Patterns of neuropsychological impairment in frontotemporal dementia

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Abstract—*Objective:* To differentiate frontotemporal dementia (FTD) subtypes from each other and from probable Alzheimer disease (AD) using neuropsychological tests. *Methods:* Patients with FTD and AD (n = 109) were studied with a comprehensive neuropsychological protocol at first contact. Data were subjected to a principal components analysis (PCA) to extract core neuropsychological features. A five-factor solution accounted for 72.89% of the variance and yielded factors related to declarative memory, working memory/visuoconstruction, processing speed/mental flexibility, lexical retrieval, and semantic memory. *Results:* Between- and within-group analyses revealed that patients with AD obtain their lowest scores on tests of declarative memory while semantic dementia (SemD) patients are particularly disadvantaged on tests of semantic memory. On tests of processing speed/mental flexibility time to completion was faster for social comportment/dysexecutive (SOC/EXEC) patients, but these patients made more errors on some tests. Patients with corticobasal degeneration (CBD) and progressive nonfluent aphasia (PNFA) were impaired on tests of working memory. Logistic regression analyses using factor scores successfully assigned FTD subgroups and AD patients into their respective diagnostic categories. *Conclusion:* Patients with differing frontotemporal dementia phenotypes can be distinguished from each other and from Alzheimer disease using neuropsychological tests.

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A variety of frontotemporal dementia (FTD) phenotypes have been identified[1-5]: a social/executive (SOC/EXEC) syndrome, semantic dementia (SemD), progressive non-fluent aphasia (PNFA), and corticobasal degeneration (CBD [6,7]). Past neuropsychological studies have focused on distinguishing FTD from Alzheimer disease (AD).[1] Indeed, clinical-pathologic studies have confirmed distinct neuropsychological patterns in patients with autopsy-proven FTD compared to AD.[8] Less attention has been devoted to the identification of neuropsychological measures that might distinguish FTD phenotypes from each other.[2,9-12] The major goals of the present research are to assess whether neuropsychological assessment can distinguish between AD and FTD, and between FTD phenotypes.

In this study, neuropsychological assessment was obtained on patients with FTD subgrouped according to their phenotype and compared to patients with AD. Neuropsychological data were first subjected to an exploratory principal components analysis (PCA). PCA-composite indices were used to categorize patients into their clinical subgroup. We expected that PCA indices would be able to distinguish the various FTD phenotypes from each other and from AD. Based on prior research,[8-12] we predicted that patients with SOC/EXEC disorder would be impaired on tests of executive control. Patients with PNFA were expected to be impaired on lexical retrieval tests. Patients with SemD were predicted to present with impairment on tests that depend on semantic memory. Patients with AD were expected to be most impaired on tests of declarative memory.

Methods. *Patients.* Data were drawn from a group of 239 patients. A total of 135 participants had complete neuropsychological protocols. Of this group, 26 participants were excluded because of a diagnosis other than AD or FTD (Lewy body dementia = 8, vascular dementia = 1, amyotrophic lateral sclerosis = 1, mild cognitive impairment = 5) or an atypical presentation of AD (AD-frontal variant = 2; AD visual variant = 9). A total of 109 participants with complete neuropsychological protocols and a clinical diagnosis of AD or FTD were studied. All patients were evaluated and recruited from the Department of Neurology, University of Pennsylvania. Subsequently, at least two trained reviewers of a consensus committee confirmed the presence of specific diagnostic criteria and also assigned patients to an FTD subgroup based on an independent review of the semi-structured history, a detailed neurologic examination, and a recently developed, brief, but standardized mental status examination (The Philadelphia Brief Assessment of Cognition [PBAC]). The PBAC consists of 20 individual tests that assess executive functioning (e.g., digit span, single letter fluency [letter F], alternating patterns), language (e.g., naming, repetition, single word and sentence comprehension, speech, reading, and writing), visual perceptual-spatial functioning (e.g., judgment of line orientation, lateral neglect, face recognition, complex figure reproduction), and memory (verbal and visual episodic memory). Of the subtests contained in the PBAC only paradigms measuring digit span and letter fluency

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tests were in common with our full neuropsychological protocol. However, these exact digit and letter fluency tests contained in the PBAC are different as compared to the full neuropsychological protocol. Thus, every reasonable precaution was taken to avoid the circularity of using the same neuropsychological tests to both identify and then classify patients into their respective groups.

The subgroups were classified based on published criteria[3] that have been modified to improve reliability.[10,13] When there was disagreement between reviewers (about 19% of cases), the case was discussed by the entire committee to arrive at a consensus diagnosis. On a different occasion trained technicians administered a detailed neuropsychological protocol comprised of different tests. This formal neuropsychological evaluation, described in detail below, was not used to diagnose these patients and the diagnosing neurologist was blind to patient performance on the neuropsychological evaluation. These patients and their legal representatives participated in an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania.

Among the participants in this study, 38 patients were given a clinical diagnosis of AD based on National Institute of Neurologic and Communicative Disorders and Stroke–AD and Related Disorders Association criteria.[13] In brief, this included a progressive syndrome involving prominent episodic memory difficulty, associated with circumlocutory speech, a visual constructional impairment, or limited executive control. Patients with AD with either an unusual presentation or who were classified as presenting with an AD visual or frontal lobe variant were excluded.

Another 71 patients were clinically diagnosed with FTD, according to published criteria.[14,15] Our sample included 16 patients with a SOC/EXEC profile. These patients presented with significant social and behavioral difficulties, and alterations of executive functioning. Our sample also included 13 PNFA patients. These patients had effortful speech that may be associated with dysarthria, phonemic substitutions, or impaired grammatic comprehension, but relatively good single word comprehension. Eighteen patients were diagnosed with SemD. The language disorder of these patients was characterized by fluent and circumlocutory spontaneous speech that was often empty in content with a prominent naming deficit and was associated with difficulty understanding single words and objects. Finally, 24 patients were diagnosed with CBD based on criteria derived from clinical-pathologic studies reported in the literature and our own autopsy series.[16-18] These patients had apraxia, gait difficulty, and a lateralized extrapyramidal disorder (e.g., unilateral limb rigidity, myoclonus, dystonia, alien hand phenomena).

The initial clinical diagnosis of a neurodegenerative disease was consistent with the results of serum studies, structural imaging studies such as MRI or CT, studies of CSF (when available), and clinical functional neuroimaging studies such as SPECT or PET (these studies were not available to the consensus committee). Exclusion criteria included the presence of other neurologic conditions such as stroke or hydrocephalus (as determined by imaging studies reviewed by MG), primary psychiatric disorders such as depression or psychosis, or a systemic illness that can interfere with cognitive functioning. Many of these patients were taking a fixed dosage of an acetylcholinesterase inhibitor (e.g., donepezil, rivastigmine, or galantamine). Some of these patients also may have been medicated with a low dosage of a nonsedating antidepressant (e.g., serotonin-specific re-uptake inhibitors such as sertraline) or an atypical neuroleptic agent (e.g., quetiapine), as indicated clinically, but none of the patients demonstrated any evidence of sedation suggesting overmedication.

Table 1 summarizes the demographic features of these patients. A multivariate analysis of variance (MANOVA) indicated no differences in education, disease, duration, or performance on the Mini-Mental State Examination.[19] A between-group difference was present only for age ($F = [4, 104] = 5.14$, $p < 0.001$), such that patients with AD were older than SOC/EXEC patients ($p < 0.001$). Patients with PNFA were older than SOC/EXEC patients ($p < 0.005$).

Neuropsychological protocol. All patients were assessed with the following neuropsychological tests. This protocol was constructed so that major areas of potential cognitive disability were assessed.

Wechsler Adult Intelligence Scale–Revised Digit Span subtest. Forward and backwards span was assessed using standardized instructions. The longest forward and backward spans were the two dependent variables derived from this test.[20]

Table 1 *Demographic information*

	Age, y	Education, y	Illness duration, mo	MMSE
AD	71.71 (9.29)	14.45 (3.05)	46.13 (26.65)	23.16 (5.08)
SOC/EXEC	60.06 (11.25)	15.38 (3.56)	38.37 (30.78)	24.13 (4.66)
PNFA	72.23 (6.60)	13.31 (2.56)	32.31 (18.01)	24.23 (6.37)
SemD	67.83 (9.68)	15.69 (3.36)	40.61 (19.42)	25.00 (3.65)
CBD	68.71 (7.93)	15.00 (3.30)	44.35 (27.87)	22.58 (5.40)

Values are mean (SD).

MMSE = Mini-Mental State Examination; AD = Alzheimer disease; SOC/EXEC = dysexecutive/social subgroup; PNFA = progressive nonfluent aphasia; SemD = semantic dementia; CBD = corticobasal degeneration.

Letter fluency. Patients were given 60 seconds to generate words, excluding proper nouns and numbers, beginning with a specified letter ("FAS"). The dependent variable was the number of responses summed across the three letters.[21]

Trail Making Test, Part B. This test was administered using standard procedures, i.e., patients were asked to draw a line alternating between numbers and letters (i.e.,1-A-2-B). Errors were pointed out to the patients when they occurred. Patients were given up to 300 seconds and asked to draw a line alternating between numbers and letters (i.e., 1-A-2-B). The dependent variable was the total time to completion.[22]

Stroop Color-Word Interference Test. Patients were shown the words red, blue, yellow, and green in discordant colors and were asked to name the color ink rather than read the words. The dependent variable was time to completion.[23,24]

Boston Naming Test. Visual confrontation naming was assessed with a 15-item version of the Boston Naming Test.[25,26] The stimuli were equally divided among high frequency, mid-frequency, and low frequency items. Patients were given as much time as they needed to respond. The dependent variable was the total number of correct responses.

Animal fluency. The animal fluency task[27] was administered by asking patients to produce as many names of animals as possible in 60 seconds. The dependent variable was the total number of responses, excluding perseverations and extra-category intrusion responses.

Semantic Category Membership Task. To assess semantic knowledge with a simple task that requires little expression and minimizes executive resource demands, patients were asked to judge the semantic category membership of individually presented stimuli in response to a simple probe ("Is it an X?").[28] One target category was tools and the other target category was vegetables. Half of the stimuli in each category were targets and half foils, and half of each category of stimuli was printed words and half color photographs (matched for frequency, familiarity, and visual complexity across categories). Stimuli were presented in a manner blocked by category and material. Patients were given as much time as they needed to complete the task. Performance on this task has been validated by behavioral and SPECT correlation studies in patients with AD with impaired semantic memory.[29] The dependent variable was the number of correct responses.

Geometric Figure Copy. To assess visuoconstructional ability patients were asked to copy four geometric designs graded in their perceptual-spatial complexity.[26] Performance was evaluated on an 11-point scale.

Verbal Serial List Learning Test. Verbal memory and learning were assessed with a 10-word list administered over three trials.[26] Delayed free recall for this list was assessed after a filled delay. This was followed by a delayed recognition test where the 10 original words were intermixed with 10 novel words. Patients were asked to simply identify which words were on the original word list. Four dependent variables were coded—the number of words recalled on trial 1, trial 3, and the delayed free recall test condition. The dependent variable on the recognition test was the

Table 2 *Descriptive statistics for neuropsychological tests*

	AD	SOC/EXEC	PNFA	SemD	CBD
Digits forward	6.13 (1.28)	6.12 (1.59)	5.46 (1.81)	5.56 (1.65)	5.93 (1.51)
Digits backward	3.89 (1.41)	4.31 (1.49)	3.31 (1.32)	4.06 (1.39)	3.00 (1.50)
Letter fluency	24.52 (11.03)	26.12 (14.61)	13.07 (7.80)	25.66 (13.42)	19.25 (13.20)
Figure copy	9.50 (1.74)	9.19 (1.83)	8.92 (1.26)	10.39 (1.14)	6.33 (3.56)
Stroop Interference	220.18 (77.95)	159.87 (92.73)	228.30 (77.98)	237.83 (96.99)	218.25 (94.52)
Trail Making—Part B	242.31 (72.33)	170.87 (95.43)	228.07 (96.58)	235.83 (73.57)	215.83 (108.96)
Boston Naming	11.58 (2.91)	12.44 (2.92)	12.38 (3.12)	10.44 (3.62)	11.58 (2.73)
Animal fluency	9.55 (5.73)	13.06 (6.19)	10.85 (5.86)	10.11 (4.87)	9.00 (4.82)
Semantic memory—correct responses (words)	2.13 (1.07)	2.43 (1.03)	2.23 (1.16)	1.70 (1.21)	2.54 (0.72)
Semantic memory—correct responses (pictures)	2.08 (1.22)	2.31 (1.25)	2.07 (1.25)	1.81 (1.32)	2.45 (1.02)
List learning—trial 1	2.63 (1.88)	3.69 (2.30)	3.23 (1.69)	2.39 (1.65)	3.29 (1.90)
List learning—trial 3	4.47 (1.91)	5.19 (2.23)	5.46 (3.04)	5.00 (2.40)	4.71 (1.97)
List learning—delayed recall	0.95 (1.27)	2.88 (2.58)	3.69 (2.36)	3.00 (2.63)	2.38 (1.93)
List learning recognition	14.97 (2.97)	16.00 (4.21)	17.15 (3.69)	16.78 (2.39)	16.58 (2.92)

Values are mean (SD).

AD = Alzheimer disease; SOC/EXEC = dysexecutive/social comportment; PNFA = frontotemporal dementia primary nonfluent aphasia; SemD = semantic dementia; CBD = corticobasal degeneration.

number of original test items correctly identified combined with the number of foils that were correctly rejected as members of the original word list. Therefore, on the recognition test condition scores ranged from 0 to 20.

Statistical analysis. Multiple comparisons were set at $p < 0.01$. All statistical tests were two-sided. Normality assumptions were verified for continuous data when analysis of variance or multivariate analysis of variance was applied. To identify patterns of neuropsychological tests, a principal components factor analysis (PCA) using a varimax rotation (SPSS version 13) was conducted. Factor loadings were accepted if they exceeded a threshold of 0.500, unless otherwise indicated. Composite indices were created from each factor derived from the PCA from factor loading scores using the SPSS default regression method. In addition, five multinomial logistic regression models were run to examine if the five neuropsychological composite indices can distinguish FTD phenotypes from each other and AD. In each multinomial logistic regression model, only one factor was used to predict group membership. A Likelihood Ratio Test was used to examine the overall significance of each neuropsychological factor. The Wald test was used to examine if each factor can distinguish between patients constituting any two clinical groups.

Results. Descriptive statistics for the 14 dependent variables from the neuropsychological protocol described above are displayed in table 2.

The principal components analysis (PCA) (with varimax rotation) yielded a five-factor solution that accounted for 72.89% of the variance (table 3). Only eigenvalues of ≥1.00 were retained. All neuropsychological tests had at least one factor loading of 0.500.

Factor 1 consisted of the four variables related to declarative memory. Span for digits forward and backwards, output on tests of letter fluency, and performance on the figure copy test loaded on Factor 2. This factor appears to assess working memory/visuoconstructional ability. Factor 3 appears to be related to lexical retrieval and consisted of performance on the Boston Naming Test and output on the animal fluency test. Output on the letter fluency test and delayed recognition of correct target items from the verbal serial list learning test condition also loaded on this factor. Factor 4 consisted of the two variables derived from the Semantic Judgment Test and appears to be related to semantic memory. Finally, time to completion on the Trail Making Test and the Stroop Color Interference Test loaded on Factor 5. This factor might be best understood as measuring processing speed and mental flexibility.

Between-group analyses. Five neuropsychological composite indices were constructed directly from the factor loading generated by the principle components solution in the manner described above (table 4).

An initial multivariate analysis of variance yielded an effect of group ($F(20,378) = 3.84$, $p < 0.001$). Individual one-way analyses of variance yielded between-group differences for four of the five neuropsychological composite indices, i.e., declarative memory, $p < 0.002$; working memory/visuoconstruction, $p < 0.001$; semantic memory, $p < 0.006$; and processing speed/mental flexibility, $p < 0.006$. There was no effect for group for the naming/lexical retrieval index.

Follow-up analyses were conducted with Tukey tests. All statistical information can be found in table 4. On the declarative memory index, patients with AD obtained a lower score than PNFA patients ($p < 0.001$). There was a trend for patients with AD to perform worse on the semantic memory index compared to patients with CBD ($p < 0.098$). SemD patients performed worse on the semantic memory index compared to patients with CBD ($p < 0.003$). Patients with CBD obtained a lower score on the working memory/visuoconstruction index compared to patients with AD ($p < 0.002$) and SemD ($p < 0.014$). Finally, on the processing speed/mental flexibility index time to completion was faster for patients with SOC/EXEC compared to the patients with SemD ($p < 0.013$). There was also a

Table 3 *Neuropsychological test performance: Factor structure*

	Factor 1: declarative memory	Factor 2: working memory/ visuoconstruction	Factor 3: lexical retrieval	Factor 4: semantic memory	Factor 5: processing speed/mental flexibility
Verbal list learning—trial 1	0.544*	0.371	0.005	0.494	−0.116
Verbal list learning—trial 3	0.668*	0.377	0.148	0.282	−0.174
Verbal list learning—delayed recall	0.874*	−0.008	0.148	0.009	−0.174
Verbal list learning—recognition	0.702*	0.008	0.390	0.190	0.007
Digits forward	−0.207	0.679*	0.112	0.219	−0.214
Digits backwards	0.154	0.872*	−0.007	0.004	−0.213
Letter fluency ("FAS")	0.002	0.500*	0.603*	0.226	−0.002
Figure copy	0.253	0.659*	0.134	−0.309	0.120
Boston Naming Test	0.225	−0.008	0.826*	0.110	−0.006
Animal fluency	0.300	0.273	0.716*	0.150	−0.205
Semantic memory (words)	0.135	−0.001	0.199	0.851*	−0.005
Semantic memory (pictures)	0.244	0.004	0.102	0.808*	0.002
Trails—Part B	−0.140	−0.202	0.007	−0.009	0.856*
Stroop Interference	−0.007	−0.004	−0.444	0.006	0.718*
Eigenvalue	4.78	1.88	1.27	1.15	1.09
Percent variance	34.19	13.46	9.13	8.24	7.84
Total variance = 72.89%					

* Performance contributing to a factor at a value >0.500.

trend suggesting faster time to completion on processing speed/mental flexibility tests for patients with SOC/EXEC as compared to patients with AD ($p < 0.024$). While time to completion on these tests was faster for patients with SOC/EXEC compared to patients with AD, SOC/EXEC made more errors on the Trails Making Test—Part B compared to patients with AD ($z = -2.13$, $p < 0.016$). Patients with SOC/EXEC also exhibited a trend toward more errors on the Trail Making Test—Part B compared to patients with SemD ($z = -1.5$, $p < 0.066$).

Within-group analyses. Poor performance on the declarative memory index was the outstanding feature for the AD group (declarative memory < working memory/visuoconstruction, $p < 0.001$; declarative memory < processing speed/mental flexibility, $p < 0.001$; declarative memory < lexical retrieval, $p < 0.009$). Patients with AD also obtained a lower score on the semantic memory index as compared to the working memory/visuoconstruction index ($p < 0.018$). The SOC/EXEC group obtained a worse score on the processing speed/mental flexibility index as compared to the lexical retrieval index ($p < 0.011$). There was a trend suggesting worse performance on the processing speed/mental flexibility index as compared to the semantic memory index ($p < 0.046$). Patients with PNFA scored lower on the working memory/visuoconstruction ($p < 0.005$) and lexical retrieval indices ($p < 0.013$) as compared to the declarative memory index. Patients with SemD obtained a lower score on the semantic memory

Table 4 *Factor analysis composite indices: Between-group comparisons*

	AD	SOC/EXEC	PNFA	SemD	CBD	Group follow-up tests	*p*
Declarative memory	−0.43 (0.62)	0.13 (1.09)	0.79 (1.12)	0.24 (1.11)	−0.03 (1.11)	AD<PNFA	<0.001
Working memory/visuoconstruction	0.31 (0.82)	0.17 (1.05)	−0.42 (0.61)	0.36 (0.96)	−0.60 (1.09)	CBD<AD	<0.002
						CBD<SemD	<0.014
Lexical retrieval	−0.05 (0.88)	0.27 (1.00)	−0.13 (0.84)	−0.06 (1.54)	−0.14 (0.79)	NS	
Semantic memory	−0.06 (0.93)	0.06 (0.92)	−0.21 (1.05)	−0.59 (1.03)	0.56 (0.81)	SemD<CBD	<0.003
						AD<CBD	<0.098
Processing speed/mental flexibility	0.22 (0.78)	−0.64 (1.14)	0.03 (0.93)	0.45 (0.76)	−0.022 (1.14)	DYSE>AD	<0.024
						DYSE>SemD	<0.013

Values are mean (SD).

AD = Alzheimer disease; SOC/EXEC = dysexecutive/social subgroup; PNFA = progressive nonfluent aphasia; SemD = semantic dementia; CBD = corticobasal degeneration; NS = not significant.

Table 5 *Logistic regression analysis*

Reference group	Cognitive domain	OR	CI	Wald test
AD group: declarative memory (likelihood ratio test − $X2 = 16.41$; $df = 4$; $p < 0.003$)				
SOC/EXEC vs AD	B = 0.83	2.31	1.14–4.65	$p < 0.019$
PNFA vs AD	B = 1.23	3.44	1.60–7.38	$p < 0.001$
SemD vs AD	B = 0.90	2.46	1.26–4.79	$p < 0.008$
CBD vs AD	B = 0.85	2.34	1.24–4.40	$p < 0.008$
AD group: working memory/visuoconstruction (likelihood ratio test − $X2 = 15.17$; $df = 4$; $p < 0.004$)				
PNFA vs AD	B = −1.02	0.35	0.16–0.77	$p < 0.009$
CBD vs AD	B = −1.00	0.36	0.19–0.70	$p < 0.003$
CBD group				
SemD vs CBD	B = 0.99	2.71	1.29–5.67	$p < 0.008$
AD group: processing speed/mental flexibility (likelihood ratio test− $X2 = 16.18$; $df = 4$; $p < 0.003$)				
SOC/EXEC vs AD	B = −1.15	0.31	0.15–0.65	$p < 0.002$
SOC/EXEC group				
PNFA vs SOC/EXEC	B = 1.26	3.54	1.39–9.02	$p < 0.008$
SemD vs SOC/EXEC	B = 1.45	4.27	1.77–10.28	$p < 0.001$
AD group: semantic memory (likelihood ratio test − $X2 = 20.86$; $df = 4$; $p < 0.001$)				
CBD vs AD	B = 1.16	3.19	1.46–6.94	$p < 0.003$
PNFA group				
CBD vs PNFA	B = 1.33	3.78	1.51–9.45	$p < 0.004$
SemD group				
CBD vs SemD	B = 1.70	5.52	2.27–13.39	$p < 0.001$

AD = Alzheimer disease; SOC/EXEC = dysexecutive/social comportment subgroup; PNFA = progressive nonfluent aphasia; SemD = semantic dementia; CBD = corticobasal degeneration.

index as compared to the declarative memory index ($p < 0.011$) and the working memory/visuoconstruction index ($p < 0.019$). Finally, patients with CBD obtained a lower score on the working memory/visuoconstruction index compared to the semantic memory index ($p < 0.001$). Worse performance on the processing speed/mental flexibility index vs the semantic memory index was also observed ($p < 0.006$). Patients with CBD also obtained a lower score on the naming/lexical retrieval index compared to the semantic memory index ($p < 0.007$).

Multinomial logistic regression analyses. A series of multinomial logistic regression analyses were conducted. Multinomial regression analyses, rather than simple logistic regression analyses, were conducted because we sought to assess the ability of neuropsychological test performance to classify patients into their respective groups. A series of five analyses were conducted with each patient group coded to be the reference group, i.e., the group against which the other four groups were compared. Thirteen comparisons reached significance ($p < 0.010$). Complete statistical information can be found in table 5. As an example, the odds of being in the SOC/EXEC group vs in the AD group increased by a factor of 2.3 for every one unit increase on declarative memory index. This implies that declarative memory can differentiate patients with SOC/EXEC from patients with AD.

Table 5 indicates that performance on tests of declarative memory differentiated patients with AD from the four subgroups of patients with FTD. The working memory/visuoconstructional index differentiated patients with PNFA or CBD from patients with AD, and differentiated patients with CBD from patients with SemD. The processing speed/mental flexibility index correctly differentiated patients with SOC/EXEC vs patients with AD, PNFA, and SemD. Finally, the semantic memory index correctly categorized patients with SemD, AD, and PNFA vs patients with CBD into their respective groups.

Discussion. Prior studies attempting to dissociate patients with AD and FTD using neuropsychological measures have produced mixed results. This is due, in part, to several reasons, including the small FTD sample sizes[30-32]; the use of brief cognitive protocols[31-34]; and the use of FTD groups with mixed presenting symptoms.[32-38] Despite these problems, some studies have shown greater impairment on executive control tests in FTD as compared to AD.[37-38] Other researchers have reported a relative dissociation, with FTD showing greater impairment on tests of executive control and patients with AD showing greater impairment on

tests of declarative memory.[8,11-12] Several studies have been able to differentiate FTD subtypes from each other.[2]

Because we did not wish to make specific assumptions about the relationships between individual neuropsychological tests and their underlying cognitive constructs, we first subjected our neuropsychological data to a principal components analysis before undertaking any between- or within-group analyses. This procedure permitted objective extraction of the core neuropsychological features that typify our sample as a whole while minimizing confounds that can emerge because of the multidimensional nature of neuropsychological measures. The goal of the PCA, therefore, was to control for the multiple cognitive abilities that underlie all clinically useful neuropsychological tests. Second, and equally important, within-group analyses of the neuropsychological composite indices were undertaken to develop a set of neuropsychological composite indices that might ultimately be associated with imaging or other biomarkers that would help improve antemortem diagnosis of FTD.

Our between- and within-group analyses suggest that each of the five patient groups is associated with a specific profile of neuropsychological impairment. For example, patients with AD obtained particularly low scores on tests of declarative memory, followed by poor performance on tests of semantic memory. The declarative memory deficit in AD is well known.[39] Consistent with prior reports,[2,12] patients with SemD presented with an opposite neuropsychological profile as compared to patients with AD such that patients with SemD were significantly more impaired on tests of semantic memory while performance on tests of declarative memory was a relative strength.

One of the strengths of the current research was the emergence of separate factors related to working memory/visuoconstruction vs processing speed/mental flexibility. This suggests that the so-called executive dysfunction associated with these dementia patients is actually quite rich, likely due to the multidimensional nature of the executive resources that can be functionally impaired in subgroups of patients with FTD. The combination of digit span and output on tests of letter fluency with geometric figure copy may be difficult to understand at first. However, recent research has shown that other dementia groups typified by poor performance on tests of executive control also produce particularly poor scores on visuoconstructional tests due to the planning needed for visual design production.[40,41]

Patients with PNFA and CBD both presented with lower scores on tests of working memory/visuoconstruction. However, within each of these two groups the interpretation of these findings is complex. For the PNFA subgroup, their low scores on digit span and letter fluency tests could be associated with their effortful speech[42] and impaired sentence comprehension.[43] This finding is not surprising in the context of their frontal disease seen on imaging studies.[44,45] A relative strength within the PNFA group was their performance on tests of declarative memory.

Low performance on the working memory/visuoconstructional index was also found in the CBD group. This is consistent with the right frontal-parietal distribution of their disease.[18,45] Of equal interest was that patients with CBD were slow on the processing speed/mental flexibility index. In addition to low scores on the geometric figure copy tests, time to completion on the Stroop and Trail Making Tests was slow (table 2). Slowed completion on the processing speed/mental flexibility tests seen in the CBD group might reflect a specific problem related to visually guided operations requiring executive control.

Time to completion on tests that assess processing speed/mental flexibility was faster for the SOC/EXEC compared to the AD and SemD groups. However, as described above, SOC/EXEC often made more errors on the Trail Making Test Part B compared to other groups, suggesting a speed/accuracy trade off. Patients who are aware of their deficits often slow their performance to improve accuracy, but the SOC/EXEC group showed the opposite pattern. They performed faster at the expense of their accuracy. This emphasizes that the social anosognosia of these patients also can be seen in their cognitive performance.[46] When neuropsychological test performance was assessed within the SOC/EXEC group, performance on the processing speed/mental flexibility index was worse as compared to other domains of cognitive functioning.

Several caveats should be kept in mind when considering our findings. First, since our cohort included patients who had completed all of the measures in our neuropsychological protocol, there may be a bias toward patients who are relatively mildly impaired. Additional work is needed to determine whether these profiles generalize to more impaired patients. Second, our protocol of neuropsychological measures, while more comprehensive than in many previous studies, did not asses all relevant cognitive abilities such as a direct measure of social comportment, visual declarative memory, or visual working memory. The inclusion of such tests may have altered our results and should be included in future research. Third, we do not have histopathologic evidence for the etiology of the disease causing the progressive disorder in these patients, although our findings are consistent with reported cognitive deficits in other clinical-pathologic studies where 75% of patients diagnosed clinically with the FTD subtypes described above were confirmed upon autopsy.[8,9] Only 17% of patients diagnosed with an FTD syndrome were found to have AD upon pathologic examination. Finally, in the present study, we used an exploratory factor analysis to derive the core features of our neuropsychological protocol. Due to the relatively small sample size within the various FTD subtypes, we acknowledge that our factor solution could be unsta-

ble. The results of our exploratory PCA should be replicated using confirmatory factor analysis[47] on a larger sample of patients with FTD.

References

1. Grossman M. Frontotemporal dementia: a review. J Int Neuropsychol Soc 2002;8:564–583.
2. Hodges JR, Patterson K, Ward R, et al. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. Neuropsychology 1999;13:31–40.
3. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51: 1546–1554.
4. Kertesz A. Pick Complex: an integrative approach to frontotemporal dementia: primary progressive aphasia, corticobasal degeneration, and progressive supranuclear palsy. Neurologist 2003;6:311–317.
5. Kertesz A. Frontotemporal dementia: one disease, or many? Probably one, possibly two. Alz Dis Assoc Disord 2005;suppl 1:S19–24.
6. Graham NL, Bak TH, Hodges JR. Corticobasal degeneration as a cognitive disorder. Mov Disord 2003;18:1224–1232.
7. Pillon B, Blin J, Vidailhet M, et al. The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology 1995;45:1477–1483.
8. Rascovsky K, Salmon DP, Ho GJ, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. Neurology 2002; 58:1801–1808.
9. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal lobe dementia: clinicopathological correlations. Ann Neurol 2006;952:952–962.
10. Grossman M, Ash S. Primary progressive aphasia: a review. Neurocase 2004;10:3–18.
11. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. Cogn Behav Neurol 2003;16:211–218.
12. Perry RJ, Hodges JR. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. Neurology 2000;54: 2277–2284.
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadian EM. Clinical diagnosis of Alzheimer's disease: report on the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944.
14. McKhann G, Trojanowski JQ, Grossman M, Miller BL, Dickson D, Albert M. Clinical and pathological diagnosis of frontotemporal dementia: report of a work group on frontotemporal dementia and Pick's disease. Arch Neurol 2001:58;1803–1809.
15. The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 1994;57:416–418.
16. Forman MS, Zhukareva V, Bergeron C, et al. Signature tau neuropathology in gray and white matter of corticobasal degeneration. Am J Pathol 2002;160:2045–2053.
17. Grimes DA, Lang AE, Bergeron CB. Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology 1999; 53:1969–1974.
18. Murray R, Forman M, Farmer J, et al. Pathological correlations of clinically diagnosed frontotemporal dementia phenotypes. Submitted 2006.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the mental state of patients for a clinician. J Psychiatr Res 1974;12:189–198.
20. Wechsler D. Wechsler Adult Intelligence Scale–Revised. San Antonio: The Psychology Corporation, 1987.
21. Spreen O, Struss E. A compendium of neuropsychological tests. New York: Oxford University Press, 1990.
22. Reitan R, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery. Tucson, AZ: Neuropsychology Press, 1985.
23. Stroop JR. Studies in interference in serial verbal reaction. J Exp Psychol 1935;18:643–662.
24. Comalli PE, Wapner S, Werner H. Interference effects of Stroop Color-Word Test in childhood, adulthood, and aging. J Genet Psychol 1962; 100:47–53.
25. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea and Febiger, 1983.
26. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39: 1159–1165.
27. Carew TG, Lamar M, Cloud BS, Grossman M, Libon DJ. Impairment in category fluency in ischemic vascular dementia. Neuropsychology 1997; 11:400–412.
28. Grossman M, D'Esposito M, Hughes E, et al. Language comprehension difficulty in Alzheimer's disease, vascular dementia, and frontotemporal degeneration. Neurology 1996;47:183–189.
29. Grossman M, Payer F, Onishi K, et al. Constraints on the cerebral basis for semantic processing from neuroimaging studies of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1997;63:152–158.
30. Miller BL, Cummings JL, Villanueva-Meyer H, et al. Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. Neurology 1991;41:1374–1382.
31. Pasquier F, Lebert F, Grymonprez L, Petit H. Verbal fluency in dementia of frontal lobe type and dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 1995;58:81–84.
32. Starkstein SE, Migliorelli R, Teson A, et al. Specificity of changes in cerebral blood flow in patients with frontal lobe dementia. J Neurol Neurosurg Psychiatry 1994;57:790–796.
33. Mendez MF, Cherrier M, Perryman KM, Pachana N, Miller B L, Cummings JL. Frontotemporal dementia versus Alzheimer's disease: differential cognitive features. Neurology 1996:47;1189–1194.
34. Perri R, Koch G, Carlesimo GA, et al. Alzheimer's disease and frontal variant of frontotemporal dementia: a very brief battery for cognitive and behavioural distinction. J Neurol 2005;252:1238–1244.
35. Glosser G, Gallo JL, Clark CM, Grossman M. Memory encoding and retrieval in Frontotemporal lobe dementia and Alzheimer disease. Neuropsychology 2002;16:190–196.
36. Thomas-Anterion C, Jacquin K, Laurent B. Differential mechanisms of impairment of remote memory in Alzheimer's disease and Frontotemporal lobe dementia. Dementia Geriatr Cogn 2000;11:100–106.
37. Jagust WJ, Reed BR, Seab JP, Kramer JH, Budinger TF. Clinical-physiologic correlates of Alzheimer's disease and frontal lobe dementia. Am J Physiologic Imaging 1989;4:89–96.
38. Knopman DS, Christensen KJ, Schut LJ, et al. The spectrum of imaging and neuropsychological findings in Pick's disease. Neurology 1989; 39:362–368.
39. Delis DC, Massman PJ, Butters N, Salmon DP, Cermak LS, Kramer JH. Profiles of demented and amnesic patients on the California Verbal Learning Test: implications for the assessment of memory disorders. Psychol Assess J Consult Clin Psychol 1991;3:19–26.
40. Grossman M, Carvell S, Pelter L, Stern MB, Gollomp S, Hurtig H. Visual construction impairments in Parkinson's disease. Neuropsychology 1993;7:536–547.
41. Freeman RQ, Giovannetti T, Lamar M, et al. Visuoconstructional deficits in dementia. Neuropsychology 2000;14:415–426.
42. Ash S, Moore P, Antani S, McCawley G, Work M, Grossman M. Trying to tell a tale: discourse impairments in progressive aphasia and frontotemporal dementia. Neurology 2006;55:1405–1413.
43. Grossman M, Rhee J, Moore P. Sentence processing in frontotemporal lobe dementia. Cortex 2005;764–777.
44. Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centered on the left anterior insula. Brain 2003;126:2406–2418.
45. Grossman M, McMillan C, Moore P, et al. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain 2004;127:628–649.
46. Eslinger PJ, Dennis K, Moore P, Antani S, Hauck R, Grossman M. Metacognitive deficits in frontotemporal dementia JNNP 2005;76:1630–1635.
47. Comrey AI. Common methodological problems in factor analytic studies. J Consult Clin Psychol 1978;46:648–559.