Executive dysfunction in frontotemporal dementia and corticobasal syndrome

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ABSTRACT

Objective: To determine the pattern of executive dysfunction in frontotemporal dementia (FTD) and corticobasal syndrome (CBS) and to determine the brain areas associated with executive dysfunction in these illnesses.

Method: We administered the Delis-Kaplan Executive Function System (D-KEFS), a collection of standardized executive function tests, to 51 patients with behavioral-variant FTD and 50 patients with CBS. We also performed a discriminant analysis on the D-KEFS to determine which executive function tests best distinguished the clinical diagnoses of FTD and CBS. Finally, we used voxel-based morphometry (VBM) to determine regional gray matter volume loss associated with executive dysfunction.

Results: Patients with FTD and patients with CBS showed executive dysfunction greater than memory dysfunction. Executive function was better preserved in the patients with CBS than the patients with FTD with the exception of tests that required motor, visuospatial ability, or both. In patients with CBS, dorsal frontal and parietal and temporal-parietal cortex was associated with executive function. In FTD, tests with a language component (Verbal Fluency) were associated with left perisylvian cortex, sorting with the left dorsolateral prefrontal cortex, and reasoning (the Twenty Questions task) with the left anterior frontal cortex. The Twenty Questions test best distinguished the clinical diagnoses of CBS and FTD.

Conclusions: The neuroanatomic findings (especially in frontotemporal dementia [FTD]) agree with the previous literature on this topic. Patients with FTD and patients with corticobasal syndrome (CBS) show disparate performance on higher-order executive functions, especially the Twenty Questions test. It may be difficult to distinguish motor and visuospatial ability from executive function in patients with CBS using tests with significant motor and visuospatial demands such as Trail Making. *Neurology*® 2009;72:453-459

GLOSSARY

bv-FTD = behavioral variant FTD; **CBS** = corticobasal syndrome; **D-KEFS** = Delis-Kaplan Executive Function System; **FDR** = false discovery rate; **FTD** = frontotemporal dementia; **FWE** = family wise error; **MDRS2** = Mattis Dementia Rating Scale 2; **NINDS** = National Institute of Neurological Disorders and Stroke; **ROI** = region of interest; **VBM** = voxel-based morphometry; **WMS-III** = Wechsler Memory Scale-third edition.

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease that primarily affects the frontal and anterior temporal lobes, resulting in changes in behavior, language, and cognition.¹ Corticobasal syndrome (CBS) is a disorder characterized by progressive asymmetric apraxia and rigidity with other findings of cortical (e.g., alien limb, cortical sensory loss, myoclonus) and basal ganglia (e.g., bradykinesia and increased resistance to passive movement) dysfunction.^{2,3} Both disorders can be associated with pathologic tau aggregation.¹⁻⁵

Patients with FTD and patients with CBS often have deficits in executive function,⁶⁻⁹ a term that encompasses complex cognitive functions such as planning, judgment, reasoning, problem

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Table 1 Mean (SD) demographic and clinical characteristics of 51 patients with FTD and 50 patients with CBS

	Male/female	Mean age at onset, y	Mean age at testing, y	R/L handed	Mean education, y	Body side affected
FTD	26/25	54.7 (7.8)	59.6 (7.9)	46/5	15.6 (2.9)	—
CBS	25/25	61.1 (8.4)	65.6 (8.2)	43/6/1 ambidextrous	14.9 (3.0)	25 L/21R/4 unclear
Normal controls	7/7	NA	60.1 (6.4)	14/0	16.9 (3.7)	NA

FTD = frontotemporal dementia; CBS = corticobasal syndrome.

solving, organization, attention, abstraction, and mental flexibility.¹⁰ Several questions, however, remain unanswered: How do the patterns of executive dysfunction of behavioral variant FTD (bv-FTD) and CBS compare? What brain areas are associated with specific symptoms of executive dysfunction in bv-FTD and CBS? These are important questions for several reasons: executive dysfunction is a clinically important symptom in FTD¹¹ and CBS,⁷ but little is known about its neurobiological basis in these disorders; and insights from patients with deficits in executive function can elucidate the neuroanatomic basis of executive function in healthy people. The distributions of atrophy observed in FTD and CBS are ideal to determine the relative contributions of regions of the frontal and parietal cortexes to executive function.

A review of the brain areas involved in the performance of executive function tests is beyond the scope of this article, but in summary, while intact executive function requires more fundamental cognitive abilities in other parts of the brain (including the parietal lobe¹²), the prefrontal cortex, especially on the left, is prominently associated with executive functions.¹³ Patients with FTD had high numbers of rule violations on the Tower Test compared to patients with Alzheimer disease and healthy controls,¹⁴ and impaired performance on a sorting task associated with decreased left frontal lobe volume.¹⁵ Performance on the Twenty Questions test has been shown to be impaired in patients with prefrontal cortex lesions,¹⁶ and letter fluency is impaired in patients with left prefrontal¹⁷ lesions. Patients with FTD who had progressive disease were especially impaired on digit span and inhibition of prepotent responses.¹⁸

The Delis-Kaplan Executive Function System (D-KEFS) is a battery of nine standardized executive function tests (Trail Making,

Verbal Fluency, Design Fluency, Color-Word Interference, Sorting, Twenty Questions, Word Context, Tower, and Proverb interpretation) designed to comprehensively assess higher cognitive function.¹⁹ In this study, we compared D-KEFS scores between the patients with CBS and patients with FTD and determined which areas of the brain are associated with these executive functions using voxel-based morphometry (VBM) of MRI. Based on the findings discussed above and the brain areas affected in FTD and CBS, we hypothesized that patients with FTD would show more severe executive dysfunction than the patients with CBS and that this executive dysfunction would be associated with left prefrontal atrophy in the patients with FTD and left prefrontal and parietal atrophy in the patients with CBS.

METHODS Participants. A total of 51 patients with behavioral variant FTD (bv-FTD) and 50 patients with CBS participated in this study. Patients with language-variant FTD (i.e., semantic dementia or primary progressive aphasia) were excluded from this study in order to remove the potential confound of the effect of language deficits on testing executive functions. Subjects were seen as part of an ongoing research study on FTD and CBS in the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH, Bethesda, MD. They were either self-referred or referred by outside neurologists. Patients arrived at the NIH with a caregiver and were diagnosed based on an initial clinical evaluation and examination by a neurologist (E.M.W.) by standard clinical criteria.^{2,20} They then spent 9 days participating in extensive neuropsychological and neurologic testing and imaging studies. Their diagnoses were re-evaluated by a neuropsychologist (J.G.) based on the results of the testing done at the NIH. However, in all but one case, the final diagnosis agreed with the initial diagnosis, suggesting that the executive function testing performed at NINDS very rarely changed the initial diagnosis. We required all subjects to have an assigned research durable power of attorney prior to admission to the protocol and the assigned individuals gave written informed consent for the study. The patients gave assent for the study. All aspects of the study and the consent procedure were approved by the NINDS Institutional Review Board. Demographic and clinical data on the patients is presented in table 1. Since the time of testing, one

patient with FTD and five patients with CBS have died and their diagnoses were confirmed by autopsy.^{5,20}

The 14 control subjects were recruited locally with an advertisement and paid for their participation in the study. They were age-matched to the patients. They were free of any neurologic or psychiatric illness at the time of evaluation and not taking any neurologic or psychiatric medications (table 1).

Materials. The D-KEFS is a standardized battery of nine executive function tests.¹⁹ It has good reliability and validity and it has been standardized with large normative and patient samples.^{19,21,22} The patients also received the Mattis Dementia Rating Scale 2 (MDRS2), a test of general cognitive function designed for patients with cognitive impairment,²³ and the Wechsler Memory Scale—third edition (WMS-III), a memory test.²⁴

Principal components analysis of executive function tests. A principal components analysis (using Varimax with Kaiser normalization) of the D-KEFS scores was conducted. In pilot testing, many of our patients had difficulty completing some of the more difficult D-KEFS tests (Proverbs, Color-word interference, Design Fluency, and Word Context). Thus, of the nine D-KEFS tests, we administered and analyzed the five tests the patients were best able to complete: Trail Making, Verbal Fluency, Sorting, Twenty Questions, and the Tower Test. We performed a principal components analysis for three reasons: to reduce the data as there are too many subtests of the D-KEFS to reasonably perform imaging analyses on each; because there is accumulating evidence that executive function is comprised of categories of functions that do not necessarily correspond to a particular test¹⁰; and to objectively provide summary measures for the VBM analysis—the D-KEFS tests do not have a single summary score and the principal components analysis provides a better summary of a component of executive function than an arbitrarily chosen D-KEFS subscore. All Primary Measures of the D-KEFS tests (excluding measures that are derived from other Primary Measures, see table 2) for the 101 patients were used in the analysis (20 variables) performed in SPSS 15.0. Optional Measures were not used in the analysis. Scaled D-KEFS scores were used in the analysis. The sample size (>100 subjects) and ratio of subjects to variables (>5 to 1) satisfies guidelines for principal components analysis.²⁵⁻²⁷ The factor scores obtained from this analysis were used as the measures of interest in the VBM analyses.

Discriminant analysis. To determine which tests of the D-KEFS best distinguish FTD and CBS, a standard (not stepwise) linear discriminant analysis was performed in SPSS 15.0 on the same 20 D-KEFS variables on which the factor analyses were performed (see table 2). Cases with missing values were excluded.

Imaging. A 1.5-T GE MRI scanner (GE Medical Systems, Milwaukee, WI) and standard quadrature head coil were used to obtain all images. A T1-weighted spoiled gradient echo sequence was used to generate 124 contiguous 1.5-mm-thick axial slices (repetition time = 6.1 msec; echo time = min full; flip angle = 20°; field of view = 240 mm; 124 slices, slices' thickness 1.5 mm; matrix size = 256 × 256 × 124).

Imaging analysis. VBM analysis of the data was performed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) and followed the principles outlined by Ridgway et al.²⁸ Except as noted below, all default SPM5 options were used. Images were segmented into gray matter, white matter, and CSF. In SPM5, spatial normalization, segmentation, and modulation are processed using a unified segmentation algorithm.²⁹ This algorithm, in contrast to optimized VBM used in SPM2 in which the steps are completed sequentially, simultaneously calculates image registration, tissue classification, and bias correction using our par-

ticipants' structural MR images combined with the tissue probability maps provided in SPM5. The segmented and modulated normalized gray matter images were smoothed with a 12 mm full width at half-maximum Gaussian kernel. An explicit mask encompassing the entire brain was used in the analyses to control for background signal outside the brain. This mask was downloaded from the SPM5 Anatomic Automatic Labeling toolbox (www.cyceron.fr/freeware). A 0.05 explicit absolute threshold for masking was used in the SPM second-level model interface.³⁰ Total intracranial volume was calculated in SPM5 from the unsmoothed, modulated gray matter, white matter, and CSF images from each patient and used as a nuisance variable to account for the possible effect of varying brain volumes.

Finally, in all our analyses we corrected the statistical significance thresholds for multiple comparisons correction using two methods widely used in the neuroimaging community: the false discovery rate (FDR) and family wise error (FWE) corrections. The FDR is the proportion of false positives among those tests for which the null hypothesis is rejected³¹ while the FWE correction, which computes a correction for all voxels controlling for the chance of any false positives, is the most stringent correction for multiple comparisons available in SPM.³²

We were interested in elucidating the different brain areas associated with each executive function score between the patients with FTD and patients with CBS. Thus, the CBS and bv-FTD patient groups were analyzed separately. Two sets of analyses were performed. First, the scans from each patient group were compared to the scans of a group of 14 age-matched healthy control subjects using a two-sample *t* test. Statistical threshold for this analysis was set at $p < 0.05$ FWE-corrected for multiple comparisons. All subsequent analyses were limited to these areas of significant gray matter volume reduction (figure e-1 on the *Neurology*® Web site at www.neurology.org). The relationship between voxel values and each Component Score from the principal components analysis was examined using five separate one-tailed *t* tests (one for each Component Score), assuming that decreasing performance in executive function performance would be associated with decreased tissue density. Total intracranial volume was added as covariate of no interest. For all these analyses, we considered as significant those voxels surviving both a threshold of $p < 0.001$ uncorrected at voxel level and of $p < 0.05$ FDR-corrected for multiple comparisons (except for those reported in the figure, D); however, many of the reported areas also survived the more stringent FWE correction with a threshold $p < 0.05$ FWE. All clusters reported were composed of at least 30 voxels. For one analysis (component 4), we used a left frontal region of interest (ROI) that we did not use for the other analyses. While this increases the power of this analysis over the others, the rationale was that previous findings have demonstrated that the left side is associated with executive functions,¹³ and we wanted to power this analysis sufficiently to detect any associations between this component and the left frontal lobe. The left frontal ROI was selected from the WFU Pickatlas (<http://fmri.wfubmc.edu/cms/software>).

RESULTS Principal components analysis. Measures of the correlation between the variables were good, indicating that a principal components analysis is appropriate (the Kaiser-Meyer-Olkin measure was 0.852 and Bartlett's Test of Sphericity had a χ^2 of 921.2, *df* 190, $p < 0.001$). Five components with eigenvalues greater than 1.0 were found (i.e., satisfied the Kaiser-Guttman rule), demonstrating that each

Table 2 Neuropsychological test results from patients with FTD and patients with CBS for selected D-KEFS, MDRS2, and WMS-III tests

	FTD	CBS	t-Test p value	Discriminant function coefficients
D-KEFS (scaled scores)				
Sorting test				
Free sorting confirmed correct	6.44 (± 3.89)	8.47 (± 3.35)	0.013*	0.232
Free sorting description	5.44 (± 3.77)	7.60 (± 3.08)	0.005*	0.256
Sort recognition description	5.18 (± 3.27)	6.80 (± 2.74)	0.018*	0.194
Tower Test				
Total achievement	4.60 (± 3.96)	5.74 (± 3.75)	0.157	0.072
Mean first move time	11.25 (± 4.18)	9.05 (± 3.64)	0.009*	-0.229
Time Per-move ratio	6.00 (± 4.65)	3.67 (± 3.28)	0.007*	-0.242
Move accuracy ratio	12.23 (± 2.71)	11.40 (± 2.33)	0.124	-0.008
Rule Violations Per-Item Ratio	7.25 (± 3.23)	9.60 (± 1.81)	<0.001*	0.406
Trail Making Test				
Visual scanning	6.06 (± 4.15)	3.50 (± 3.28)	0.001*	-0.390
Number sequencing	5.13 (± 4.03)	4.00 (± 3.35)	0.155	-0.234
Letter sequencing	4.63 (± 4.34)	4.37 (± 3.88)	0.765	-0.127
Number-letter switching	5.86 (± 4.73)	4.97 (± 4.34)	0.409	-0.110
Motor speed	7.09 (± 3.86)	6.05 (± 4.01)	0.221	-0.159
Twenty Questions Test				
Initial abstraction	6.24 (± 2.44)	9.77 (± 3.94)	<0.001*	0.372
Total questions asked	4.71 (± 4.25)	8.57 (± 4.06)	<0.001*	0.348
Total weighted achievement	4.87 (± 3.99)	10.11 (± 8.44)	<0.001*	0.414
Verbal Fluency Test				
Letter fluency	4.08 (± 3.81)	4.92 (± 3.39)	0.253	-0.007
Category fluency	3.46 (± 3.31)	5.71 (± 3.23)	0.001*	0.190
Total correct responses	3.90 (± 3.81)	5.90 (± 3.89)	0.012*	0.115
Total switching accuracy	4.24 (± 3.83)	6.39 (± 6.75)	0.006*	0.139
MDRS2 (t scores)				
Total	3.96 (2.96)	5.38 (3.67)	0.039*	
Attention	7.66 (3.83)	8.16 (3.97)	0.522	
Initiation/perseveration	4.10 (3.17)	4.75 (2.94)	0.295	
Construction	7.34 (3.00)	4.23 (3.30)	<0.001*	
Conceptualization	5.82 (3.15)	8.69 (2.71)	<0.001*	
Memory	5.52 (3.82)	7.51 (4.07)	0.014*	
WMS-III (index scores)				
Auditory immediate	78.75 (20.19)	88.53 (16.49)	0.014*	
Visual immediate	74.11 (16.02)	86.65 (15.11)	<0.001*	
Immediate memory	72.88 (19.12)	85.50 (17.35)	0.002*	
Auditory delayed	81.18 (20.35)	89.60 (16.62)	0.034*	
Visual delayed	72.93 (15.52)	88.56 (17.62)	<0.001*	
Auditory recognition delayed	77.50 (19.87)	93.62 (19.38)	<0.001*	
General memory	73.93 (19.17)	88.41 (18.09)	<0.001*	
Working memory	79.58 (18.77)	83.35 (18.12)	0.339	

Means with standard deviations are reported with results from two-tailed t tests between the patient groups (not corrected for multiple comparisons). All D-KEFS scores are scaled. Ten is the mean for healthy subjects on the D-KEFS tests and the MDRS index scores with a standard deviation of 3. One hundred is the mean for healthy subjects on the WMS-III index scores with a standard deviation of 15.

*p < 0.05.

FTD = frontotemporal dementia; CBS = corticobasal syndrome; D-KEFS = Delis-Kaplan Executive Function System; MDRS2 = Mattis Dementia Rating Scale 2; WMS-III = Wechsler Memory Scale-third edition.

Figure Brain areas associated with executive dysfunction in frontotemporal dementia and corticobasal syndrome

Areas of significantly lower gray matter density associated with the Delis-Kaplan Executive Function System components shown in table e-1. For the statistical thresholds of the individual analysis, see Methods. Significant areas of correlations are shown in green for the patients with frontotemporal dementia and in red for the patients with corticobasal syndrome. (A) Component 1, Verbal Fluency; (B) Component 2, Trail Making; (C) Component 3, Sorting; (D) Component 4, Twenty Questions.

component explained a considerable portion of the total variance. Together, they accounted for 72.8% of the total variance. A loading of a D-KEFS subtest with a component was considered significant if it had

an absolute value greater than 0.70 on the rotated component matrix (table e-1).²⁷ Each of the five components found in the principal components analysis corresponded to only one of the five D-KEFS tests. Thus, each of the components was named by the D-KEFS test with which it corresponded (i.e., Sorting, Tower, Trail Making, Twenty Questions, and Verbal Fluency).

Discriminant analysis. A good eigenvalue of 1.64 was obtained. A discriminant function was calculated. The value of this function was significantly different between the patients with FTD and patients with CBS ($\chi^2 = 47.5$, $df = 20$, $p < 0.001$). Five variables had a p value less than, or equal to, 0.001 to distinguish the groups: all three Twenty Questions test measures (Initial Abstraction Score, Total Questions Asked, Total Weighted Achievement Score), the Tower Test Rule-Violations-Per-Item Ratio, and the Trail Making test Visual Scanning Score (table 2). Of these, the patients with CBS performed better than the patients with FTD on the Tower and Twenty Questions variables, but worse than the patients with FTD on the Trail Making Score. Overall, 86.9% of the patients (89.3% of patients with FTD and 84.8% of patients with CBS) were correctly distinguished using the discriminant function.

VBM analysis. Deficits in Verbal Fluency (component 1) are associated with decreased gray matter volume in the left frontal operculum (BA 47) (table e-1; figure, A) in FTD and in the dorsal frontal and parietal and temporal-parietal cortex, and the thalamus, in CBS (table e-1; figure, A). A similar pattern was observed with Trail Making (component 2) in CBS (table e-1; figure, B). Deficits in Sorting (component 3) are associated with decreased volume in the left frontal operculum extending to dorsolateral prefrontal cortex (BA 6, 47) and thalamus in FTD and, in patients with CBS, with decreased volume in the left mesial frontal lobe (table e-1; figure, C).

The analysis of component 4 (Twenty Questions) did not yield significant areas of association. However, if one limits the analysis to a left frontal lobe ROI, one area of decreased gray matter volume is found in the patients with FTD to have a significant association with the component: the left anterior middle frontal gyrus (BA 47) (table e-1; figure, D). Using a left frontal lobe ROI for component 4 for the patients with CBS does not yield significant results, nor does using right frontal lobe or left parietal ROIs for component 4 for patients with FTD or CBS.

DISCUSSION Our hypothesis that patients with FTD would show relatively greater executive dys-

function than patients with CBS was mostly supported (table 2); patients with FTD performed significantly worse than patients with CBS on the majority of the Sorting, Twenty Questions, and Verbal Fluency measures (table 2). The patients with CBS performed significantly worse than the patients with FTD on one of the Trail Making measures, and on the two timed measures of the Tower Test (table 2). The relatively poor performance of the patients with CBS on Trail Making and the timed measures of the Tower Test could be due, in part, to the motor and visuospatial demands of these tests. A similar pattern was observed on the MDRS2: patients with CBS performed significantly better than the patients with FTD overall, but significantly worse than the patients with FTD on the Construction subtest, which requires motor and visuospatial abilities to draw shapes (table 2). This finding corroborates previous studies which found that tau+ patients with frontotemporal lobar degeneration (including patients with CBD) had greater visuospatial deficits than tau- patients with frontotemporal lobar degeneration (a group that did not include patients with CBD),^{8,9} and likely reflects the greater involvement of brain areas involved in motor and visuospatial function in CBS than in FTD.

Executive function appears to be selectively impaired in both disorders. When the D-KEFS scores are converted to the same scale (normed at 100 points, SD of 15 points) as the WMS-III,²⁴ a memory test, the mean D-KEFS score of the patients with bv-FTD (60.8) and CBS (69.0) is approximately one SD lower than the mean WMS-III score for the patients with FTD (76.4) and CBS (88.0). This finding in patients with CBS replicates a study⁷ that reported that patients with CBD have relatively preserved memory function. The patients with bv-FTD performed significantly worse than the patients with CBS on the majority of the WMS-III memory measures even though preservation of memory is a diagnostic criterion of FTD.²⁰ This could reflect the negative effects of behavioral symptoms and executive dysfunction (i.e., deficits in motivation, attention, and strategic search) on memory testing, or that the disease has progressed in the patients with bv-FTD to involve the medial temporal lobes. On the principal components analysis, the D-KEFS variables cluster well by test, indicating that the separate tests of the D-KEFS correspond to separable executive functions.

The VBM results affirm the hypothesized importance of the left frontal lobe in executive function. In the patients with CBS posterior and right-sided areas were also associated with executive function. This could be because these areas selectively contribute to

executive function in CBS, or, more likely, because the patients with CBS's motor and visuospatial deficits interfere with the assessment of executive function (especially on the Trail Making test, which has significant motor and visuospatial components).^{8,9} The patients with FTD show regionally specific associations: Verbal Fluency (with a significant language component) was associated with left frontal perisylvian cortex, Sorting with dorsolateral prefrontal cortex, and Twenty Questions, a reasoning task, with left anterior frontal cortex. These findings fit well with a large previous literature on the neuroanatomic localization of these specific executive functions.^{13,19} A limitation of this study is that we were unable to completely rule out the effects of general cognitive dysfunction and disease severity. However, since the D-KEFS was designed (and validated) to isolate executive functions,^{19,22} and imaging differences between the components were observed within the same patient group, we are confident that our results are valid.

On the discriminant analysis, the greatest discrepancy between the patients with FTD and CBS is on tests that require higher-order executive functions such as reasoning, planning, and abstraction (the Twenty Questions and Tower Tests), on which the patients with FTD perform worse than the patients with CBS.¹⁴ This finding corresponds well to the brain areas affected in FTD and CBS. FTD is more likely than CBS to affect the anterior frontal lobes,^{1,2} which are thought to be preferentially involved in higher-order executive functions.³³ While the anterior PFC appears to have a key role in mediating executive function, it is also important for other kinds of processes not evaluated in this study, including social cognition.

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