Visuoperception test predicts pathologic diagnosis of Alzheimer disease in corticobasal syndrome

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ABSTRACT

Objective: To use the Visual Object and Space Perception Battery (VOSP) to distinguish Alzheimer disease (AD) from non-AD pathology in corticobasal syndrome (CBS).

Methods: This clinicopathologic study assessed 36 patients with CBS on the VOSP. All were autopsied. The primary dependent variable was a binary pathologic outcome: patients with CBS who had primary pathologic diagnosis of AD (CBS-AD, n = 10) vs patients with CBS without primary pathologic diagnosis of AD (CBS-nonAD, n = 26). We also determined sensitivity and specificity of individual VOSP subtests.

Results: Patients with CBS-AD had younger onset (54.5 vs 63.6 years, $p = 0.001$) and lower memory scores on the Mattis Dementia Rating Scale-2 (16 vs 22 points, $p = 0.003$). Failure on the VOSP subtests Incomplete Letters (odds ratio [OR] 11.5, $p = 0.006$), Position Discrimination (OR 10.86, $p = 0.008$), Number Location (OR 12.27, $p = 0.026$), and Cube Analysis (OR 45.71 $p = 0.0001$) had significantly greater odds of CBS-AD than CBS-nonAD. These associations remained when adjusting for total Mattis Dementia Rating score, disease laterality, education, age, and sex. Receiver operating characteristic curves demonstrated significant accuracy for Incomplete Letters and all VOSP spatial subtests, with Cube Analysis performing best (area under the curve 0.91, $p = 0.0004$).

Conclusions: In patients with CBS, failure on specific VOSP subtests is associated with greater odds of having underlying AD. There may be preferential involvement of the dorsal stream in CBS-AD.

Classification of evidence: This study provides Class II evidence that some subtests of the VOSP accurately distinguish patients with CBS-AD from those without AD pathology (e.g., Cube Analysis sensitivity 100%, specificity 77%). *Neurology*® 2014;83:510–519

GLOSSARY

AD = Alzheimer disease; **CBD** = corticobasal degeneration; **CBS** = corticobasal syndrome; **DRS-2** = Mattis Dementia Rating Scale-2; **FTLD-TDP** = frontotemporal lobar degeneration with TDP43-positive inclusions; **OR** = odds ratio; **PD** = Parkinson disease; **PSP** = progressive supranuclear palsy; **ROC** = receiver operating characteristic; **VOSP** = Visual Object and Space Perception Battery; **WMS-III** = Wechsler Memory Scale III.

The corticobasal syndrome (CBS) is characterized by significant cognitive impairment.[1–3] Corticobasal degeneration (CBD), the classic pathologic entity, is often not seen on autopsy in patients with CBS. Frequently, patients with CBS are found, postmortem, to have pathology of Alzheimer disease (CBS-AD), progressive supranuclear palsy (CBS-PSP), or other non-CBD pathologies.[3–10]

Of the various pathologic substrates of CBS, AD is common, accounting for more than 20% of cases.[3,5,9,10] Antemortem diagnosis of CBS-AD is important, because patients may benefit from cholinesterase inhibitors or future AD-targeted treatments. Furthermore, understanding atypical presentations of AD may reveal aspects of AD pathophysiology, leading to novel therapies. Research on aspects of CBS-AD has not been hypothesis-driven, but a review has identified shared CBS-AD features between studies, including visuospatial deficits.[11]

Supplemental data at Neurology.org

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Impairment of visual perception in CBS has been measured using the Visual Object and Spatial Perception Battery (VOSP), a test that is divided into object and space processing, associated with temporal "ventral" and parietal "dorsal" stream pathways, respectively. Neuroimaging research has revealed that atrophy in CBS-AD extends posteriorly, to regions in the parietotemporal lobe.[4,5,12–14] Given the preferential involvement of the parietal lobe in CBS-AD, specific impairment in dorsal stream visual perception would be expected.

We hypothesized that visual perception testing would distinguish CBS-AD from CBS patients without a primary pathologic diagnosis of AD (CBS-nonAD). Our secondary hypothesis was that failure on VOSP subtests of spatial perception would be associated with greater risk of CBS-AD when compared with CBS-nonAD.

METHODS

Subjects and clinical testing. Subjects were derived from a cohort of 98 patients with CBS who were enrolled at the National Institute of Neurological Disorders and Stroke from 2001 to 2009. Patients were recruited from across the country via advertisement. There were numerous referral centers and some patients were referred by individual neurologists. After referral, diagnosis of CBS was confirmed by a behavioral neurologist with experience in movement disorders (E.M.W.) and a neuropsychologist (J.G.) via consensus following a week's evaluation. Patient evaluations included brain imaging, genetic testing, and core clinical neuropsychological and neurologic workups. The case definition for CBS was based on published criteria[15] and consisted of progressive, predominantly lateralized ideomotor apraxia and/or non–DOPA-responsive extrapyramidal motor dysfunction (limb dystonia or rigidity) with cortical sensory loss (astereognosis, agraphesthesia), and no explanatory focal pathology on MRI (supplemental data on the *Neurology*® Web site at Neurology.org). Every patient was extensively discussed, and observations of the signs were noted over the week for their consistency and reliability. Inclusion criteria consisted of our confirmation of CBS. Patients were excluded if they lacked a participating caregiver, if they were diagnosed with another neurodegenerative condition, or if their behavior precluded neuropsychological testing. Surviving patients were not followed after 2009.

Laterality of the affected brain region was defined as contralateral to the initial motor deficit. Dementia severity was assessed using the Mattis Dementia Rating Scale–2 (DRS-2). Praxis was assessed using the composite standardized score from the Test of Oral and Limb Apraxia. Visual memory was examined using the visual memory subscales of Wechsler Memory Scale III (WMS-III). Neuropsychiatric components were quantified using the Neuropsychiatry Inventory. Category and letter fluency were also assessed.

Symptom duration was defined as the time of symptom onset (historical report) until evaluation. Disease duration was defined as time of symptom onset until death.

Visual Object and Space Perception Battery. Visual perception was the primary predictor and was evaluated using the VOSP. This test has shown construct validity in assessing ventral and dorsal streams of visual processing.[16] Subjects are first screened for requisite acuity with cards containing a degraded "X" and must indicate whether or not the X is present. See figure 1 for test description.

Standard protocol approvals, registrations, and patient consents. The patients gave assent for the study. The study and consent procedure were approved by the National Institute of Neurological Disorders and Stroke review board.

Neuropathologic diagnosis. The 39 patients who came to autopsy comprised the cohort. Primary diagnosis of AD was established using National Institute on Aging–Reagan criteria, while other diagnoses were made using published criteria.[17–21] To belong to the CBS-AD group, cases had to have a primary diagnosis of high-likelihood AD. Those subjects with alternate primary diagnoses (with or without secondary diagnoses of intermediate- or low-probability AD) were categorized as CBS-nonAD.

Genetics. Genetic testing for *APOE* was performed on a subset of subjects.

Statistical analysis. The cohort was divided into 2 subgroups for primary analysis: CBS patients with primary underlying pathologic diagnosis of AD (CBS-AD) vs CBS patients without primary underlying pathologic diagnosis of AD (CBS-nonAD). A secondary analysis was performed on 3 subgroups, consisting of CBS-AD, CBS-CBD, and CBS-other (CBS patients without a primary pathologic diagnosis of either AD or CBD). For bivariate analysis, continuous outcome variables were assessed using Kruskal-Wallis or Mann-Whitney *U* tests, and categorical outcome variables were assessed with χ^2 or Fisher exact test. Logistic regression was performed for all multivariable analyses. VOSP subtest failure was selected as a categorical binary predictor variable. Individual VOSP subtests were assessed one at a time in isolation. Each VOSP subtest was then separately combined with one covariate at a time (i.e., multivariable analysis included separate logistic regression models for each covariate of interest). Covariates were selected on the basis of biologically being potential confounders and included Mattis DRS-2 score, age at visit, sex, education, and symptom laterality.

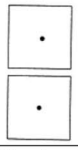
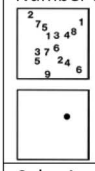
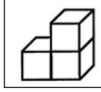
Receiver operating characteristic (ROC) curves were constructed, and their accuracy was determined. Using the VOSP as a clinical test, 2 diagnostic parameters were calculated: (1) sensitivity for test cutoff value—the percentage of pathologically confirmed CBS-AD cases that would be clinically diagnosed as having CBS-AD based on a listed VOSP subtest score; and (2) specificity for test cutoff value—the percentage of pathologically confirmed CBS-nonAD cases that would be clinically diagnosed as not having CBS-AD, based on a listed VOSP subtest score. We chose cutoff values that yielded the largest combined sensitivity and specificity. Predictive values would depend on the prevalence of CBS-AD in our CBS cohort, while sensitivity and specificity would not. Because this is a pathologic study including only those who came to death during the study period (39/98), the prevalence of various pathologies may not be representative of the population; thus, predictive values were not calculated.

Statistical analysis was performed using statistical software IBM Statistical Package for the Social Sciences (SPSS 19.0; IBM Corp., Armonk, NY). Level of statistical significance was set to $\alpha < 0.05$. Correction for multiple comparisons was not utilized, because impairment on the VOSP in general (and on spatial subtests in particular) was identified a priori as a predictor for CBS-AD.

RESULTS

Primary pathologic findings and grouping by pathology. The most frequently encountered

Figure 1 Visual Object and Space Perception Battery

Object Perception (Ventral Stream)	
Incomplete Letters 	• Screening test: subjects name individual letters (1 per card) degraded by 30% • Test items: subjects name individual letters (1 per card) degraded by 70% • Total trials: 20 • **Cut-Off Value for Failure: 16/20***
Silhouettes 	• Subjects identify 15 silhouettes of animals and 15 silhouettes of inanimate objects, presented at unusual angles • Subjects may name, gesture, mimic use, or describe the object (language is minimized) • Test is discontinued after 5 errors for animals and after 5 errors for inanimate objects • Total Trials: 30 • **Cut-Off Value for Failure: 15/30**
Object Decision 	• Subject must select a picture of a real object juxtaposed among 3 nonsense objects Subjects are not required to name the object, and need only identify which one is real • Total Trials: 20 • **Cut-Off Value for Failure: 14/20**
Progressive Silhouettes *not depicted.*	• Cards with shadows of one of two objects, presented at sequentially more recognizable viewpoints • Subjects are shown 10 cards of a gun and 10 cards of a trumpet, with the goal of identifying the object with the fewest number of presented cards • Total Trials: 20 • **Cut-Off Value for Failure: 15/20**
Space Perception (Dorsal Stream)	
Dot Counting 	• Counting random assortments of five to nine scattered dots on a card • If subjects fail the first item, they do not move on to the remainder of the test • Total Trials: 10 • **Cut-Off Value for Failure: 8/10**
Position Discrimination 	• Subjects are shown two cards, each containing a single black dot that is either exactly centered or slightly off-center; subject must specify which card contains the centered dot • Total Trials: 20 • **Cut-Off Value for Failure: 18/20**
Number Location 	• Subjects are presented with two cards, one with scattered numbers (from one to nine) and the other with a single dot, corresponding to the position of an individual number. Subjects must indicate which number corresponds to the single dot. • Total Trials: 10 • **Cut-Off Value for Failure: 7/10**
Cube Analysis 	• Subjects must count stacked blocks (including hidden ones) rendered as drawings on cards. There is one practice item. • Total Trials: 10 • **Cut-Off Value for Failure: 6/10**

Visual Object and Space Perception Battery (VOSP). Copyright © (1991) by Elizabeth K Warrington & Merle James, published by Pearson Education Ltd. Reproduced with permission. All rights reserved. *Cutoff values for failure based on the VOSP manual and established by published norms.

pathology was CBD, which was present in 15 of 39 subjects (39%). AD was the second most common pathology (12/39, 31%), followed by PSP (6/39, 15%). The remaining pathologic diagnoses consisted of frontotemporal lobar degeneration (FTLD) (3/39; all FTLD-TDP), multisystem atrophy (2/39), and Parkinson disease (PD) (1/39). The VOSP was available for 36 of 39 subjects; excluded subjects consisted of 2 subjects with CBS-AD and 1 subject with CBS-CBD.

Secondary pathologic diagnoses. Of the 12 CBS-AD cases, secondary pathologic diagnoses included cerebrovascular disease (7), neocortical Lewy body disease (3), and amygdala α-synucleinopathy (2). The remaining cases belonged to the CBS-nonAD group: of the 15 CBS-CBD cases, secondary pathologic diagnoses included cerebrovascular disease (4), low-probability AD (Braak stage II), and PD (2). Secondary pathologic diagnoses for the 12 CBS-other

Table 1 Subject demographics, clinical symptoms and signs, and genetics

	CBS-AD vs CBS-CBD vs CBS-other				CBS-AD vs CBS-nonAD		
	CBS-AD (n = 10)	CBS-CBD (n = 14)	CBS-other (n = 12)	*p* Value[a]	CBS-AD (n = 10)	CBS-nonAD (n = 26)	*p* Value[a]
Sex, %	M 50, F 50	M 57, F 43	M 50, F 50	0.916	M 50, F 50	M 54, F 46	0.564
Age at symptom onset, y	54.50 (5.86)	63.00 (5.36)	64.33 (9.63)	0.004[b,c]	54.50 (5.86)	63.62 (7.50)	0.001[b]
Ethnicity, %	100 WNH	100 WNH	100 WNH	NA	100 WNH	100 WNH	NA
Education, y	15.40 (3.06)	14.00 (2.72)	14.83 (2.29)	0.584	15.40 (3.06)	14.38 (2.52)	0.411
Handedness, %	R 100	R 93, L 7	R 92, L 8	0.507	R 100	R 92, L 8	0.516
Age at evaluation, y	58.60 (5.02)	67.93 (5.33)	68.92 (10.15)	0.002[b,d]	58.60 (5.02)	68.38 (7.77)	0.0005[b]
Symptom duration at evaluation, y	4.10 (2.07)	4.79 (1.88)	4.43 (2.50)	0.757	4.10 (2.07)	4.62 (2.15)	0.614
Time evaluation until death, y	2.69 (1.12)	2.46 (1.66)	2.30 (1.32)	0.727	2.69 (1.12)	2.39 (1.49)	0.454
Disease duration, y	6.90 (2.56)	7.29 (2.05)	6.83 (2.12)	0.982	6.90 (2.56)	7.08 (2.06)	0.988
Progression = symptom duration at evaluation/disease duration	0.58 (0.19)	0.66 (0.22)	0.62 (0.24)	0.619	0.58 (0.19)	0.64 (0.23)	0.413
Disease laterality, brain, %	L 50, R 50	L 57, R 43	L 43, R 57	0.912	L 50, R 50	L 50, R 50	0.644
Mattis DRS-2 total (SD)	98.30 (28.59)	105.50 (26.02)	123.58 (15.61)	0.074	98.30 (28.59)	113.85 (23.32)	0.109
Mattis DRS-2 Attention (SD)	28.40 (7.41)	30.29 (6.80)	34.67 (2.74)	0.030[b,e]	28.40 (7.41)	32.31 (5.68)	0.053
Mattis DRS-2 Initiation (SD)	19.50 (10.81)	20.14 (11.89)	27.50 (10.01)	0.192	19.50 (10.81)	23.54 (11.47)	0.393
Mattis DRS-2 Construction (SD)	1.40 (1.84)	1.93 (2.40)	3.08 (2.23)	0.155	1.40 (1.84)	2.46 (2.35)	0.286
Mattis DRS-2 Conceptualization (SD)	33.10 (6.51)	32.43 (5.14)	35.75 (2.53)	0.177	33.10 (6.51)	33.96 (4.40)	0.903
Mattis DRS-2 Memory (SD)	16.00 (5.48)	20.71 (4.20)	22.58 (2.43)	0.009[b,f]	16.00 (5.48)	21.58 (3.56)	0.003[b]
Neurobehavior Rating Scale (SD)	48.40 (10.53)	44.50 (10.66)	44.17 (5.98)	0.395	48.40 (10.53)	44.35 (8.65)	0.189
Praxis, TOLA composite SS (SD)	99.50 (7.18)	94.86 (13.36)	101.83 (7.00)	0.378	99.50 (7.18)	98.08 (11.27)	0.958
Letter Fluency (SD)	17.50 (7.72)	13.64 (9.83)	22.78 (8.77)	0.028[b,g]	17.50 (7.72)	17.22 (10.29)	0.773
Category Fluency (SD)	20.50 (11.55)	20.14 (11.57)	25.22 (5.67)	0.447	20.50 (11.55)	22.13 (9.86)	0.499
WMS-III Visual, VI Index (SD)	80.50 (11.98)	83.93 (9.04)	88.75 (19.26)	0.790	80.50 (11.98)	86.15 (14.55)	0.520
WMS-III Visual, VD Index (SD)	80.40 (16.12)	87.29 (12.91)	95.92 (21.38)	0.304	80.40 (16.12)	91.27 (17.52)	0.155
Frequency/no. tested for 1 *APOE* ε4 allele	4/8	5/14	1/11	0.165	4/8	6/25	0.164

Abbreviations: AD = Alzheimer disease; CBD = corticobasal degeneration; CBS = corticobasal syndrome; DRS-2 = Mattis Dementia Rating Scale–2; NA = not applicable; SS = standardized score; TOLA = Test of Oral and Limb Apraxia; VD = visual delayed; VI = visual immediate; WMS-III = Wechsler Memory Scale III; WNH = white non-Hispanic.
Age (at symptom onset, at evaluation), education, symptom duration (at evaluation, from evaluation until death), total disease duration, and progression are reported as means (SD).
[a] Kruskal-Wallis test used for continuous variables, χ^2 or Fisher exact test used for categorical variables.
[b] Significant values.
[c] Post hoc Mann-Whitney *U*: CBS-AD vs CBS-CBD $p = 0.001$; CBS-AD vs CBS-other $p = 0.012$; CBS-CBD vs CBS-other = 0.519.
[d] Post hoc Mann-Whitney *U*: CBS-AD vs CBS-CBD $p = 0.001$; CBS-AD vs CBS-other $p = 0.008$; CBS-CBD vs CBS-other $p = 0.589$.
[e] Post hoc Mann-Whitney *U*: CBS-AD vs CBS-CBD $p = 0.411$; CBS-AD vs CBS-other $p = 0.006$; CBS-CBD vs CBS-other $p = 0.100$.
[f] Post hoc Mann-Whitney *U*: CBS-AD vs CBS-CBD $p = 0.034$; CBS-AD vs CBS-other $p = 0.002$; CBS-CBD vs CBS-other $p = 0.390$.
[g] Post hoc Mann-Whitney *U*: CBS-AD vs CBS-CBD $p = 0.150$; CBS-AD vs CBS-other $p = 0.182$; CBS-CBD vs CBS-other $p = 0.012$.

Table 2 Visual perception (VOSP) vs global measure of dementia (Mattis DRS-2) as predictors of CBS-AD compared with CBS-nonAD

	Unadjusted OR (95% CI)	Unadjusted p value[a]	Adjusted OR (95% CI)	Adjusted p value[b]
VOSP subtest failure on outcome of CBS-AD, with and without adjustment for Mattis DRS-2 total score				
Failed subtest used				
Incomplete Letters	11.50 (2.01–65.91)	0.006[c]	9.61 (1.42–64.84)	0.020[c]
Silhouettes	1.24 (0.26–5.97)	0.793	0.98 (0.95–1.01)	0.976
Object Decision	1.50 (0.33–6.82)	0.600	0.91 (0.16–5.09)	0.916
Progressive Silhouettes	1.92 (0.27–13.63)	0.516	0.97 (0.10–9.30)	0.980
Dot Counting	4.41 (0.91–21.30)	0.065	3.18 (0.55–18.21)	0.195
Position Discrimination	10.86 (1.84–64.08)	0.008[c]	11.50 (1.37–96.24)	0.024[c]
Number Location	12.27 (1.35–111.61)	0.026[c]	10.85 (1.01–119.22)	0.050[c]
Cube Analysis	45.71 (2.39–874.17)[d]	0.0001[c]	—[e]	—[e]
Mattis DRS-2 (reverse-coded) mean total score and mean subtest scores on outcome of CBS-AD, with and without adjustment for VOSP				
Test mean used				
Total	1.02 (0.99–1.06)	0.111	0.96 (0.90–1.01)	0.122
Attention	1.10 (0.98–1.23)	0.114	0.74 (0.55–0.99)	0.043
Initiation	1.03 (0.97–1.10)	0.335	0.88 (0.78–1.01)	0.066
Construction	1.28 (0.87–1.87)	0.211	0.77 (0.44–1.33)	0.340
Conceptualization	1.03 (0.90–1.19)	0.640	0.85 (0.67–1.07)	0.169
Memory	1.31 (1.08–1.58)	0.007[c]	1.17 (0.92–1.47)	0.205

Abbreviations: AD = Alzheimer disease; CBS = corticobasal syndrome; CI = confidence interval; DRS-2 = Mattis Dementia Rating Scale-2; OR = odds ratio; VOSP = Visual Object and Space Perception Battery.
[a] χ^2 or Fisher exact test.
[b] Logistic regression.
[c] Significant values.
[d] One hundred percent of patients with CBS-AD failed this test, leading to an unpopulated cell. A value of 0.5 was thus added to each cell to achieve an OR.
[e] Logistic regression invalid for binary predictor because of 100% failure of patients with CBS-AD. When a continuous scale for Cube Analysis was adjusted with Mattis DRS-2 in logistic regression, the p value = 0.009.

group included low- to intermediate-probability AD (4 patients: 1 multiple system atrophy with Braak stage III AD; 1 PD with Braak III AD; and 2 PSP with Braak stage II AD) and cerebrovascular disease (2). In all groups, cerebrovascular disease primarily consisted of atherosclerosis, arteriolosclerosis, or isolated lacunar infarct.

Subject characteristics. In the primary analysis comparing CBS-AD vs CBS-nonAD, the subjects with CBS-AD were significantly younger at symptom onset and time of assessment. A secondary analysis comparing CBS-AD, CBS-CBD, and CBS-other revealed that the CBS-AD group was significantly younger than both the CBS-CBD group and the CBS-other group at symptom onset and time of assessment (table 1). Clinical features of CBS-AD vs CBS-nonAD can be found in table e-1.

Memory. The CBS-AD group showed impaired Mattis DRS-2 Memory subscale scores compared with CBS-nonAD and also compared with CBS-CBD and with CBS-other. Secondary analysis also demonstrated significantly lower Mattis DRS-2 Attention subscale scores for CBS-AD vs CBS-other (see table 1).

Visual perception test failure on outcome CBS-AD vs CBS-nonAD. The VOSP was available for only 36 of 39 patients because of incomplete records. Test failure on the VOSP was used to determine an outcome of CBS-AD (where test failure indicated a "test positive" result). In bivariate analysis, failure on VOSP subtests Incomplete Letters, Position Discrimination, Number Location, and Cube Analysis was significantly associated with greater odds of CBS-AD as compared with CBS-nonAD (table 2). These associations remained significant when the 3 patients with CBS-AD who had

Table 3 ROC curve area, cutoff values, sensitivity, and specificity of tests for CBS-AD

	Area (accuracy)	Area *p* value	Positive for AD if less than or equal to	Sensitivity, %	Specificity, %
VOSP					
Object subtests					
Incomplete Letters	0.877 (0.758–0.996)	0.001[a]	18.5	90	69
Silhouettes	0.592 (0.384–0.801)	0.397	NA	NA	NA
Object Decision	0.660 (0.459–0.860)	0.143	NA	NA	NA
Progressive Silhouettes	0.502 (0.301–0.703)	0.986	NA	NA	NA
Spatial subtests					
Dot Counting	0.794 (0.629–0.960)	0.007[a]	8.5	90	62
Position Discrimination	0.800 (0.654–0.946)	0.006[a]	17.5	80	69
Number Location	0.800 (0.655–0.945)	0.006[a]	6.00	90	58
Cube Analysis	0.913 (0.823–1.000)	0.0004[a]	4.50	100	77
Mattis DRS-2					
Attention	0.712 (0.540–0.883)	0.052	NA	NA	NA
Initiation	0.596 (0.393–0.800)	0.377	NA	NA	NA
Construction	0.619 (0.425–0.813)	0.274	NA	NA	NA
Conceptualization	0.485 (0.244–0.725)	0.888	NA	NA	NA
Memory	0.815 (0.664–0.967)	0.004[a]	19.50	70	77

Abbreviations: AD = Alzheimer disease; CBS = corticobasal syndrome; DRS-2 = Mattis Dementia Rating Scale–2; NA = not applicable (the area under the curve was not deemed to be significantly different than 50%); ROC = receiver operating characteristic; VOSP = Visual Object and Space Perception Battery.
[a] Significant values.

secondary Lewy body pathology were removed from the analysis (data not shown).

In multivariable analysis, the association between VOSP subtest failure and CBS-AD was maintained while adjusting for Mattis DRS-2 score (table 2), and after independently adjusting for education, age at visit, sex, and symptom laterality (data not shown). Similar *p* values were obtained when adjusting for the Mattis DRS-2 Attention subscale (data not shown).

Only Mattis DRS-2 Memory subscale was significantly associated with CBS-AD, but this effect was abolished when adjusting for total VOSP score. Furthermore, failure on Incomplete Letters, Position Discrimination, and Cube Analysis yielded much larger odds ratios (ORs) for CBS-AD, and these remained significant while adjusting for Mattis DRS-2 (table 2).

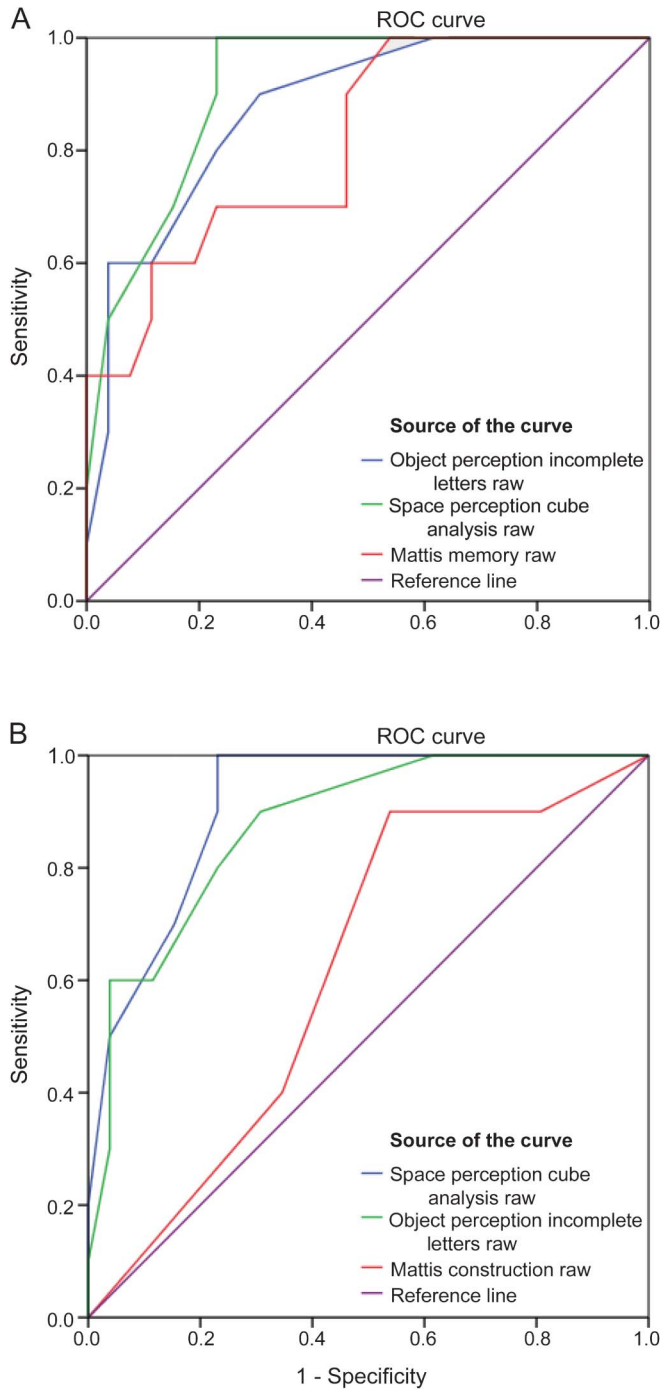
ROC curves for VOSP subtests and Mattis DRS-2 subtests. ROC curves were constructed to compare area, sensitivity, and specificity for particular cutoff values on VOSP and Mattis DRS-2 subtests. Of the VOSP subtests, area under the curve was significantly greater than 50% for Incomplete Letters and all of the dorsal stream subtests. Conversely, area under the curve for Mattis DRS-2 Memory was significantly greater than 50% while none of the other Mattis DRS-2 subtests were significantly greater than 50% (table 3). The most favorable sensitivity and specificity profiles were achieved for VOSP Incomplete Letters and Cube Analysis. A visual representation of VOSP Incomplete Letters and Cube Analysis vs Mattis DRS-2 Memory and Mattis DRS-2 Construction can be viewed in figure 2.

DISCUSSION We identified visuoperception dysfunction a priori in general as a predictor of underlying AD pathology in CBS. Our secondary hypothesis was that spatial perception in particular would be affected. The present study demonstrated an association between impaired performance on subtests of the VOSP and an outcome of CBS-AD.

Both substreams of the dorsal (spatial) pathway end in the parietal lobe. Given the preferential involvement of parietal areas in CBS-AD as reported by previous authors,[4,5,12–14] we hypothesized that impaired performance on spatial subtests would be associated with CBS-AD when compared with CBS-nonAD. Indeed, among the 4 spatial subtests, 3 were associated with greater odds of CBS-AD. The final spatial subtest, Dot Counting, had a borderline-significant association. Furthermore, ROC curves demonstrated statistical significance for all spatial subtests, including Dot Counting, and appeared to distinguish CBS-AD from CBS-nonAD.

Among all VOSP subtests, failure on Cube Analysis best distinguished CBS-AD. This test demonstrated the

Figure 2 ROC curves for subtests



Incomplete Letters and Cube Analysis as compared with Mattis Memory (A) and Mattis Construction (B). Diagonal segments are produced by ties. ROC = receiver operating characteristic.

most favorable sensitivity and specificity combination because of the 100% failure on this task among patients with CBS-AD. The Cube Analysis task is the most challenging spatial subtest, even among healthy controls.[22] This task differs from the other spatial tests because although it is rendered as a 2-dimensional drawing, it requires 3-dimensional perception. Furthermore, this subtest entails identification of hidden cubes whose presence must be inferred.

Three-dimensional perception in nonhuman primates is localized to the caudal intraparietal area,[23] and in humans, stereoscopic processing is also seen in the parietooccipital junction.[24] Impaired depth perception is also a feature of typical AD,[25,26] and has been observed early in the disease course.[27] The better discriminatory ability of the Cube Analysis test for CBS-AD may reflect particularly poor depth perception or impaired 3-dimensional perception. A recent study on logopenic progressive aphasia found that impaired performance on the Cube Analysis task was associated with reduced gray matter volume in bilateral parietal and occipital regions.[28] Further neuroimaging studies are necessary to relate performance on this test with structural and functional neuroanatomy.

Age is an important factor in tests of dorsal stream function because spatial perception diminishes with age; our data are consistent with other studies that have revealed earlier age at onset for CBS-AD compared with other pathologies.[5,11,13] The relatively young age of the patients with CBS-AD in this cohort would likely bias our result toward the null (if increasing age were causing an undetected spatial performance decline on the dorsal stream subtests). Furthermore, age-adjusted ORs were still significant for each spatial subtest.

CBS-AD is thought to represent a form of early-onset AD, but, at present, no genes have been identified[11] (in our cohort, *APOE* ε4 status did not statistically differ between groups; nonetheless, the only 2 ε4 homozygotes did belong to the CBS-AD group). Insofar as CBS-AD may represent a form of early-onset AD, it is consistent that one study found greater impairment of the dorsal stream in early-onset AD than in late-onset AD.[29]

The relatively impaired performance on the spatial subtests in CBS-AD was not likely due to worse generalized cognition, despite the trend toward worse total Mattis DRS-2 score for the CBS-AD group compared with CBS-nonAD. Dementia severity is correlated with worse performance on neuropsychological tests, and other studies have demonstrated that patients with CBS-AD may be more cognitively impaired than patients with other pathologies.[11] Thus, we adjusted for total Mattis DRS-2 score in our analyses and the ORs remained significant. Given the involvement of the right hemisphere in spatial tasks, we also assessed the effect of disease laterality on our findings, and found that hemispheric asymmetry did not alter the result. Other potential confounders, such as education and sex, were not significantly different between groups but were nonetheless individually adjusted for in multivariable analyses. Finally, secondary diffuse Lewy body pathology, which could conceivably account for visuoperceptual

dysfunction, did not appear to be driving the results in the CBS-AD group.

The strong association of poor Incomplete Letters performance with CBS-AD was unexpected, given that the task is arguably the least challenging of the subtests. This task requires identification of fragmented letters, and subjects may have had difficulty mentally filling in the missing elements. This poor perceptual closure capacity would represent a visual-form, or apperceptive, visual agnosia, a disorder that is theoretically measured by all of the object (or ventral stream) subtests. Tasks involving incomplete visual stimuli, such as Incomplete Letters, are the least sensitive to visual organization difficulty, except in relatively severe impairment.[22]

The CBS-AD group scored significantly lower on the orientation-memory subtest of the Mattis DRS-2 in primary and secondary analyses. Of note, patients with CBS-AD also perform worse on the orientation-memory subcomponent of the Addenbrooke's Cognitive Examination,[9] and a recent review of 42 CBS cases identified memory impairment as being associated with CBS-AD[11] (although the nature of this impairment was not precisely defined). It remains difficult to determine which aspect of memory may be impaired because of the inclusion of orientation in this scale. The Mattis DRS-2 Memory subcomponent also includes verbal recall, verbal forced-choice recognition memory, and visual forced-choice recognition memory. Future studies should assess specific types of memory in isolation.

Of note, the association of VOSP subtests with CBS-AD was stronger than the association of Mattis DRS-2 Memory and CBS-AD, as measured by ORs. Furthermore, while VOSP subtest associations remained significant after adjustment for Mattis DRS-2 total score, the reverse was not true (Mattis DRS-2 Memory subscale adjusted for total VOSP score was no longer significantly associated with CBS-AD).

Visual memory, assessed using the WMS-III, did not differ among groups in primary and secondary analysis. This is consistent with another CBS autopsy study, which used the WMS-III.[13] In a recent report, visual memory, assessed by visuoconstruction of the Rey Complex Figure, was impaired in CBS-AD.[5] The disparity between WMS-III and Rey Copy results may be attributable to the fact that the WMS-III relies on memory for faces, which may be localized to more extensive brain regions.[30] Despite this, we did observe a trend toward worse performance by the CBS-AD group on the WMS-III, especially on delayed visual recall.

Strengths of this study include its hypothesis-driven design and the separation of visuoperception from visuoconstruction and visual memory. Another merit is the use of a test that minimizes the importance of language and motor ability, and is therefore clinically appropriate to CBS, where these domains are impaired. One limitation is that we did not formally assess for primary ocular pathology in our subjects, particularly glaucoma, which is thought to contribute to visual impairment in classic AD.[31] However, the subjects in our CBS-AD group were relatively young, and the prevalence of glaucoma in those younger than 75 years has been estimated to be only 0.9%.[32] Furthermore, the VOSP requires subjects to pass a screening test, which establishes acuity. Another limitation is generic to autopsy studies: because our sample contains only those 39 of 98 patients who came to autopsy during the study period, the sample may be biased toward a shorter, more aggressive course, resulting in the overrepresentation of certain types of pathology. Therefore, we calculated only ORs, sensitivity, and specificity because of the possibility of this study misrepresenting population prevalence of CBS-AD. Finally, the external validity of this study may be limited, because subjects were recruited to a tertiary academic medical center.

We showed that pathologically confirmed CBS-AD compared with CBS-nonAD is associated with poor performance on the Incomplete Letters, Position Discrimination, Number Location, and Cube Analysis subtests of the VOSP. All VOSP spatial subtests and the Incomplete Letters subtest showed acceptable sensitivity for CBS-AD, and significantly elevated ORs for CBS-AD. The sensitivity, specificity, and ORs for these VOSP subtests exceeded those of other neuropsychological measures, including tests of memory.

Because of the pathologically heterogeneous nature of CBS, diagnostic tools that predict underlying pathology are required, especially as etiology-specific treatments become available. This study shows that patterns of visuoperceptual impairment in CBS may be linked to underlying AD pathology, and this may benefit more accurate diagnosis, classification, and treatment of this disease. The VOSP is an inexpensive clinical tool that is quick and easy to administer, and individual subtests can be used in isolation. Incomplete Letters and Cube Analysis may be particularly helpful in diagnosing underlying AD in patients presenting with CBS.

AUTHOR CONTRIBUTIONS

Clara D. Boyd, MD: manuscript concept and design, acquisition of data, analysis and interpretation, primary author, critical revision of the manuscript for important intellectual content. Michael Tierney, MA, Eric M. Wassermann, MD, Salvatore Spina, MD, PhD, Adrian L. Oblak, PhD, and Bernardino Ghetti, MD: acquisition of data, critical revision of the manuscript for important intellectual content. Jordan Grafman, PhD: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Edward Huey, MD:

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