Clinicopathological correlations in corticobasal degeneration

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Abstract

Objective—To characterize cognitive and behavioral features, physical findings and brain atrophy patterns in pathology-proven corticobasal degeneration (CBD) and corticobasal syndrome (CBS) with known histopathology.

Methods—We reviewed clinical and MRI data in all patients evaluated at our center with either an autopsy diagnosis of CBD (n=18) or clinical CBS at first presentation with known histopathology (n=40). Atrophy patterns were compared using voxel-based morphometry.

Results—CBD was associated with four clinical syndromes: progressive nonfluent aphasia (5), behavioral variant frontotemporal dementia (5), executive-motor (7), and posterior cortical atrophy (1). Behavioral or cognitive problems were the initial symptoms in 15/18 patients; less than half exhibited early motor findings. Compared to controls, CBD patients showed atrophy in dorsal prefrontal and peri-rolandic cortex, striatum and brainstem (p<0.001 uncorrected). The most common pathologic substrates for clinical CBS were CBD (35%), Alzheimer's disease (AD, 23%), progressive supranuclear palsy (13%), and frontotemporal lobar degeneration (FTLD) with TDP inclusions (13%). CBS was associated with perirolandic atrophy irrespective of underlying pathology. In CBS due to FTLD (tau or TDP), atrophy extended into prefrontal cortex, striatum and brainstem, while in CBS due to AD, atrophy extended into temporoparietal cortex and precuneus (p<0.001 uncorrected).

Interpretation—Frontal lobe involvement is characteristic of CBD, and in many patients frontal, not parietal or basal ganglia symptoms, dominate early-stage disease. CBS is driven by medial peri-rolandic dysfunction, but this anatomy is not specific to one single underlying histopathology. Antemortem prediction of CBD will remain challenging until clinical features of CBD are redefined, and sensitive, specific biomarkers are identified.

INTRODUCTION

Few neurodegenerative disorders have proven more clinically elusive than corticobasal degeneration (CBD). Many patients found with CBD post-mortem are never suspected of

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having the disease during life, while nearly half of those clinically diagnosed with CBD are diagnosed with alternative pathology at autopsy.[1–10] CBD was first described by Rebeiz and colleagues, who reported on three patients with a progressive disorder of movement and posture during life and swollen neurons with poorly staining inclusions at autopsy, a condition they named "corticodentatonigral degeneration with neuronal achromasia."[11] Cognitive function was reportedly spared until the end stages. While acknowledging neuropathological overlap with Pick's disease, the authors concluded that clinical features were not consistent with this condition. This article heralded an approach to CBD that focused on movement rather than cognition. CBD was defined as a syndrome of asymmetric cortical sensory loss, myoclonus, alien limb, apraxia, rigidity and akinesia, action tremor, limb dystonia, hyperreflexia and postural instability.[12, 13]

European researchers, however, categorized similar patients under Pick's disease.[14] Constantinidis and colleagues described patients with early frontal cognitive and behavioral symptoms, frequent extrapyramidal and pyramidal motor features, gross frontal atrophy and swollen neurons with non-argyrophilic inclusions, a syndrome they dubbed "Pick's disease type 2."[15] Hence, for one community CBD was a movement disorder with parietal features; for another, the same pathological entity was a Pick's disease variant with prominent frontal features, but more severe movement abnormalities than classical Pick's disease. This dichotomous perspective on CBD has persisted.

In the 1990s, the neuronal aggregates in CBD[16] were shown to consist of the microtubule associated protein tau (MAPT). Similarly, neuronal achromatic inclusions in progressive aphasia (PA)[17] and Pick's disease[18] were found to be tau-positive, underscoring the overlap with CBD. These links to tau were further strengthened by genetic studies demonstrating that MAPT mutations can present clinically as frontotemporal dementia (FTD), PA, PSP or CBD.[19, 20] Moreover, pathological studies suggested that CBD could present as a disorder of behavior, executive control or language.[2, 10] Conversely, CBD pathology was found in only ~50% of all clinically diagnosed patients,[2–4, 8] with others showing PSP, Pick's disease, frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Creutzfeldt-Jakob disease at autopsy.[1–7] Thus, Boeve introduced the term corticobasal syndrome (CBS) to distinguish the clinical syndrome from the pathologic entity, CBD.[21]

As we enter the era of protein-specific therapies for neurodegenerative diseases, clinicopathological relationships in CBD need to be re-examined. We present clinical, cognitive, genetic, and neuroimaging data of all patients seen at our behavioral neurology clinic who were either found to have CBD at autopsy, or who met clinical criteria for CBS and had neuropathological studies. Our goal was to describe the full spectrum of clinical features and neurodegenerative patterns that distinguish CBD from other entities.

METHODS

Subjects

Eighteen patients with autopsy-proven CBD[22] (CBD cohort) and 40 patients with autopsy (N=39) or brain biopsy (N=1) who met our criteria for possible or probable CBS at first visit (CBS cohort) were identified via search of the University of California San Francisco Memory and Aging Center (UCSF-MAC) database (see "UCSF-MAC Criteria for CBS" in the Supplementary Materials). Fourteen patients with CBS had underlying CBD pathology, and thus were included in both the CBD and CBS cohorts (Table 1).

Forty-four healthy subjects (NC, mean age 69.0±5 years, 50% female) were selected as imaging controls. NCs were matched to patients for age and sex; all had a normal

neurological examination, normal cognitive function confirmed by an informant, and a brain MRI free of lesions or significant white matter changes.

Abstraction of Clinical Features

Clinical evaluations took place at the UCSF-MAC between 1999 and 2008. The MAC is an academic dementia center; most referrals come from general neurologists. Patients with CBS are referred to the MAC from the UCSF movement disorders clinic, irrespective of whether they present with cognitive or motor-predominant symptoms.

The clinical evaluation included a semi-structured history and physical examination by a behavioral neurologist, a caregiver interview by a nurse, a standardized battery of cognitive tests administered by a neuropsychologist,[23] and a structural brain MRI. The neurological history included standardized questions designed to probe motor function in addition to cognitive and behavioral symptoms; a comprehensive neurological examination included tests for apraxia and a detailed examination of motor systems. First symptoms are routinely sought and documented. Functional status was measured using the Clinical Dementia Rating (CDR) scale,[24] and behavioral symptoms were measured using the Neuropsychiatric Inventory (NPI).[25] Clinical diagnosis was made by consensus at a multi-disciplinary conference blinded to imaging studies. On average, patients in this study received follow-up visits every 5 months (range 2 weeks–2.6 years) and had 5.1 follow-up visits to UCSF (range 1–15).

A senior neurologist (BLM) reviewed the clinical notes of CBD patients and designated the dominant clinical syndrome at first presentation to the UCSF-MAC, applying published criteria for behavioral variant FTD (bvFTD),[26] progressive nonfluent aphasia (PNFA)[26, 27] and posterior cortical atrophy (PCA).[28] An Executive-Motor (EM) phenotype was defined for patients with a combination of motor and dysexecutive features that overlap in part with current definitions of CBS. EM had a predominance of motor features that included axial or appendicular rigidity, dystonia, or progressive loss of limb function, and poor performance on measures of executive function on neuropsychological testing. Criteria for EM were less restrictive than CBS criteria in terms of the number of motor findings required, but more selective in that they required executive deficits. The EM syndrome is distinct from PSP in that patients do not have restricted or slowed vertical saccades or falls in the first year of symptoms. A second clinician review (SEL) found that most of these patients also met criteria for CBS (Table 1). A neurologist (SEL) blinded to pathology results reviewed clinical notes for CBS patients and documented a predetermined set of symptoms and signs at first presentation. Symptoms or signs were deemed absent if not specifically mentioned in the records. All clinical designations were made blinded to imaging results.

Genetic Methods

Genetic testing was performed on a subset of patients based on presence of a family history, availability of testing, and patient/family preferences. Genes screened included apolipoprotein ε (APOE), MAPT, the MAPT H1 haplotype, and progranulin. (See "Genetic Testing", Supplementary Materials).

Neuropathological Assessment

Consensus criteria were used for AD (NIA-Reagan)[29] and FTLD spectrum disorders including CBD (Mackenzie).[22] Autopsies were performed at UCSF (N=29), University of Pennsylvania (N=14), and Vancouver General Hospital (N=1). (See "Neuropathological Assessment" in the Supplementary Materials).

Statistical Analysis

Group comparisons in continuous data were evaluated using Kruskal-Wallis or Mann-Whitney U tests, while dichotomous variables were compared using the Chi-square test. Kaplan-Meier or Cox proportional hazards analyses were performed to compare survival across clinical presentations or causative pathologies. Analyses were implemented in the PASW 18 statistical package (18.0.0; SPSS, Chicago, IL). We did not correct statistical thresholds for multiple comparisons.

MRI Acquisition and Neuroimaging Analyses

A research quality MRI was obtained at initial presentation on a 1.5 Tesla Magnetom VISION system (Siemens, Iselin, NJ) in 28 of the 40 CBS patients, 13 of 18 CBD patients and all 44 controls.[27] Voxel-based morphometry (VBM) was performed on the earliest available MRIs (SPM5). Scans were reviewed to exclude lesions such as infarcts or significant white matter disease. Results were considered significant at p<0.001 uncorrected for multiple comparisons with a minimum cluster size of 50 voxels. In order to determine volumetric symmetry, MRI images were analyzed using Freesurfer.[30] See "Neuroimaging Analysis" in the Supplementary Materials for full details.

UCSF and University of Pennsylvania institutional review boards for human research approved the study. All participants or their surrogates consented to study protocols.

RESULTS

Subjects

Histopathology—In the CBD cohort, 16 patients had pure CBD pathology, while two had primary CBD pathology with low probability AD (NIA-Reagan, CERAD sparse, Braak 2). No patients with CBD had alpha-synuclein pathology.

Autopsy diagnoses for patients with CBS included: 9 AD, 14 CBD, 5 PSP, 5 FTLD-TDP, 5 mixed cases, one Pick's disease, and one multiple system tauopathy without argyrophilia. Mixed cases included 2 PSP, one CBD, and one FTLD-TDP, all mixed with intermediate probability AD (Supplementary Table 1).

Patient characteristics—The CBD cohort manifested four clinical syndromes: PNFA (N=5),[26] an executive-motor (EM) syndrome (N=7), bvFTD (N=5),[26] or posterior cortical atrophy (PCA, N=1).[28] There were no significant group differences in demographic features (Table 1). In the CBD cohort, 14 met CBS criteria (2 possible, 7 possible, asymmetric cortical, and 5 probable) while 4 did not meet criteria for CBS at first presentation. Thirteen of 18 CBD patients were followed longitudinally (mean 2.4 years; range 0.5 to 4.8 years). By the last visit, CBS features emerged in all patients (Supplementary Table 2).

Among patients with clinical CBS, CBS-AD patients were younger and showed higher functional impairment at first evaluation. Education, MMSE, and symptom duration were similar among all CBS groups. At first presentation, the CBS-AD group had the highest proportion of patients with "probable CBS" (78%), followed by CBS-TDP (40%), CBS-CBD (29%), and CBS-mixed (20%). No CBS-PSP case met probable CBS criteria. Twenty-eight of 40 CBS patients were followed longitudinally (mean 2.9 years; range 0.5 to 6.3 years). The likelihood of CBS in this cohort increased over time: 23/28 met probable CBS criteria at their last visit (Supplementary Table 2), compared with 14/40 with probable CBS at presentation. Interestingly, 100% of CBS-AD, CBS-TDP, and CBS-mixed met probable CBS criteria at last visit, compared to only 64% of CBS-CBD patients.

Survival—There was no difference in survival among subgroups of the CBD cohort. Kaplan-Meier analysis revealed shorter survival in CBS patients with mixed pathology (mean 5.0 years) compared to patients with CBS-AD (8.3 years and CBD-PSP (8.1 years). These differences were not significant when survival was adjusted for age at first presentation using Cox proportional hazards analysis (p=0.12).

Genetics—The APOE E4 genotype was rare in patients with CBD (1/8 patients). (Table 1). Among patients with CBS, there were no differences in APOE E4 frequency among pathological subtypes. All patients tested with CBD (N=6) and most with CBS (18/19 patients) were homozygous for the MAPT H1 haplotype. Among those screened for progranulin mutations (4 CBD, 16 CBS), one patient with mixed FTLD-TDP and AD pathology had the c.1145delC mutation[31] and the rest tested negative. All patients (8 CBD, 13 CBS) screened negative for MAPT mutations.

Clinical Symptoms and Signs

Initial symptoms for CBD-PNFA patients involved (by definition) speech or language difficulties, followed by motor symptoms 1–5 years later; behavioral symptoms were uncommon (Supplementary Table 3). EM-CBD presented with a variety of motor symptoms, although 3/7 had the coincident onset of cognitive or behavioral changes. Social withdrawal was the most common first behavioral symptom in bvFTD-CBD, and motor symptoms, usually gait changes, emerged 2–8 years after the onset of behaviors (Table 2). The one patient with PCA-CBD presented with difficulty reading, and developed trouble using the right hand two years later.

Only 5/18 patients with pathologic CBD met criteria for probable CBS at first visit (4/5 EM-CBD), and 4/18 patients (3 bvFTD-CBD) did not even meet criteria for possible CBS. At first presentation, core motor features of CBS were most prevalent in EM-CBD (Supplementary Table 3). Only motor speech deficits (most common in PNFA-CBD) and axial rigidity (only in EM-CBD) differed among groups. At last visit, all groups had higher rates of motor signs, although PNFA-CBD and bvFTD-CBD still had lower rates compared with EM-CBD (Supplementary Table 4). The patient with PCA developed motor symptoms at the last visit, including asymmetric tone and dystonia.

For CBS, there were trends for higher rates of falls in CBS-PSP (80%), and short-term memory loss (78%) and difficulty using objects (56%) in CBD-AD (Table 3). CBS-AD had more frequent visual neglect and a trend for higher rates of cortical sensory loss. Other core CBS findings occurred at similar rates. By the last evaluation, patients had global deficits regardless of underlying pathology (see Supplementary Table 5).

Neuropsychological Testing

BvFTD-CBD had lower performance on most cognitive measures, although this was only significant for delayed verbal recall and errors on the Modified Trails task (Table 4). The NPI trended highest in bvFTD-CBD and lowest in PNFA-CBD. CBS-AD patients showed worst performance on Benson figure copy and recall and calculations.

Voxel-based Morphometry

Compared to NC, all patients with pathology-confirmed CBD (grouped together) showed gray matter loss in bilateral frontal cortex including supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and pre- and postcentral gyrus, striatum, and brainstem Figure 1). In EM-CBD atrophy was found primarily in bilateral perirolandic cortex and striatum, while PNFA-CBD showed primarily left-sided atrophy of these regions. BvFTD-CBD showed the most widespread atrophy extending beyond perirolandic cortex

and striatum into orbitofrontal, dorsomedial and dorsolateral prefrontal cortex (Figure 1). Common regions of atrophy across the three main clinical syndromes included left perirolandic cortex and striatum. PCA-CBD atrophy included regions of temporal and occipital cortex, bilateral fusiform gyrus, and left hippocampus (Supplementary Figure 2).

Compared to NC, CBS-AD showed atrophy primarily in large bilateral regions of temporoparietal and medial parietal cortex and SMA, insula, and striatum (Figures 2 and 3). CBS-CBD had a frontal-striatal predominant pattern, similar to the analysis of all CBD patients. CBS-PSP showed fewer regions involved including DLPFC, SMA, insula, striatum and brainstem. CBS-TDP demonstrated atrophy in the fewest regions, including inferior frontal gyrus, and insula (Figure 2, Supplementary Figure 1). Regions of atrophy in CBS-mixed cases included DLPFC and medial frontal areas, bilateral insula, postcentral gyri, and striatum (Supplementary Figure 3).

CBS with tau pathology (CBD and PSP combined) demonstrated widespread frontal, striatal, brainstem and cerebellum atrophy compared with CBS-TDP (Supplementary Figure 1). CBS with FTLD pathology (tau or TDP) showed frontal, striatal, brainstem and cerebellum atrophy, while CBS-AD showed a more posterior atrophy pattern with overlap occurring in perirolandic regions and striatum (Figure 3). Compared to CBS-FTLD, CBS-AD showed relative atrophy in extensive bilateral temporoparietal cortex, while compared to CBS-AD, CBS-FTLD showed relative atrophy primarily in the brainstem. Peak voxels of VBM contrasts are shown in Supplementary Tables 6 and 7.

CBD cohort volumetric asymmetry analysis

We examined asymmetry in frontal and parietal cortices in their entirety, and in the superior frontal gyrus,[30] chosen because it subsumes the supplementary motor area, a region consistently affected in CBD across clinical syndromes. Average percent asymmetry and standard deviations in normal controls were calculated (as absolute values, regardless of which hemisphere was larger) for the frontal lobe (2%±2%), the parietal lobe (4%±2%), and the superior frontal gyrus (8%±4%). Two-thirds of PNFA-CBD and all bvFTD-CBD patients had pronounced frontal asymmetry (defined as greater than 2 standard deviations (sd) from mean asymmetry in healthy controls, Figure 4). Pronounced frontal asymmetry occurred in only two of five EM-CBD patients. Asymmetry was less prevalent among CBD patients in the superior frontal gyrus; two patients (with bvFTD-CBD and PNFA-CBD) showed prominent asymmetry (3.0 and 2.7 sd from controls). Parietal asymmetry was found in only one bvFTD-CBD and one EM-CBD patient (3.3 and 3.0 sd from controls).

Among all patients with CBS, 42% had pronounced frontal asymmetry, including 1/5 CBS-AD, 4/10 with CBS-CBD, 1/4 CBS-PSP, 2/2 CBS-TDP, and 2/3 with mixed pathology. Parietal asymmetry was pronounced in 33%, including 2/5 CBS-AD, 2/10 CBS-CBD, 1/4 CBS-PSP, 2/2 CBS-TDP, and 1/3 CBS-mixed. Only three patients showed pronounced asymmetry in the superior frontal gyrus, one each with CBS-AD, CBS-CBD and CBS-TDP. Thus, while pronounced asymmetry in both frontal and parietal regions was found in a subset of patients with CBS, these asymmetries occurred across pathologies. It is possible that CBS-CBD has more frequent frontal asymmetry than the other pathologies, although larger numbers are needed to confirm this.

DISCUSSION

In this study, we describe cognitive, behavioral, motor and anatomical features in a consecutive series of 44 pathologically-confirmed patients who met clinical criteria for CBS at first presentation or pathological criteria for CBD. While previous series have focused on the motor features of the disease,[1–4, 6] and others have demonstrated cognitive and

behavioral features,[32–36] our goal was to integrate detailed cognitive, behavioral and motor phenotyping with neuroimaging to identify the full spectrum of clinical and anatomical features that truly define CBD. Patients with CBD pathology presented with three main clinical syndromes: PNFA, EM, or bvFTD. Except for one patient with PCA, all manifested a frontal syndrome, and most lacked early motor symptoms. On VBM, the frontal lobes, basal ganglia and brainstem proved to be the major sites of degeneration in CBD. Only 35% of patients meeting CBS criteria at first presentation had CBD post-mortem, confirming that CBS does not reliably predict CBD.[2–4, 8] VBM demonstrated that perirolandic atrophy is common to all patients with CBS. Extension of atrophy into frontal cortex and brainstem was associated with underlying FTLD histopathology (usually FTLD-tau though not necessarily CBD), while extension into temporoparietal cortex correlated with underlying AD.

CBD is a frontally predominant disorder

Our data suggest that patients with CBD often present with a frontal-predominant behavioral or cognitive syndrome, with 10/18 patients meeting criteria for bvFTD or PNFA at first presentation. CBD can present with predominantly cognitive and behavioral syndromes and executive dysfunction,[37] with motor symptoms emerging later, [32–35] and features of bvFTD, PNFA and CBS can evolve in individual patients over time.[33,38] Our series suggests that bvFTD, PNFA, and executive dysfunction with motor deficits are primary presentations of CBD. For bvFTD-CBD, dorsal, rather than ventral frontal-insular-striatal degeneration, gave rise to prominent apathy and executive control deficits as opposed to disinhibition and overeating. PNFA-CBD presented with the classical left frontoinsular language syndrome with apraxia of speech and executive dysfunction, which only later evolved into CBS. Similarly, the cognitive and behavioral features of EM-CBD were primarily frontal. The only exception to this rule in our series was one patient with PCA-CBD, however clinicopathologic series suggest that most PCA cases have underlying AD,[39] and that CBD is a rare cause of PCA.[40]

Atrophy patterns on VBM were consistent with clinical and neuropsychological data, demonstrating that CBD is associated with frontal and striatal much greater than parietal atrophy, as reported previously.[41] Whether the predominant clinical presentation was PNFA, EM or bvFTD, all patients with CBD showed atrophy in dorsal prefrontal cortex, SMA, peri-rolandic cortex and striatum, suggesting that these are the core regions affected by CBD. In contrast to more classical bvFTD,[26] bvFTD-CBD patients had relatively greater dorsal than ventral insula involvement. Although subtle anterior parietal atrophy occurred, it was not prominent in CBD. These findings support Constantinidis's original suggestion[15] that the frontal lobes are a major site of degeneration in CBD.

CBD often presents without early motor manifestations

Abnormal movement has been emphasized consistently as a core feature of CBD.[3, 11, 13, 15] Our findings, concordant with others,[32–36] support the notion that clinicians should not assume that the absence of early motor findings excludes CBD. In our cohort, a movement disorder was present at onset in only 4/18 patients, and evolved in others many years after onset of the cognitive or behavioral symptoms. Like the vast majority of patients with neurodegenerative disorders, most (but not all) patients developed motor findings by last evaluation. Yet CBS criteria were not designed for advanced dementia, diminishing the value of motor features for detecting CBD during late stage disease.

Further, the early motor findings in our cohort were not those typically emphasized in the literature. Difficulty with gait, lower extremity control or falls was the initial motor symptom in 8/18 patients, while difficulty controlling the upper extremities, considered a

classical marker of CBD, was the presenting motor symptom in only four patients. The propensity for leg involvement and falls may be related to the prominent medial posterior frontal atrophy seen in CBD across clinical syndromes, which undermines the SMA and the medial motor strip. The prominence of falls also emphasizes the overlap between CBD and PSP.[5, 7]

Our data highlight the limitations of current CBS clinical criteria, which at first presentation were neither sensitive nor specific for CBD pathology. Only 28% of patients with CBD met probable CBS criteria at presentation (similar to previously reported sensitivities of 31%–56%),[7, 32, 35] while 22% (most with bvFTD) did not even meet criteria for possible CBS. In contrast, 78% of CBS-AD met probable CBS criteria at first evaluation. The current formulation of CBS may give too much weight to motor symptoms while underemphasizing behavioral, executive and language dysfunction that are core features of the disease and often are the presenting symptoms.

It could be argued that the small number of patients with abnormal movement at presentation and the high prevalence of frontal syndromes reflect a referral bias due to the cognitive focus of our group. Mitigating against this is the fact that patients at UCSF with CBS are referred from the Movement Disorders Clinic whether they have a cognitive-behavioral or motor predominant presentation. Moreover, our center serves as a broad referral site for northern California and we actively seek patients with focal cortical syndromes, whether anterior or posterior. We perform systematic motor evaluations on all patients, although we acknowledge that there could be potential bias because our group has a behavioral orientation. We suspect, however, that the neuropsychiatric and cognitive prodrome of CBD has been underemphasized. Interestingly, the breakdown of major pathologies in CBS in a movement disorder-focused series (CBD or PSP 53%, AD 24%, other FTLD 14%)[7] was strikingly similar to the findings in our study (CBD or PSP 48%, AD 23%, other FTLD 18%).

Asymmetric anatomy does not predict CBD pathology

While asymmetry has been stressed as a core feature of CBD, our volumetric asymmetry analysis demonstrates that many patients with CBD fall within the range of asymmetry seen in healthy controls. When present, frontal asymmetry was more common than parietal asymmetry. In CBS, asymmetric atrophy was not specific to CBD, and was found with similar frequency in patients with alternative pathologic substrates. Similar findings reported by other groups[41–43], suggest that CBD often has a clinically and anatomically symmetric presentation.

CBS redefined as perirolandic dysfunction

Regardless of underlying pathology, CBS was associated with posteromedial frontal and peri-rolandic cortex and dorsal insula atrophy, a pattern that most resembled EM-CBD and overlaps in part with the regions of common atrophy in CBD. Seeley and colleagues demonstrated that these regions show structural covariance in cognitively normal elderly and functional connectivity in young adults, suggesting that patients with CBS develop atrophy within a specific neural network.[44] Neuroimaging studies of CBS [45–47] from other groups have similarly demonstrated that atrophy in these regions correlates with the CBS phenotype. This pattern, however, is not specific for a particular pathology. Therefore, while anatomically specific, CBS criteria are not helpful in determining the underlying pathology. The high prevalence of the H1/H1 genotype in CBS brings up the possibility that this haplotype may drive pathology into the dorsal frontal and anterior parietal regions.

In CBS, frontal dysfunction indicates FTLD and parietal dysfunction indicates AD

Our data demonstrate that affected regions beyond the "core" CBS network may predict underlying pathology. Anterior extension into frontal cortex and involvement of the brainstem is suggestive of FTLD, especially FTLD-tau. When frontal atrophy predominates, CBD is the most likely cause of CBS, and when brainstem and subcortical atrophy are out of proportion to cortical volume loss, CBS-PSP is most frequent. There were too few cases of CBS-TDP in our study to derive any conclusions regarding a TDP-specific atrophy pattern.[45] In contrast, posterior extension of atrophy into precuneus and temporoparietal cortex suggests underlying AD, supporting the notion that atrophy in these regions predicts AD pathology regardless of clinical presentation.[27, 48–51] Our findings largely are congruent with the recent study by Whitwell and colleagues, particularly in the anatomic distinctions between CBS-CBD and CBS-AD.[45] While clinical and neuropsychological data did little to help predict pathology, the exception to this rule was that patients with CBS-AD showed relative impairment in visuospatial function and visual memory, referable to right parietal and medial temporal dysfunction. Thus, in a patient with CBS, frontal dysfunction implicates FTLD and tauopathy in particular; conversely when parietal dysfunction predominates, AD is the most likely histopathology.

Caveats

The cognitive and anatomical differences described in this study are based on group-level analysis, and their discriminatory power in individual cases remains to be proven. While we performed a standardized review of cognitive, behavioral and motor features, retrospective chart review has limitations, and future prospective studies are needed to confirm our findings. We found no differences in survival among CBD phenotypes or CBS pathological subtypes, however, retrospective sampling may have excluded subjects with long survival times creating bias. Analyses of clinical and neuropsychological findings grouped patients with possible and probable CBS, and it is possible that a subanalysis of each group (which were underpowered to perform) would have demonstrated further differences between pathologic subtypes. As the goal of the comparisons in this study was exploratory, we evaluated a large number of signs and symptoms in CBS and CBD and did not correct our statistical threshold for multiple comparisons. Genetic information was not available in 43% of our cohort, limiting these analyses in scope and power.

Future Directions

New research criteria for CBD are now being formulated, integrating observations from this study and other clinicopathological series (Litvan, personal communication). Collaboration between movement disorders and cognitive-behavioral specialists is critical to successfully encompass the wide spectrum of CBD. Ultimately, molecular biomarkers may be needed for pathological prediction due to the heterogeneity of CBD. With the advent of protein-specific treatments, separation of CBD from AD and non-tau forms of FTLD remains a future challenge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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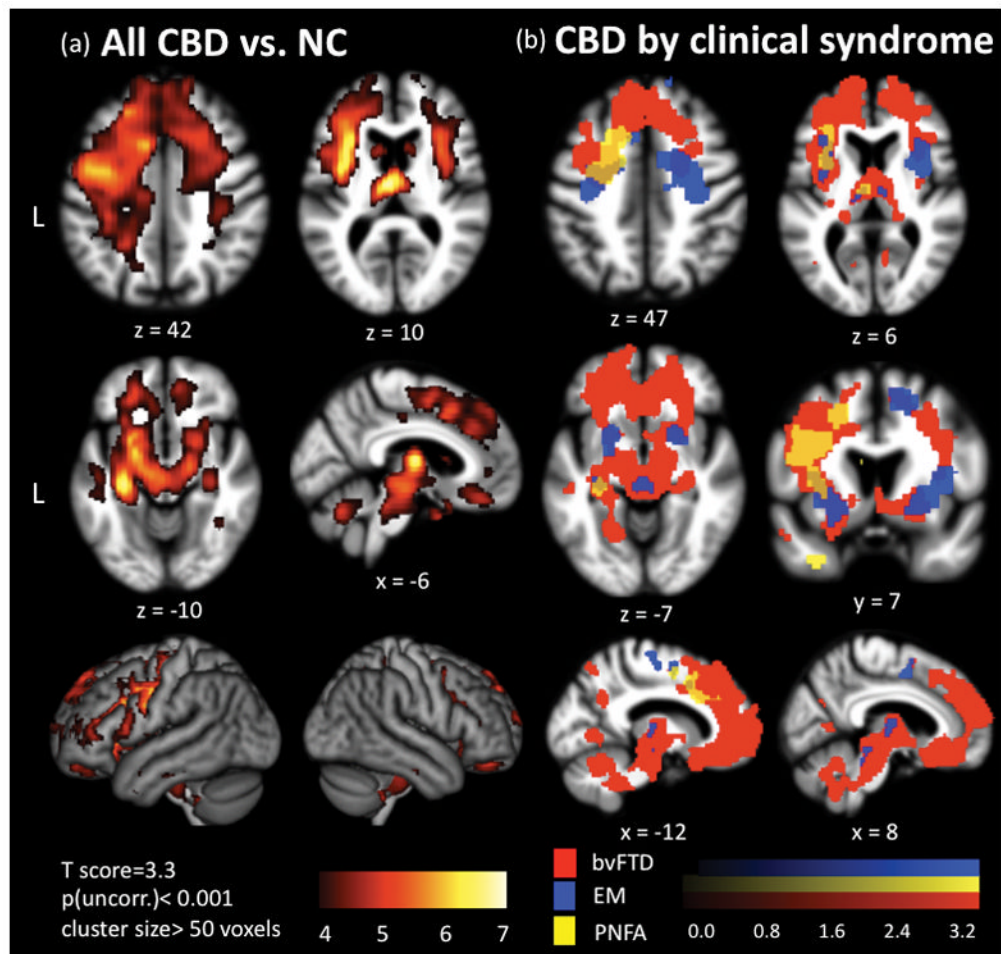
Figure 1.
SPM5 VBM analysis contrasting gray and white matter volume in (a) all patients with corticobasal degeneration (CBD) who had VBM-compatible 1.5T structural T1 scans (N=13) with healthy older controls (NC, N=44) and (b) the three main clinical syndromes seen in CBD compared to NC viewed on a DARTEL-derived template based on 48 healthy controls (voxel resolution: 1 mm). Patients with VBM-compatible scans in the three clinical syndromes included PNFA-CBD (N=4), EM-CBD (N=5), and bvFTD-CBD (N=3).
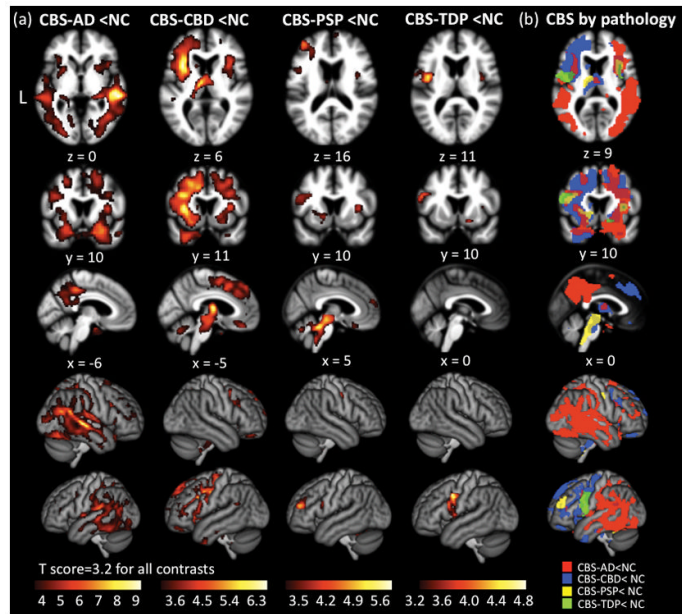
Figure 2.
SPM5 VBM analysis showing the patterns of gray and white matter volume loss in (a) left panel: each CBS subgroup (CBS-AD N=7, CBS-CBD N=11, CBS-PSP N=4, and CBS-TDP N=3) relative to healthy controls (NC, N=44) and (b) right panel: all CBS subgroups relative to NC viewed on a DARTEL-derived template based on 48 healthy controls (voxel resolution: 1 mm).

Figure 3.
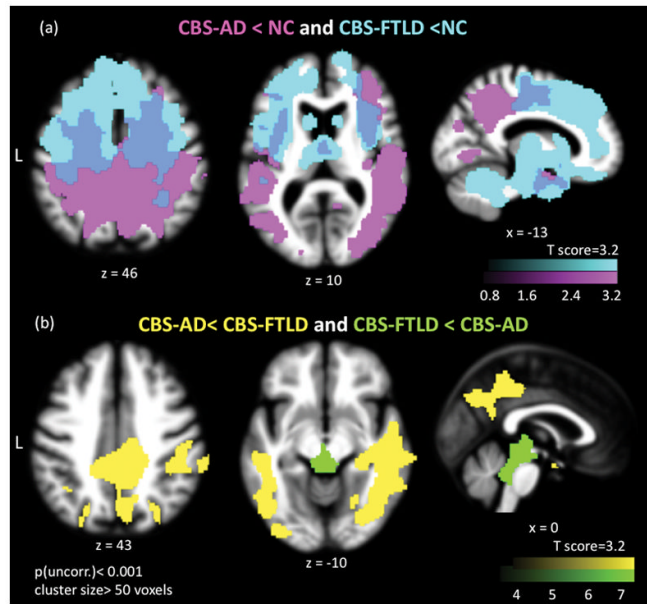SPM5 VBM analysis showing the patterns of gray and white matter volume loss in patients with (a) CBS-AD (N=7) and CBS-FTLD (N=18) relative to healthy controls (NC), and (b) CBS-AD relative to CBS-FTLD and CBS-FTLD relative to CBS-AD. All contrasts are displayed on a DARTEL-derived template based on 48 healthy controls (voxel resolution: 1 mm).
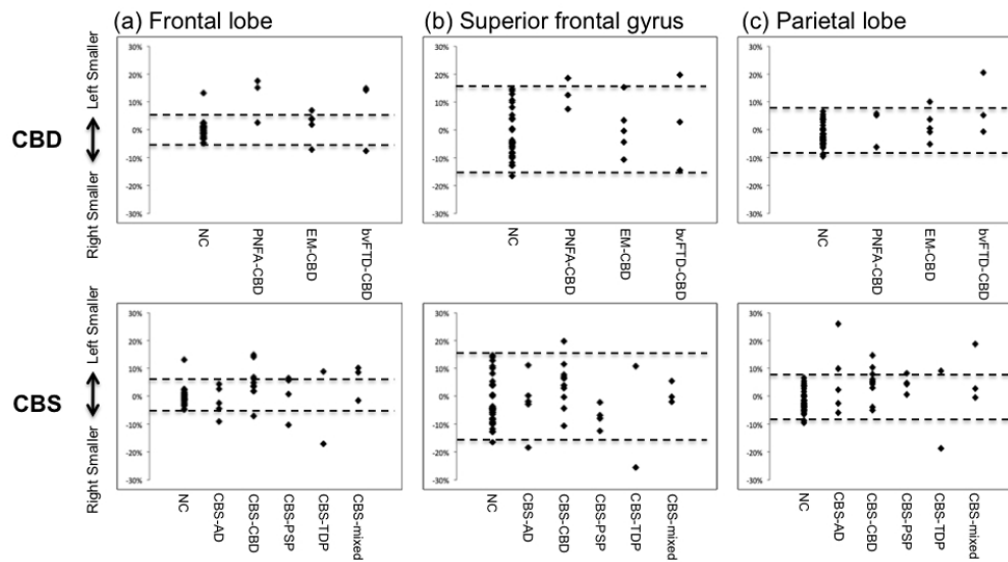
Figure 4.
Analysis of the degree of (a) frontal (b) superior frontal gyrus, and (c) parietal asymmetry in patients with CBD and CBS with 1.5T MRI scans compatible with Free-surfer-based volumetric analysis with regions of interest as defined in Desikan29. Degree of asymmetry was derived from a right-left ratio for each lobe ([R/L]-1), converted to a percentage. In the CBD analysis (top panel), subjects included healthy older controls (NC, N=34), and patients from the three main clinical syndromes seen in CBD, including PNFA-CBD (N=3), EM-CBD (N=5), and bvFTD-CBD (N=3). In the CBS analysis (bottom panel), subjects included the same healthy older controls (NC, N=34), and patients from the 5 main underlying pathologies seen in CBS, including CBS-AD (N=5), CBS-CBD (N=10), CBS-PSP (N=4), CBS-TDP (n=2), and CBS-mixed (N=3). Dashed lines indicate 2 standard deviations beyond mean asymmetry of normal controls.

Table 1

Patient Demographics: Corticobasal Degeneration and Corticobasal Syndrome Cohorts

	PNFA-CBD	EM-CBD	bvFTD-CBD	PCA-CBD	p value	CBS-AD	CBS-CBD	CBS-PSP	CBS-TDP	CBS-mixed	p value
Number of cases	5	7	5	1		9	14	5	5	5	
Gender (M:F)	1:4	2:5	3:2	0:1	0.37	5:4	4:10	3:2	2:3	4:1	0.31
Handedness (R:L)	5:0	7:0	5:0	1:0	n/a	9:0	14:0	5:0	4:1	5:0	0.15
Age at first evaluation	71.0 (52.5–81.4)	64.4 (57.5–73.2)	65.9 (61.2–78.6)	54.8	0.42	59.2 (52.2–71.5)	66.0 (52.5–81.4)	69.3 (60.0–75.9)	72.1 (63.5–80.9)	75.8 (69.9–80.8)	**0.01**[1]
Education	17.6 (12.0–20.0)	14.9 (13.0–18.0)	15.6 (12.0–19.0)	17.0	0.39	16.3 (12.0–20.0)	16.3 (12.0–20.0)	17.6 (15.0–22.0)	16.6 (12.0–20.0)	15.4 (14.0–17.0)	0.83
MMSE Total	25.0 (20.0–28.0)	25.3 (15.0–30.0)	18.5 (9.0–26.0)	27	0.29	18.0 (5.0–29.0)	23.9 (9.0–30.0)	21.8 (1.0–29.0)	26.2 (19.0–30.0)	25.0 (23.0–28.0)	0.24
CDR Box score	2.3 (2.0–3.0)	3.6 (0.0–6.0)	6.3 (3.0–12.0)	6	0.11	6.7 (5.0–11.0)	3.6 (0.0–7.0)	3.2 (1.0–10.0)	0.8 (0.0–2.0)	3.2 (3.0–5.0)	**0.01**[2]
Symptom duration at first CSF visit (years)	2.1 (1.1–3.8)	2.8 (1.9–4.0)	5.0 (2.9–8.9)	2.2	0.06	3.5 (0.8–5.0)	3.1 (1.1–8.9)	4.8 (1.2–9.3)	3.5 (1.2–6.1)	3.0 (2.3–3.4)	0.54
Disease duration or survival (years)	5.6 (4.5–6.5)	5.6 (3.6–7.8)	7.9 (5.3–12.1)	8.6	0.08	8.3 (5.7–11.2)	6.7 (3.6–12.1)	8.1 (4.8–9.6)	7.9 (5.8–9.8)	5.0 (3.2–6.8)	**0.12**[3]
Frequency/number tested for one APOE E4 allele[4]	0/3	0/2	1/3	n/a	0.42	2/7	0/7	0/4	1/2	1/2	0.32
Frequency/number tested for MAPT H1/H1 haplotype[5]	3/3	2/2	1/1	n/a	n/a	4/5	6/6	4/4	2/2	1/1	0.31
1.5T MRI brain performed	4	5	3	1		7	11	4	3	3	
CBS criteria: Possible	0	1	1	0		0	3	4	1	4	
CBS criteria: Possible, Asymmetric cortical	4	1	1	1		2	7	1	2	0	
CBS criteria: Probable	1	4	0	0		7	4	0	2	1	
No CBS criteria met	0	1	3	0		0	0	0	0	0	

Abbreviations: MMSE= Mini Mental Status Examination; CDR= Clinical Dementia Rating Scale

Age, education, MMSE, CDR, symptom duration and disease duration are reported as mean (range); for the CBD cohort, comparisons were made between PNFA-CBD, EM-CBD, and bvFTD.

[1] Post-hoc comparisons with significant differences included: CBS-AD v. CBS-PSP, CBS-AD v. CBS-TDP, CBS-AD v. CBS-mixed, CBS-CBD v. CBS-mixed.

[2] Post-hoc comparisons with significant differences included: CBS-AD v. CBS-CBD, CBS-AD v. CBS-TDP, CBS-AD v. CBS-mixed, CBS-CBD v. CBS-TDP.

[3] Cox regression analysis covarying age at first evaluation.

[4] APOE genotype was available for 8 CBD (3 PNFA-CBD, 2 EM-CBD, 3 bvFTD-CBD) and 24 CBS (7 CBS-AD, 7 CBS-CBD, 4 CBS-PSP, 2 CBS-TDP, 2 CBS-mixed, 1 CBS-Pick's, 1 CBS-tau.) The CBS-Pick's and CBS-tau patients had no APOE E4 allele. None were homozygous for APOE E4.

[5] MAPT H1 haplotype was available for 6 CBD (3 PNFA-CBD, 2 EM-CBD, 1 bvFTD-CBD) and 19 CBS (5 CBS-AD, 6 CBS-CBD, 4 CBS-PSP, 2 CBS-TDP, 1 CBS-mixed, 1 CBS-tau). The CBS-tau patient was homozygous for MAPT H1 haplotype.

Table 2

CBD Patient Cohort Signs at First Evaluation

	PNFA-CBD	EM-CBD	bvFTD-CBD	PCA-CBD	p value[1]
Language-Motor/Fluency	80%	14%	20%	100%	**0.04**[2]
Language-Naming	20%	14%	40%	0%	0.57
Language-Other	60%	29%	60%	100%	0.44
Asymmetric Apraxia	20%	57%	20%	0%	0.29
Visual Neglect	0%	14%	0%	0%	0.47
Square wave jerks	0%	14%	0%	0%	0.47
Increased saccade latency	20%	14%	20%	0%	0.96
Slow saccade velocity	0%	14%	0%	0%	0.47
Asymmetric tone	20%	86%	40%	0%	0.60
Cogwheeling	0%	29%	20%	0%	0.44
Dystonic posture	20%	43%	0%	0%	0.22
Axial rigidity	0%	57%	0%	0%	**0.02**[3]
Myoclonus	0%	0%	0%	0%	n/a
Asymmetric cortical sensory	0%	29%	0%	0%	0.20

[1] Comparisons made between PNFA-CBD, EM-CBD, and bvFTD-CBD

[2] Post-hoc comparisons with significant differences included: PNFA-CBD v. EM-CBD

[3] Post-hoc comparisons with significant differences included: EM-CBD v. PNFA-CBD, EM-CBD v. bvFTD-CBD

Table 3

CBS Patient Cohort Symptoms and Signs at First Evaluation

Frequency of symptoms and physical exam findings in patients with CBS-AD, CBS-CBD, CBS-PSP, CBS-TDP, and CBS-mixed.

Symptoms	CBS-AD	CBS-CBD	CBS-PSP	CBS-TDP	CBS-mixed	p value
Falls	22%	29%	80%	20%	60%	0.14
Gait changes	44%	36%	20%	20%	40%	0.84
Fine motor	67%	43%	40%	40%	80%	0.50
Involuntary movement (alien limb)	44%	29%	20%	40%	0%	0.47
Misusing objects	56%	29%	0%	0%	20%	0.10
Short-term memory loss	78%	36%	20%	40%	40%	0.22
Word finding difficulties	44%	57%	60%	40%	40%	0.91
Spatial disorientation	22%	0%	0%	40%	0%	0.07
Visual hallucinations	22%	7%	20%	0%	0%	0.54
Personality change	22%	57%	60%	20%	80%	0.15
Signs						
Language-Motor/Fluency	33%	50%	20%	0%	20%	0.27
Language-Naming	11%	29%	0%	40%	0%	0.28
Language-Other	33%	57%	40%	20%	20%	0.47
Asymmetric Apraxia	33%	36%	40%	0%	40%	0.60
Visual Neglect	44%	7%	0%	0%	0%	0.03 [*]
Square wave jerks	0%	7%	20%	20%	0%	0.52
Increased saccade latency	33%	14%	60%	0%	20%	0.17
Slow saccade velocity	11%	7%	20%	20%	0%	0.79
Asymmetric tone	33%	36%	60%	60%	40%	0.77
Cogwheeling	56%	14%	40%	20%	60%	0.18
Dystonic posture	33%	21%	0%	20%	0%	0.45
Axial rigidity	22%	21%	40%	20%	40%	0.86
Myoclonus	22%	0%	0%	40%	20%	0.14
Asymmetric cortical sensory	56%	14%	0%	20%	20%	0.12

[*] Post-hoc comparisons with significant differences included: CBS-AD v. all other groups

Table 4

CBD and CBS Patient Cohort Neuropsychological Testing at First Evaluation

| | Corticobasal Degeneration | | | | Corticobasal Syndrome | | | | | |
	PNFA-CBD	EM-CBD	bvFTD-CBD	p value	CBS-AD	CBS-CBD	CBS-PSP	CBS-TDP	CBS-mixed	p value
MMSE total	25.0 (20.0–28.0)	25.3 (15.0–30.0)	18.5 (9.0–26.0)	0.19	18.0 (5.0–29.0)	23.9 (9.0–30.0)	21.8 (1.0–29.0)	26.2 (19.0–30.0)	25.0 (23.0–28.0)	0.24
CVLT total	22.5 (17.0–31.0)	22.4 (12.0–33.0)	14.3 (5.0–22.0)	0.32	14.9 (7.0–25.0)	21.1 (5.0–33.0)	18.8 (0.0–30.0)	21.5 (12.0–32.0)	17.0 (17.0–17.0)	0.53
CVLT: 10 minute delay	6.3 (5.0–9.0)	5.3 (2.0–8.0)	2.0 (0.0–4.0)	0.05	3.0 (0.0–8.0)	4.8 (0.0–9.0)	4.8 (0.0–7.0)	4.0 (0.0–9.0)	4.0 (3.0–5.0)	0.76
CVLT: recognition	8.7 (8.0–9.0)	7.4 (5.0–9.0)	6.3 (1.0–9.0)	0.41	8.1 (6.0–9.0)	7.9 (5.0–9.0)	6.4 (0.0–9.0)	6.0 (3.0–9.0)	7.3 (6.0–8.0)	0.53
Modified Trails lines/min	11.3 (4.5–21.5)	8.6 (0.5–24.0)	3.2 (0.5–7.1)	0.26	3.3 (0.5–12.0)	8.1 (0.5–24.0)	10.0 (0.0–25.5)	13.6 (5.0–25.5)	2.2 (0.5–5.0)	0.19
Modified Trails errors	1.8 (1.0–2.0)	1.0 (0.0–3.0)	3.5 (2.0–6.0)	**0.04**[1]	1.0 (0.0–2.0)	1.9 (0.0–6.0)	1.8 (0.0–6.0)	1.2 (0.0–3.0)	2.0 (1.0–4.0)	0.81
Benson Figure Copy	15.0 (14.0–16.0)	11.5 (8.0–16.0)	13.5 (12.0–15.0)	0.21	4.7 (0.0–12.0)	12.8 (8.0–16.0)	12.5 (7.0–16.0)	14.4 (10.0–17.0)	11.0 (9.0–13.0)	**0.01**[2]
Calculations	4.5 (3–5)	3.4 (0–5)	2.2 (0–4)	0.19	2.6 (1–5)	3.3 (0–5)	4.5 (4–5)	5.0 (all 5)	3.3 (2–4)	**0.03**[3]
Digits Backward	3.3 (2.0–5.0)	3.6 (2.0–6.0)	2.0 (0.0–4.0)	0.25	3.3 (2.0–5.0)	3.0 (0.0–5.0)	3.5 (3.0–7.0)	4.3 (2.0–6.0)	2.7 (2.0–3.0)	0.58
Phonemic Fluency	5.0 (0.0–10.0)	4.9 (1.0–13.0)	2.3 (0.0–4.0)	0.38	8.0 (1.0–20.0)	4.5 (0.0–13.0)	5.0 (2.0–8.0)	7.6 (3.0–11.0)	3.0 (2.0–4.0)	0.23
Category Fluency	9.5 (4.0–14.4)	8.1 (0.0–18.0)	4.0 (0.0–0.7)	0.27	10.5 (5.0–18.0)	7.5 (0.0–18.0)	6.2 (0.0–10.0)	12.6 (6.0–18.0)	10.3 (7.0–13.0)	0.25
Benson Figure Delayed Recall	12.0 (9.0–17.0)	8.8 (0.0–14.0)	7.3 (2.0–11.0)	0.41	0.9 (0.0–3.0)	9.1 (0.0–17.0)	10.0 (6.0–12.0)	6.0 (0.0–10.0)	5.7 (3.0–10.0)	**0.01**[4]
Boston Naming test	12.5 (11.0–14.0)	12.3 (9.0–15.0)	12.7 (9.0–15.0)	0.86	11.7 (1.0–15.0)	11.5 (2.0–15.0)	9.8 (0.0–15.0)	14.3 (13.0–15.0)	13.3 (13.0–14.0)	0.37
Stroop interference	12.0 (12.0–12.0)	18.2 (0.0–40.0)	7.7 (0.0–15.0)	0.85	13.5 (0.0–34.0)	16.0 (0.0–40.0)	22.5 (13.0–39.0)	30.5 (26.0–35.0)	16.3 (14.0–20.0)	0.44
Stroop interference errors	0.0 (0.0–0.0)	5.3 (0.0–16.0)	9.0 (1.0–18.0)	0.31	2.8 (0.0–8.0)	4.4 (0.0–16.0)	1.3 (0.0–4.0)	0.0 (0.0–0.0)	2.0 (1.0–3.0)	0.47
GDS total	8.0 (8.0–8.0)	8.3 (0.0–24.0)	9.3 (2.0–19.0)	0.79	9.0 (6.0–18.0)	9.0 (0.0–24.0)	18.3 (11.0–26.0)	5.3 (1.0–12.0)	14.7 (11.0–19.0)	0.07
NPI total	7.3 (1.0–12.0)	16.8 (10.0–25.0)	29.4 (9.0–80.0)	0.15	10.3 (1.0–23.0)	12.7 (1.0–25.0)	15.6 (0.0–35.0)	6.3 (0.0–10.0)	12.7 (9.0–15.0)	0.43

Means reported with range in parentheses.

Abbreviations: MMSE= Mini-Mental Status Exam; CVLT= California Verbal Learning Test; GDS=Geriatric Depression Scale; NPI=Neuropsychiatric Inventory

[1] Post-hoc comparisons with significant differences included: EM-CBD v. bvFTD-CBD.

[2] Post-hoc comparisons with significant differences included: CBS-AD v. CBS-CBD, CBS-AD v. CBS-PSP, CBS-AD v. CBS-TDP.

[3] Post-hoc comparisons with significant differences included: CBS-AD v. CBS-PSP, CBS-AD v. CBS-TDP, CBS-CBD v. CBS-TDP.

[4] Post-hoc comparisons with significant differences included: CBS-AD v. CBS-CBD, CBS-AD v. CBS-PSP, CBS-AD v. CBS-TDP, CBS-AD v. CBS-mixed.