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Relationship between positive and negative symptoms and neuropsychological scores in frontotemporal dementia and Alzheimer's disease

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Abstract

Patients with dementia, particularly those with frontotemporal dementia (FTD), are reported to display marked negative symptoms, including apathy, lack of initiative, and flattened affect, similar to those observed in schizophrenic patients. However, negative symptoms have yet to be formally quantified in an FTD population. Twenty-seven patients with FTD (11 primarily right-sided, 8 primarily left-sided, and 4 symmetric) and 7 patients with Alzheimer's disease were rated on the Scale for the Assessment of Negative Symptoms, the Positive and Negative Syndrome Scale, and the Emotional Blunting scale. The FTD patients registered significantly more negative symptoms than the Alzheimer's patients, averaging a threefold increase; groups did not significantly differ in positive symptoms. Negative symptom scale scores were negatively correlated with nonverbal executive skills (23–44% shared variance), verbal executive skills (up to 25% shared variance) and verbal memory (up to 20% shared variance), but were unrelated to measures of attention, verbal and nonverbal information processing, nonverbal memory, language, and constructional skill. In contrast, positive symptoms were positively correlated with constructional skill (19% shared variance) and attentional scores (15% shared variance). These findings add to the existing literature relating negative symptoms to anterior cerebral hypofunction, and suggest that positive symptoms, at least in this population, may be tied to increased posterior activation. (*JINS*, 2003, *9*, 698–709.)

Keywords: Positive and negative symptoms, Frontotemporal dementia, Alzheimer's disease, Executive scores, Cognition

INTRODUCTION

Recent research into the neuropsychology of psychiatric disorders has begun to focus on the cognitive correlates of specific symptom clusters. For example, several studies have assessed the differential relationship between positive and negative symptoms and neuropsychological scores in schizophrenia. Most investigations suggest that positive symptoms (which can include hallucinations, delusions, conceptual disorganization, suspiciousness, hostility, grandiosity, and excitement; Kay et al., 1987), generally have no cognitive correlates (Basso et al., 1998; Bilder et al., 1985; Brekke et al., 1995; Capleton, 1996; Harvey et al., 1996; Howanitz et al., 2000; Johnstone & Frith, 1996; Liddle, 1987; Voruganti et al., 1997).

In contrast, numerous investigations have documented a consistent relationship between negative symptoms [as defined by alogia (poverty of speech and speech content), affective flattening, apathy, asociality, and attentional impairment (Andreasen, 1981)] and poor performance on cognitive tests (Basso et al., 1998; Bilder et al., 1985; Brekke et al., 1995; Harvey et al., 1996, Liddle, 1987), especially those involving frontal lobe/executive skills (Mattson et al., 1997; Scully et al., 1997), such as Trailmaking (Berman et al., 1997; Buchanan et al., 1994; O'Leary et al., 2000), Stroop (Brekke et al., 1995; Buchanan et al., 1994; Liddle

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et al., 1989; Liddle & Morris, 1991; Mattson et al., 1997), design fluency (Stolar et al., 1994), and Similarities (Liddle, 1987). In addition, some investigators have reported poorer performance on the Wisconsin Card Sorting Test (Basso et al., 1998; Bell et al., 1997; Berman et al., 1997; Capleton, 1996; Cuesta et al., 1995; Voruganti et al., 1997) and verbal fluency/word generation (Allen et al., 1993; Basso et al., 1998; Berman et al., 1997; Howanitz et al., 2000; Johnstone & Frith, 1996; Liddle et al., 1989; Liddle & Morris, 1991; Mattson et al., 1997; O'Leary et al., 2000; Robert et al., 1998; Stolar et al., 1994; Voruganti et al., 1997) in negative symptom patients, with other investigators failing to observe these associations (Buchanan et al., 1994; Liddle & Morris, 1991; Morrison-Stewart et al., 1992; Nopoulos et al., 1994; O'Leary et al., 2000).

While negative symptoms are typically discussed within the context of schizophrenia, it is recognized that this symptom cluster may also occur in other psychiatric and neurologic disorders. For example, negative symptoms have been quantified in Alzheimer's disease (Galynker et al., 1997, 2000; Reichman et al., 1996) and vascular dementia (Galynker et al., 1997). Specific negative symptoms, such as apathy, have been investigated in the context of depression (Krishnan et al., 1995; Lavretsky et al., 1999; Marin et al., 1994), HIV-1 infection (Castellon et al., 1998), stroke (Okada et al., 1997; Robinson, 1997; Starkstein et al., 1993), Parkinson's disease (Aarsland et al., 1999; Starkstein et al., 1992; Levy et al., 1998), various types of dementia (Craig et al., 1996; Haupt et al., 1998; Kuzis et al., 1999; Levy et al., 1996, 1998; Marin et al., 1994), right hemisphere stroke (Marin, 1991; Marin et al., 1994), head injury (Andersson et al., 1999; Kant et al., 1998), prefrontal brain insult ("pseudodepression" in Blumer & Benson, 1975), myotonic dystrophy (Rubinsztein et al., 1998) and Kluver-Bucy syndrome (Marin, 1991).

Patients with frontotemporal dementia, especially those with primarily right-sided as compared to relatively focal left-sided hypoperfusion on SPECT, have been reported to exhibit prominent behavioral abnormalities including disinhibition, flattened affect, psychosis, and social withdrawal (Miller et al., 1991, 1993). However, to date, no attempt has been made to quantify the behavioral/psychiatric changes in frontotemporal dementia groups in terms of standard measures of positive and negative symptoms and to compare these symptom ratings against those from other types of dementia, or to investigate whether the relationships between positive/negative symptoms and cognition identified in schizophrenic populations generalize to nonschizophrenic clinical samples.

The purpose of the present study is twofold: (1) to quantify the behavioral/psychiatric changes in subgroups of patients with frontotemporal dementia (primarily right-sided, primarily left-sided, and symmetric hypoperfusion) in terms of positive and negative symptoms and to determine whether the subgroups significantly differ from each other and from Alzheimer's patients on these symptoms, and (2) to assess whether the relationship between negative symptoms and neuropsychological (especially executive) scores documented in schizophrenic subjects are replicable in a dementia population.

METHODS

Research Participants

Subjects were 30 outpatients determined to have frontotemporal dementia (FTD; $n = 23$) or Alzheimer's disease ($n = 7$) by a behavioral neurologist with extensive experience in the diagnosis of these dementias (B.L.M.). These patients represented consecutive testable patients referred to the clinical practice of Dr. Miller from the southern California community over a 3-year period. All FTD patients met research criteria for FTD set by the Lund-Manchester Group (Brun et al., 1994), and all showed frontal-temporal hypoperfusion with sparing of parietal and occipital regions on single photon emission computed tomography (SPECT) brain studies on both 133Xenon and 99mTC-HMPAO scans. All Alzheimer's patients met criteria set forth by the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) and all showed bilateral temporal-parietal hypoperfusion with relative sparing of anterior regions on SPECT scans.

As previously described (Edwards-Lee et al., 1997), two clinicians blinded to clinical history rated FTD patient SPECT scans with regards to symmetry. Eight showed primarily left frontotemporal hypoperfusion (Left FTD), 11 showed primarily right-sided frontotemporal hypoperfusion (Right FTD), and four exhibited symmetric hypoperfusion (symmetric FTD).

Procedures

Positive and negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981), Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and the Emotional Blunting scale (EB; Abrams & Taylor, 1978). Ratings were made by a behavioral neurologist (B.L.M.) or psychiatrist with expertise in geriatric disorders (R.S.) and were made independently of the cognitive test results. Scores used for statistical analysis included the SANS total score and individual subscale scores (Alogia, Apathy/Avolition, Affective Flattening, Asociality/Anhedonia, and Attentional Impairment), EB scores, and the PANSS− and PANSS+ scores.

Patients were administered a comprehensive 4-hr neuropsychological battery including the WAIS–R (Satz-Mogel format except for Picture Arrangement which was administered in its entirety). The additional cognitive domains sampled, the tests used to assess the domains, and the specific test variables used for analysis, are detailed in Table 1. An attempt was made to administer Trails B and the color-interference trial of the Stroop Test (Stroop C), but very

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Table 1. Cognitive domains and associated tests

- Attention:
  - Verbal:
    - Digit Span scaled score from the WAIS–R[a]
- Information Processing Speed:
  - Verbal:
    - Stroop Test (Comalli version; Mitrushina et al., 1991; number of seconds to complete Parts A and B)[a]
  - Nonverbal:
    - Trailmaking (Lezak, 1995; number of seconds to complete Part A)[c]
    - Digit Symbol scaled score from the WAIS–R[a]
- Language:
  - Boston Naming Test (Kaplan et al., 1983; total correct out of 60)[a]
  - Vocabulary scaled score from the WAIS–R[a]
- Constructional Ability:
  - Rey-Osterrieth Complex Figure–copy trial (Lezak, 1995; total out of 36)[a]
  - Beery Developmental Test of Visual-Motor Integration—long form (Beery, 1997; total raw score out of 50)[c]
  - Block Design scaled score (raw score) on the WAIS–R[a]
- Memory
  - Verbal:
    - Logical Memory (LM) subtest of the Wechsler Memory Scale–Revised (WMS–R: Wechsler, 1987; raw score for delayed recall)[c]
    - Shopping List (Boone et al., 1999; raw scores for Trials 5 and 15-min delayed recall)[b]
  - Nonverbal:
    - Rey-Osterrieth Complex Figure–3 min delayed recall (Boone et al., 1993; total score out of 36)[a]
- Executive
  - Verbal:
    - Verbal Fluency–FAS (Lezak, 1995; total words summed across three trials)[a]
    - Verbal Fluency Animals (Gladsjo et al., 1999; total words generated in 1 min)[b]
    - Word Sequencing (Boone et al., in press; number of capture errors total possible of 10)[b]
    - Similarities scaled score from the WAIS–R[a]
    - Comprehension scaled score from the WAIS–R[a]
  - Nonverbal:
    - Design Fluency (Jones-Gotman & Milner, 1977; total designs generated in 5 min)[b]
    - Emotional Situations (Stuss & Benson, 1983; total errors)[c]
    - Wisconsin Card Sorting Test (WCST; Heaton et al., 1993; number of perseverative responses)[a]
    - Picture Arrangement scaled score from the WAIS–R[a]
    - Recency Memory Errors[c]

[a]Control group A ($n = 155$).
[b]Control group B ($n = 11$).
[c]Control group C ($n = 10$).

few FTD patients could complete these tasks, and as a result, these data could not be analyzed.

Three of the tests are either unpublished or not in wide usage and will be briefly described.

In the Recency Memory Test, patients are shown a series of color photographs of 10 common items on 5 × 7-inch index cards (dishes, TV, clock, umbrella, barbecue grill, guitars, football, camera, tent, luggage), presented at a rate of 3 s each, and are instructed to look at each picture carefully. Patients are then shown pairs of pictures for 20 trials in a standardized presentation, and asked to indicate which picture in the pair was shown before the other in the initial presentation. The score is number of errors out of a possible 20. Patients with right frontal lesions have been reported to show chance level performance in recency discrimination involving pictured stimuli (Milner, 1971).

The Emotional Situations Test consists of three pictures of facial expressions (happy/grinning, sad/crying, and neutral/no expression) and 10 scenes with either a negative emotional context (e.g., open coffin with body inside, lynched body hanging from tree, boy being scolded by mother), positive emotional context (e.g., clown, Christmas tree with presents, table with Thanksgiving meal, boy roasting dinner over an open fire), or neutral context (e.g., empty chair, boy standing by tree, man sitting in chair). Patients are instructed to "find the picture down here (three faces) which goes best with this picture (scenes)," with each scene presented in standard order, one at a time. Score is number of errors out of a possible 10. Patients with orbitofrontal pathology have been found to perform more poorly than controls on this task (Stuss & Benson, 1983).

The Word Sequencing Test (Boone et al., 2001), based on a similar task developed by Della Malva et al. (1993), involves 20 sentences. The individual words for each sentence are placed in front of the patient in a standard scrambled order. The patient is instructed to create a sentence using all the words. Performance is timed with a limit of 120 s per sentence. All of the scrambled sentences include embedded overlearned word pairs; for half the sentences these word pairs must be uncoupled to correctly arrange the sentence. "Capture errors" refer to failure to dissociate the overlearned word pairs. For the purposes of this study, only the 10 sentences involving capture errors were employed in the analyses. The score used for analysis was the number of capture errors out of a possible 10. Della Malva et al. (1993) reported that patients with left anterior lesions exhibited difficulty in word sequencing, particularly when the task involved uncoupling overlearned associations.

Not all scores were available for all patients due to the cooperation issues frequently encountered in a frontotemporal dementia population (Smeding & deKoning, 2000) and the fact that some tests were added to the battery after data collection had commenced.

Summary domain scores were generated by converting raw test scores into standard equivalents (i.e., *z* scores) using the test means and standard deviations from three archival control samples. Three control groups were necessary because no one group was administered all of the neuropsychological tasks employed in the current study. The controls had no history of neurologic illness, substance abuse, or major psychiatric disorder such as psychosis, major depres-

sion, or bipolar illness. Group A (n = 155; Boone, 1999) consisted of 53 men and 102 women and averaged 63.07 ± 9.29 years of age and 14.57 ± 2.55 years of education. Group B (n = 11; Boone et al., 1999) included 5 men and 6 women and averaged 60.36 ± 9.6 years of age and 14.82 ± 3.3 years of education. Group C (n =10) consisted of 2 men and 8 women who averaged 64.6 ± 11.68 years of age and 15.00 ± 3.57 years of education. Patient test scores were collapsed into nine summary scores by averaging each patients' z scores on tests assessing the same functional domain. To enhance the stability of z scores derived from control samples with small ns (i.e., Groups B and C), outliers (defined as subjects with performance exceeding ±2 SDs from group means) were excluded. This procedure resulted in the deletion of one subject each from z score calculations involving Shopping List delay, Rey-Osterrieth delay, and design fluency. The superscript letters in Table 1 indicate which control group was used to derive z scores.

RESULTS

Group Comparisons on Positive and Negative Symptoms

Table 2 contains the means and standard deviations or frequencies for the four patient groups for gender, age, education, IQ, and symptom scores.

As shown in the table, using a p value of .05 required for statistical significance, ANOVA comparisons revealed that the patient groups did not differ in educational level or age. In addition, no significant differences were observed in Full Scale IQ, indicating that the groups were generally comparable in dementia severity. For the remainder of the group comparisons, the p value required for statistical significance was lowered to .01 as an adjustment for the multiple comparisons.

Because of the unequal cell sizes, tests of homogeneity of variance for each of the nine symptom scale scores were computed. Results confirmed that population variances did not significantly differ.

As shown in Table 2, group comparisons on symptom scores revealed significant group differences on the Emotional Blunting, PANSS−, and the SANS Total, Flattened Affect, Apathy, and Asociality scales. Post-hoc analyses indicated that the left, right, and symmetric FTD patients scored significantly higher than the Alzheimer's patients on the EB, SANS Total, SANS Flattened Affect, and SANS Asociality scales; the right and symmetric FTD patients scored significantly higher than the Alzheimer's patients on the SANS Apathy scale; and the right FTD patients scored significantly higher than Alzheimer's patients on the PANSS− scale. The right, left, and symmetric FTD patients did not significantly differ from each other on any of the scales.

Means and standard deviations for the four patient groups on the various cognitive tasks are reproduced in Table 3. Group comparisons on the cognitive tests have been previously reported (Boone et al., 1999; Razani et al, 2001).

Correlations Between Positive and Negative Symptoms and Cognitive Scores

To reduce the large number of symptom scale variables, a principle components analysis (PCA), incorporating 8 variables (excluding SANS total), was computed on the combined patient groups. PCA extracted two components with eigenvalues greater than 1, representing a total of 84% of the variance. Using the criterion of .55 or greater as indicative of a substantial loading (reflecting a common variance between factor and variables of 30%), all scores except PANSS+ were observed to load on the first factor, and only the PANSS+ loaded on the second factor. The first factor

Table 2. Group comparisons on demographic variables and positive/negative symptom scales

	AD	Left	FTD symmetric	Right	F	df	p	W^2
n	7	8	4	11				
Age	66.4 ± 10.6	61.4 ± 9.9	62.8 ± 5.9	59.3 ± 11.0	.729	3,26	.544	
Education	16.0 ± 2.2	15.0 ± 4.5	13.8 ± 3.3	15.6 ± 2.2	.470	3,25	.706	
Gender	4 m/3 f	6 m/2 f	2 m/2 f	5 m/6 f				
Full Scale IQ	77.9 ± 13.7	78.2 ± 12.7	71.0 ± 16.8	85.4 ± 21.3	.758	3,24	.529	
Symptom scales								
Emotional Blunting	5.4 ± 3.7	18.4 ± 9.2	20.3 ± 10.2	24.0 ± 6.7	9.20	3,26	.0001	.451
SANS								
Total	28.7 ± 9.8	78.4 ± 35.7	91.3 ± 30.7	92.6 ± 27.9	8.41	3,26	.0001	.427
Alogia	8.1 ± 4.7	16.5 ± 8.1	15.3 ± 9.0	17.3 ± 7.3	2.54	3,26	.078	.134
Apathy	6.0 ± 3.4	12.5 ± 3.8	16.8 ± 4.6	14.7 ± 5.6	6.69	3,26	.002	.363
Asocial	5.4 ± 3.2	15.6 ± 7.4	20.0 ± 5.5	19.6 ± 5.4	10.12	3,26	.0001	.477
Attention	6.7 ± 3.3	9.9 ± 5.5	13.5 ± 1.7	13.6 ± 5.1	3.83	3,26	.021	.220
Flattened Affect	5.0 ± 5.0	22.8 ± 10.9	24.3 ± 11.5	27.2 ± 9.6	8.56	3,26	.0001	.431
PANSS−	16.0 ± 4.3	25.8 ± 8.4	25.5 ± 9.9	30.9 ± 9.0	4.85	3,26	.008	.278
PANSS+	10.4 ± 2.6	14.5 ± 4.6	12.5 ± 7.0	17.1 ± 5.2	2.96	3,26	.051	.164

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Table 3. Means and standard deviations on cognitive scores for the four patient groups

	AD	Left	FTD symmetric	Right
Verbal Attention				
Digit Span SS	5.43 ± 3.05	6.00 ± 2.61	6.75 ± 4.57	8.09 ± 3.81
Info Processing Speed				
Verbal				
Stroop A	78.33 ± 19.66	86.50 ± 27.95	84.33 ± 18.82	53.33 ± 9.47
Stroop B	138.20 ± 40.75	146.67 ± 42.60	156.00 ± 96.17	85.44 ± 24.24
Nonverbal				
Trails A	124.00 ± 99.72	92.33 ± 44.37	58.50 ± 12.02	73.80 ± 76.11
Digit Symbol	2.71 ± 1.70	3.86 ± 1.87	2.50 ± 1.73	4.36 ± 2.06
Language				
Boston Naming	42.00 ± 18.21	10.88 ± 18.83	27.25 ± 26.97	46.82 ± 9.54
Vocabulary	7.71 ± 5.82	2.67 ± 2.58	4.00 ± 3.83	8.73 ± 5.29
Constructional Ability				
Rey Figure copy	16.86 ± 9.80	28.75 ± 7.32	19.00 ± 15.90	25.00 ± 9.10
Beery	19.86 ± 7.20	30.88 ± 12.17	19.25 ± 12.31	31.27 ± 9.83
Block Design	3.14 ± 1.07	6.14 ± 2.85	4.00 ± 3.56	5.09 ± 2.34
Memory				
Verbal				
WMS–R LM II	2.71 ± 4.27	3.25 ± 5.83	0.75 ± 1.50	4.09 ± 6.43
Shopping List				
Trial 5	5.29 ± 3.20	3.63 ± 3.42	2.67 ± 2.52	4.82 ± 2.89
Delayed Recall	3.29 ± 3.95	1.50 ± 2.78	0.33 ± .58	2.91 ± 3.05
Nonverbal				
Rey figure delay	5.36 ± 4.32	6.06 ± 7.93	3.25 ± 2.75	4.68 ± 6.46
Executive				
Verbal				
FAS	17.71 ± 11.10	5.38 ± 6.80	6.25 ± 9.47	19.18 ± 16.97
Animals	7.57 ± 4.20	2.63 ± 3.82	1.50 ± 2.38	7.70 ± 5.23
Word Sequencing	3.40 ± 3.05	6.50 ± 4.68	9.00 ± 0	4.75 ± 3.33
Similarities	5.00 ± 5.97	3.17 ± 2.40	2.75 ± 2.06	5.55 ± 5.85
Comprehension	6.57 ± 5.53	3.33 ± 1.37	3.50 ± 1.73	5.64 ± 4.61
Nonverbal				
Design Fluency	9.57 ± 10.64	7.50 ± 6.97	1.00 ± 1.73	6.45 ± 9.70
Emotional Sit.	3.50 ± 1.76	5.88 ± 2.70	3.50 ± 1.92	3.73 ± 1.79
WCST (pers. resp.)	32.43 ± 22.40	16.40 ± 13.94	40.50 ± 24.75	47.25 ± 18.27
Picture Arrangement	4.86 ± 2.12	5.43 ± 2.15	3.25 ± 2.63	3.82 ± 2.04
Recency Memory	5.17 ± 2.56	5.50 ± 3.83	9.67 ± 0.58	5.00 ± 2.58

(negative symptoms) accounted for 71% of total score variance, while the second factor (positive symptoms) accounted for 13% of score variance.

Correlational analyses were computed between the two symptom factors and the composite cognitive domain scores. Negative symptoms were negatively related to nonverbal executive skills ($r = -.624$, $p = .006$), verbal executive skills ($r = -.415$, $p = .022$), and verbal memory ($r = -.397$, $p = .033$), while positive symptoms were positively related to attention ($r = .413$, $p = .029$), with trend level relationships observed with nonverbal speed ($r = .368$, $p = .07$) and constructional skill ($r = .321$, $p = .09$).

To assess whether unique relationships existed between specific symptom scales and cognitive performance, correlations between the symptom scales and the composite cognitive domain scores were examined. When significant relationships were detected, additional correlations were computed between the symptom scales and the individual tests included in the cognitive domain. In Table 4 are reproduced the summary cognitive domain scores and the individual tests that were significantly correlated with the symptom scales. As can be seen in the table, negative symptom scales were only related to nonverbal and verbal executive skills and verbal memory, while positive symptoms were positively related to visual constructional skill and attention. The significant correlations between cognitive domains and symptom scales did not significantly differ from each other ($p > .11$).

DISCUSSION

Comparison of patients with Alzheimer's disease *versus* patients with subtypes of FTD (primarily left-sided, primarily right-sided, and symmetric), revealed that the FTD patients

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Table 4. Listing of significant correlations for emotional blunting, SANS, and PANSS scales

SANS Total	SANS Apathy	SANS Alogia
Nonverbal Executive = −.630, p = .005 Recency Memory Errors = .523, p = .012 Picture Arrangement = −.463, p = .011 Design Fluency = −.379, p = .042	Nonverbal Executive = −.579, p = .012 Recency Memory Errors = .529, p = .011 Design Fluency = −.414, p = .026 Picture Arrangement = −.408, p = .028	Verbal Executive = −.501, p = .005 Capture Errors = .528, p = .017 Comprehension = −.466, p = .012 Similarities = −.434, p = .021
Verbal Executive = −.496, p = .005 Capture Errors = .538, p = .014 Animal Generation = −.392, p = .035 Comprehension = −.393, p = .038	Verbal Executive = −.373, p = .043 Capture Errors = .531, p = .016 Comprehension = −.431, p = .022	Nonverbal Executive = −.477, p = .045 Picture Arrangement = −.524, p = .004
Verbal Memory = −.436, p = .018 Word List Delayed = −.429, p = .020 Word List Trial 5 = −.399, p = .032		
SANS Asocial	**SANS Attention**	**SANS Flattened Affect**
Nonverbal Executive = −.565, p = .012 Recency Memory Errors = .432, p = .045	Nonverbal Executive = −.564, p = .015 Picture Arrangement = −.623, p = .0001 Recency Memory Errors = .482, p = .023	Nonverbal Executive = −.658, p = .003 Recency Memory Errors = .472, p = .027 Design Fluency = −.457, p = .013 Picture Arrangement = −.398, p = .033 Emotional Situations Errors =.373, p = .046
	Verbal Memory = −.430, p = .020 Word List Delayed = −.413, p = .026 Word List Trial 5 = −.410, p = .027	Verbal Executive = −.478, p = .007 Capture Errors = .571, p = .009 Animal Generation= −.402, p = .031
		Verbal Memory = −.414, p = .026 Word List Delay = −.398, p = .039 Word List Trial 5 = −.385, p = .032
Emotional Blunting	**PANSS+**	**PANSS−**
Nonverbal Executive = −.649, p = .004 Recency Memory Errors = .516, p = .014 Picture Arrangement = −.400, p = .031	Constructional Ability = .428, p = .021 Block Design = .440, p = .017 Beery = .427, p = .019 Rey Copy = .378, p = .040	Nonverbal Executive = −.669, p = .002 Recency Memory Errors = .567, p = .006 Design Fluency = −.463, p = .011 Picture Arrangement = −.462, p = .012
Verbal Executive = −.385, p = .035 Capture Errors = .540, p = .014	Verbal Attention = .392, p =.039	Verbal Memory = −.424, p = .022 Word List Delay = −.410, p = .027 Word List Trial 5 = −.391, p = .036
		Verbal Executive = −.411, p = .024 Capture Errors = .474, p = .035 Comprehension = −.433, p = .021 Animal Generation = −.396, p = .034 Similarities = −.394, p = .038

had significantly greater negative symptoms, but showed only a trend toward greater positive symptoms. Specifically, the three FTD subgroups all differed from Alzheimer's patients on the EB Scale and select SANS variables (Total, Asocial, Flattened Affect), although only the right and symmetric FTD patients scored significantly higher on the SANS Apathy subscale, and only the right FTD patients scored significantly higher on the PANSS− scale. The differences between FTD and Alzheimer's patients were robust despite the small sample sizes, with the FTD groups averaging three times the magnitude of negative symptoms found in Alzheimer's group. These findings, derived on patients with anterior cerebral disturbance as documented by SPECT hypoperfusion patterns, add to accumulating data indicating that negative symptoms are closely yoked to anterior brain dysfunction (Baare et al., 2000; Galynker et al., 2000; Gur et al., 2000; Kemali et al., 1987; Lewis et al., 1992; Mattson et al., 1997; Paulman et al., 1990; Wong

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et al., 1997), and perhaps right anterior disturbance in particular (Paulman et al., 1990; Stolar et al., 1994).

The three frontotemporal dementia groups did not significantly differ from each other on any of the negative or positive symptom scales, although this may have been an artifact of small sample sizes and reduced power to detect mild to moderate group differences. Visual inspection of the data revealed that in fact the right and symmetric FTD groups obtained scores on some negative symptom scales that were 30% higher than those seen in the left FTD groups.

Negative symptoms, as measured by the SANS, PANSS−, and EB Scales, were significantly correlated with nonverbal executive, verbal executive, and verbal memory scores. The nonverbal executive score accounted for between 23% and 44% of negative symptom scale score variance, while verbal executive performance accounted for up to 25% and verbal memory up to 20% of score variance. In contrast, no significant correlations were found between these symptom scales and the nonverbal memory, verbal attention, verbal and nonverbal processing speed, language, and constructional domains.

Previous research has shown that the nonverbal executive skills employed in this study are primarily related to right frontal lobe function, while the verbal executive tasks are predominantly tied to left frontal lobe function. Specifically, patients with right anterior dysfunction have been found to perform poorly on the Picture Arrangement subtest of the WAIS/WAIS–R (Boone et al., 1999; Goodglass & Kaplan, 1979; McFie, 1975; McFie & Thompson, 1972), design fluency (Boone et al., 1999; Jones-Gotman & Milner, 1977; Ruff et al., 1994), the Wisconsin Card Sorting Test (Boone et al., 1999; Robinson et al., 1980), and temporal memory involving visual stimuli (Milner, 1971). In addition, while no investigation has specifically addressed whether the Emotional Situations Test is differentially related to right or left frontal function, there is a large literature tying ability to process emotional information to the right hemisphere (Adolphs et al., 1996; Bobes et al., 2000; Mandal et al., 1999; Starkstein et al., 1994; Strauss & Moscovitch, 1981), and to right anterior function in particular (Muller et al., 1999; Nakamura et al., 1999).

In contrast, patients with left anterior disturbance have been reported to perform poorly on word generation (Baldo & Shimamura, 1998; Boone et al., 1999; Elfgren & Risberg, 1998; Elfgren et al., 1996; Milner, 1971; Stuss et al., 1998), and word sequencing (Boone et al., 1999; Della Malva et al., 1993; Kaczmarek, 1984), and to obtain mean scores below those of right frontal lesion patients on the Comprehension and Similarities IQ subtests (Reitan, 1964).

The fact that negative symptoms were related primarily to measures of executive function, especially nonverbal executive skills, adds further support that negative symptoms are tied to frontal lobe function, and perhaps, primarily right frontal lobe function. In addition, the evidence that verbal memory performance was correlated with some negative symptoms (i.e., alogia, flattened affect, attention) suggests that left frontotemporal functional systems involved in learning/memory (Chiaravalloti & Glosser, 2001; Daselaar et al., 2001; Golby et al., 2001; Ragland et al., 1997; Tomita et al., 1999) may have a relationship with these negative symptoms.

In support of the neuropsychological evidence that negative symptoms in our dementia patients appear to be associated with bilateral frontal and left temporal lobe integrity, Galynker et al. (2000) observed that negative symptoms were related to decreased bilateral dorsolateral prefrontal and left anterior temporal cortical perfusion in their sample of Alzheimer's patients. In addition, apathy in particular has been reported to be associated with decreased prefrontal and anterior temporal perfusion in Alzheimer's disease (Craig et al., 1996), while Okada et al. (1997) observed that stroke patients with apathy exhibited reduced perfusion in right dorsolateral frontal and left frontotemporal regions. Craig et al. (1996) hypothesized that the correlations between apathy and these various anterior regions suggest that neuronal networks rather than individual cortical areas are involved in personality traits of drive, initiative, and interest.

Analysis of the specific tests within each cognitive domain which correlated to the negative symptom scales revealed interesting and somewhat unexpected patterns. Within the nonverbal executive domain, negative symptoms were correlated with tests involving temporal memory (Recency Memory Test), visual sequencing (Picture Arrangement), and design fluency, and to a lesser extent, processing of emotional context (Emotional Situations Test), but not with the Wisconsin Card Sorting Test, despite evidence from other studies of a relationship between the Wisconsin Card Sorting Test and negative symptoms (Basso et al., 1998; Bell et al., 1997; Berman et al., 1997; Capleton, 1996; Cuesta et al., 1995; Voruganti et al., 1997). To insure that the lack of observed relationship between negative symptoms and the Wisconsin Card Sorting Test in the present study was not an artifact of the specific test score selected, correlations were computed between all Wisconsin Card Sorting Test scores and the negative symptom scales, and again, no significant correlations were observed.

Within the verbal executive domain, negative symptoms were related to the ability to dissociate overlearned word pairs (Word Sequencing Test), generate words within category (Verbal Fluency–Animals), verbalize "common sense" knowledge (Comprehension subtest), and, to a lesser extent, verbal abstraction (Similarities subtest). However, no significant relationships were found between negative symptoms and phonemic word generation (FAS), despite other research indicating an association between FAS and negative symptoms (Allen et al., 1993; Basso et al., 1998; Berman et al., 1997; Howanitz et al., 2000; Johnstone & Frith, 1996; Lewis et al., 1992; Liddle et al., 1989; Liddle & Morris, 1991; Mattson et al., 1997; O'Leary et al., 2000; Robert et al., 1998; Stolar et al., 1994; Voruganti et al., 1997).

It is possible that the small sample size in this study limited our ability to identify relationships between negative symptoms and WCST and FAS variables. However, the

fact that we did detect relationships between negative symptoms and other executive test scores suggests that these latter variables may be more sensitive to the presence of negative symptoms, at least in this population, than the concept formation/ability to shift set and phonemic generation required by the WCST and FAS, respectively.

There is considerable overlap in the cognitive correlates of the specific negative symptoms of apathy/avolition, alogia, asociality/anhedonia, decreased attention, and flattened affect, although slight variations emerged. Design generation was only related to apathy and flattened affect, and decreased animal name production was only related to flattened affect. Similarly, Stolar et al. (1994) reported that affective flattening in schizophrenic patients is related to generation, especially design production as compared to verbal fluency. The relationship between decreased generation, apathy, and flattened affect found in the present study may reflect a deficit in initiation common to all of these variables. In addition, the fact that these generation tasks related to apathy and/or flattened affect appears to indicate that these negative symptoms are tied to deficits in spontaneous flexibility (i.e., ability to generate a diversity of responses; Eslinger & Grattan, 1993), rather than the reactive flexibility/veridical decision making (i.e., the ability of shift behavior in response to environmental demands), required by such tests as the Wisconsin Card Sorting Test (Eslinger & Grattan, 1993; Goldberg & Podell, 2000). Errors on the Emotional Situations Test were only tied to flattened affect, suggesting that the ability to understand/process emotional information and to express emotion is intimately related. Performance on the Similarities subtest was only related to alogia; a similar relationship has been documented in schizophrenic patients with Similarities performance related to poverty of speech but not blunting of affect (Liddle, 1987). The fact that more unique relationships were not documented between the various symptoms subscales and specific cognitive tasks is no doubt reflective of the fact that the SANS subscales were highly intercorrelated [$r < .7$ except for alogia and apathy ($r = .558$) and alogia and asociality/anhedonia ($r = .642$)].

Of interest, significant positive relationships were documented between positive symptoms and the cognitive domains of constructional ability (Block Design subtest, Rey-Osterrieth copy, and Beery Developmental Test of Visual Motor Integration) and attention (Digit Span subtest). This finding was unexpected given the relatively large literature showing little relationship between cognitive scores and positive symptoms in schizophrenic populations (Basso et al., 1998; Bilder et al., 1985; Brekke et al., 1995; Capleton, 1996; Harvey et al., 1996; Howanitz et al., 2000; Johnstone & Frith, 1996; Liddle, 1987; Voruganti et al., 1997). However, of note, O'Leary et al. (2000) found an isolated positive relationship between constructional memory and positive symptoms in a large sample of schizophrenic patients.

Constructional ability has been consistently reported to be tied to right posterior function (Heilman & Valenstein, 1985). Attention, as measured by Digit Span, is less closely yoked to specific brain regions, but has been reported to be associated with both frontal and parietal function (Collette et al., 1997). The positive association between positive symptoms and constructional skill and attention could suggest that positive symptoms are associated with brain overactivation, particularly in posterior areas, as posited by Buchsbaum et al. (1984) and Ingvar and Franzen (1974), in contrast to the anterior cerebral underactivation found in negative symptoms. Of note, Epstein et al. (1999), using PET data, documented decreased prefrontal activity but increased mesotemporal and ventral striatal activity in patients with hallucinations and delusions. Similarly, Paulman et al. (1990) observed that the number of positive symptoms in their sample of schizophrenic patients was associated with decreased frontal and temporal perfusion, but increased whole brain rCBF. They conclude that "increased hemisphere CBF with bilaterally decreased frontal/temporal rCBF ratios suggests that some brain regions may be overactive and others are underactive." They further postulate that "frontal lobe hypoactivity may result in dysregulation of this region's normal control over mesocortical and posterior cortical sensory-processing sites, leading to subsequent overactivation of these regions" (p. 393). In support of this hypothesis, we have recently reported that patients with FTD frequently show increased artistic talent following diagnosis (Miller et al., 1998), suggesting that the anterior degeneration disrupts inhibitory controls over, and enhances function of, posterior areas, including the right parietal areas necessary for visual constructional ability.

Alternatively, it is possible that positive symptoms are overrepresented in patients with less marked and/or diffuse cognitive impairment, resulting in the significant positive relationship between constructional skill/attention and positive symptoms.

In conclusion, results from the present study contribute to an emerging literature quantifying the behavioral deficit in FTD, and add to current understanding regarding the relationship between positive and negative symptoms and cognition. However, there are several limitations to the current study.

First, given the small sample sizes and some missing data, the findings should be viewed as preliminary in nature. The reduced statistical power due to the small n's may have prevented the identification of additional group differences. As such, the current findings may be an underestimate of the behavioral differences between groups.

A second limitation of the study is that the correlations were computed on the patient sample as a whole, and as such the correlations reflect relationships between cognitive domains and negative/positive symptoms specific to a heterogenous dementia group. Unfortunately, the small n's precluded the computation of reliable and stable correlations within individual subgroups. Future research with larger samples is needed to document any unique relationships which may be present between positive/negative symptoms and cognition in differing types of dementia.

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Finally, it is also possible that the relationships found between the cognitive domains and symptom scales may be an artifact of how many tests were contained in the domains, with larger correlations a function of more tests. However, verbal attention, represented by only one measure (Digit Span) was significantly related to positive symptoms. Thus, the number of tests contained in the domains would not appear to be the primary factor in determining the significant associations.

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