[23] = 2.08$; $p = 0.05$); however, patients with DLB/PDD with ($t[36] = 4.97$; $p < 0.001$) or without ($t[37] = 2.12$; $p = 0.04$) visual hallucinations had higher motion discrimination thresholds than patients with AD dementia. Similarly, motion discrimination thresholds did not differ in patients with DLB/PDD with (mean = 0.25,

Table Age, education, MMSE, and UPDRS scores for the final sample of NC participants and patients with DLB, PDD, PD, or AD dementia

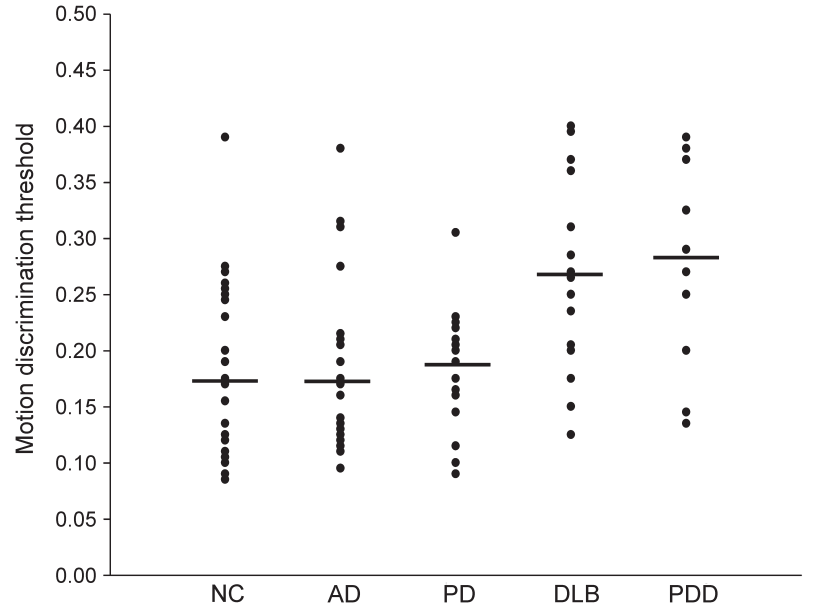
	NC, n = 24	PD, n = 16	DLB, n = 15	PDD, n = 10	AD, n = 26
Age, y	73.7 (6.8)	71.0 (8.0)	75.1 (8.2)	77.3 (8.2)	75.0 (4.3)
% Men	50	75	87	90	58
Education, y	16.2 (2.4)	16.0 (3.0)	15.93 (2.2)	15.6 (1.8)	15.2 (3.1)
MMSE	29.4 (0.9)	28.3 (1.9)[a]	24.1 (3.8)	24.4 (4.4)	23.5 (3.4)
UPDRS	1.5 (4.1)	19.5 (7.3)	21.3 (13.8)	19.0 (5.6)	2.0 (4.4)
Hallucinations, %	—	—	60	30	15
Fluctuations, %	—	—	40	10	19

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies; MMSE = Mini-Mental State Examination; NC = normal control; PD = Parkinson disease; PDD = Parkinson disease dementia; UPDRS = Unified Parkinson's Disease Rating Scale.

Values are mean (SD). The percentage of men in each group and the percentages of patients with DLB, PDD, and AD dementia with past or current visual hallucinations or fluctuations are also shown.

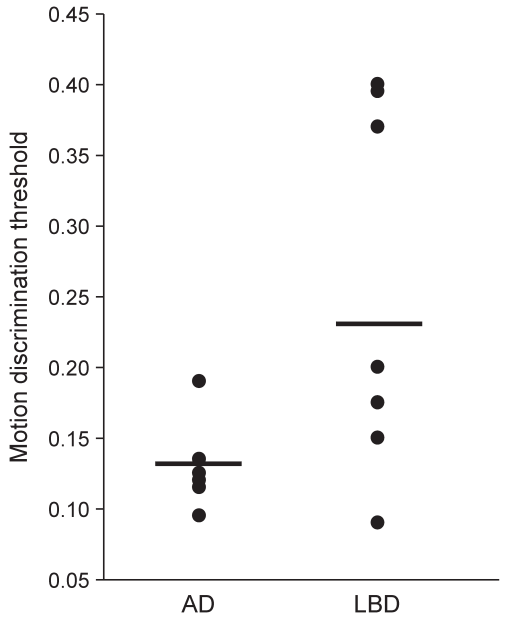
[a] Mattis Dementia Rating Scale instead of the MMSE was administered to 2 patients with PD without dementia. In both cases, the scores were within the normal range (142/144 and 143/144).

Figure 1 Motion discrimination threshold scores



The motion discrimination thresholds achieved by individual patients with dementia with Lewy bodies (DLB), Parkinson disease (PD) with dementia (PDD), Alzheimer disease (AD) dementia or PD, and normal control (NC) participants. The mean motion discrimination threshold for each group is indicated by a black bar. The DLB and PDD groups had significantly higher thresholds than other groups, but did not differ from each other. Thresholds for the AD dementia, PD, and NC groups did not significantly differ from each other.

Figure 2 Motion discrimination threshold scores for autopsy-confirmed Lewy body dementia and Alzheimer disease cases



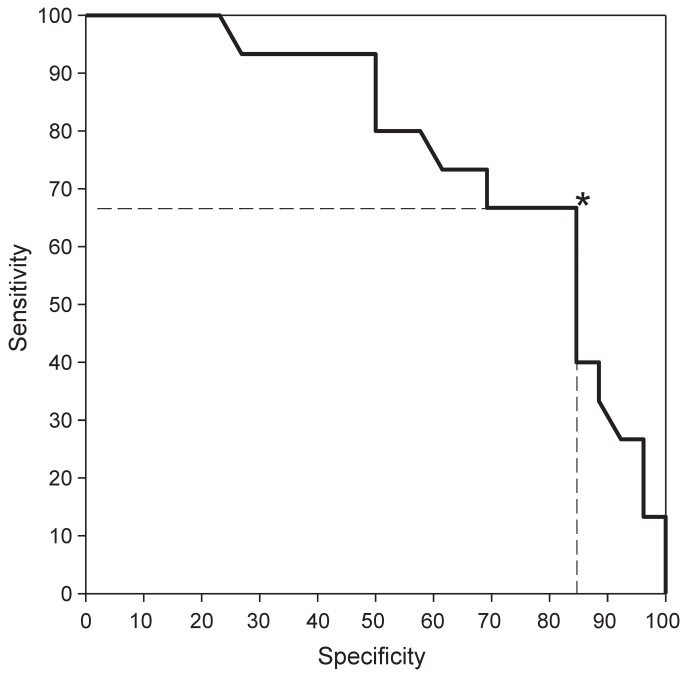
The motion discrimination thresholds achieved by individual patients with autopsy-confirmed Lewy body dementia (LBD) (i.e., dementia with Lewy bodies or Parkinson disease with dementia) or Alzheimer disease (AD). The mean motion discrimination threshold for each group is indicated by a black bar. The LBD group had a significantly higher threshold than the AD group.

SD = 0.08) or without (mean = 0.31, SD = 0.10) fluctuations, but patients with DLB/PDD with ($t[31] = 4.01$; $p < 0.001$) or without ($t[42] = 3.14$; $p = 0.003$) fluctuations had higher motion discrimination thresholds than patients with AD dementia. Analysis of covariance showed that motion discrimination thresholds of patients with DLB/PPD remained higher than those of patients with AD dementia after controlling for visual acuity ($F_{4,48} = 5.95$; $p < 0.018$; ${}_p\eta^2 = 0.16$).

A receiver operating characteristic curve was plotted to compare how effectively motion discrimination threshold differentiated patients with DLB from those with AD dementia (figure 3). The area under the curve was 0.78. An optimal cutoff threshold score (i.e., where the sum of sensitivity and specificity was maximal) of 0.23 provided 67% sensitivity for having DLB and 85% specificity for not having DLB (i.e., for having AD dementia). Values were similar when the combined DLB/PDD group was compared to AD dementia. The area under the curve was 0.79, and sensitivity was 68% and specificity 85% at an optimal cutoff threshold of 0.23. In both cases, sensitivity may be underestimated because a greater percentage of patients with DLB/PDD than patients with AD had exceptionally poor thresholds (i.e., thresholds greater than 0.40) and were not included in analyses.

DISCUSSION The major findings of this study are that patients with mild dementia with DLB or PDD were impaired in the ability to discriminate direction of simple horizontal motion, whereas patients with equal dementia with AD dementia performed at a level that was indistinguishable from normal controls. These results are consistent with those of 2 previous studies.[14,15] The first showed worse performance in patients with DLB than in those with AD dementia on a task that required determining which of 2 side-by-side displays of moving dots had faster motion.[14] It is possible, however, that the groups differed in attention processes needed to simultaneously monitor 2 displays rather than in the ability to judge speed of motion. By using a simpler paradigm, the present study was able to confirm that patients with DLB display a motion perception deficit that is not attributable to deficits in attention. The second, an fMRI study of complex biological motion processing, showed lower activation in cortical area V5 in DLB than in AD dementia, but only a trend toward slower reaction times in deciding direction of motion.[15] Difficulty in behaviorally distinguishing between DLB and AD dementia with this biological motion discrimination task may be because it engages both

Figure 3 Motion discrimination ROC curve: Dementia with Lewy bodies vs Alzheimer disease



Receiver operating characteristic (ROC) curve comparing patients with dementia with Lewy bodies and patients with Alzheimer disease dementia on the motion discrimination task. The sensitivity and specificity of the most effective cutoff threshold score (0.23*) is indicated with broken lines.

motion processing and occipitotemporal-dependent object identity processing, which can be affected in both disorders. Previous studies show that patients with AD dementia are impaired on complex motion discrimination tasks that require perceiving shapes from motion.[16,20]

The present results are also consistent with numerous studies that show that structural and metabolic abnormalities in areas of the brain related to visual processing are more pronounced in patients with DLB than in those with AD dementia. Functional neuroimaging studies using SPECT, PET, or arterial spin labeling MRI consistently show a pattern of posterior cortical hypometabolism in patients with DLB that is not apparent in patients with AD dementia.[1,3–6,8–10] A study using diffusion tensor imaging found decreased integrity of occipitoparietal white matter tracts in patients with DLB compared to more diffuse white matter damage in patients with AD dementia.[11] In addition, neuropathologic studies show that white matter spongiform change,[4] gliosis,[4] and α-synuclein immunoreactivity (but not number of Lewy bodies) in visual areas (i.e., Brodmann areas 17 and 18) are greater in DLB than in AD dementia.[7]

Patients with DLB and patients with PDD displayed comparable motion discrimination deficits. This finding is consistent with the similarity in the neuropathology of the 2 disorders. Although brainstem pathology may be more pronounced in PDD than DLB and contribute to earlier and more prominent movement disorder, both groups have extensive cortical pathology that includes Lewy bodies, Lewy neurites, and in many cases, neuritic plaques and neurofibrillary tangles of AD.[30] Aspects of this neocortical pathology extend into posterior cortical areas[4,7] and likely contribute to the motion discrimination deficits observed in the present study. The finding that basic horizontal motion discrimination was normal in patients without dementia with PD is consistent with previous results[31] and suggests that the deficit observed in DLB and PDD is not related to subcortical dysfunction common to the 3 conditions.

Replicating previous studies,[17] simple horizontal motion discrimination was normal in patients with AD dementia. This finding is consistent with the relative preservation of primary visual and occipitoparietal visual association cortices in AD.[32] Although patients with AD dementia are often impaired on tests of visuospatial or visuoperceptual ability,[33] these deficits may be largely related to dysfunction in the ventral visual processing stream and primarily affect performance on tasks that require object recognition[34] or the integration of information across visual streams.[16,17] Even when these visuospatial and visuoperceptual processing deficits are apparent, they are generally milder in patients with AD dementia than in those with DLB who are at a similar level of global cognitive impairment.[35,36]

From a clinical perspective, the motion discrimination task was moderately effective at distinguishing between patients with mild dementia with DLB or AD dementia. The most effective cutoff threshold score had 67% sensitivity and 85% specificity for differentiating patients with DLB from those with AD dementia. The high specificity and moderate sensitivity indicates that good performance on the test was more strongly associated with the absence of DLB (and the presence of AD dementia) than poor performance was associated with the presence of DLB (and the absence of AD dementia). Better ability to identify those patients with dementia who do not have DLB than those with DLB is consistent with a previous study that showed that the absence of marked visuospatial impairment early in the disease predicts the likely absence of Lewy body pathology in patients with dementia who have AD pathology at autopsy (i.e., visuospatial impairment is a negative predictor of DLB[37]). Given the relatively low sensitivity, the motion discrimination test should not be primarily viewed as a clinical means of accurately diagnosing DLB vs AD dementia, but rather more as a means to confirm the physiologic counterpart of the

neuropathologic distribution of lesions. It should be noted, however, that since 29% of the patients with DLB were already excluded from this analysis because of poor thresholds (i.e., thresholds greater than 0.40) compared to just 10% of the patients with AD dementia, the actual sensitivity of this task to identify patients with DLB on the basis of poor motion discrimination ability could be substantially higher. It should also be noted that these results apply specifically to the group of patients utilized in this study, and it remains to be determined whether similar findings would be obtained in more or less severe DLB or AD dementia.

Clinical identification of visuoperceptual deficits in patients with DLB using the simple motion discrimination task may also provide important prognostic information. Previous research shows that the early occurrence of marked visuoperceptual or visuospatial deficits in patients with DLB is predictive of a more malignant disease course[38] and correlated with a higher prevalence and incidence of visual hallucinations.[39] Visual hallucinations were associated with worse motion discrimination in the present study, but even patients with DLB without visual hallucinations had worse motion discrimination than patients with AD dementia. The relationship between these features of DLB and simple motion discrimination deficits warrants further research.

AUTHOR CONTRIBUTIONS

Kelly M. Landy: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis, study supervision, obtaining funding. David P. Salmon: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Douglas Galasko: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision, obtaining funding. J. Vincent Filoteo: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Elena K. Festa: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. William C. Heindel: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Lawrence A. Hansen: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Joanne M. Hamilton: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis, study supervision, obtaining funding.

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DISCLOSURE

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