Spontaneous Social Behaviors Discriminate Behavioral Dementias From Psychiatric Disorders and Other Dementias

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Objective: Changes in social behavior are often the first symptoms of neurodegenerative disease. Patients with frontotemporal lobar degeneration (FTLD) often go undiagnosed, or are misclassified as psychiatric patients, because in the absence of cognitive deficits, nonexperts fail to recognize these social changes as dementia symptoms. The object of this study was to improve screening for behavioral dementias in primary care and mental health settings by quantifying spontaneous social behaviors specific to FTLD.

Method: In a university hospital dementia clinic, examiners blind to subject diagnosis performed 1 hour of cognitive testing, then completed the Interpersonal Measure of Psychopathy, an 18-item checklist of observed inappropriate behaviors. Patients then underwent a multidisciplinary evaluation to derive a neurodegenerative or psychiatric diagnosis. Data were collected from 288 subjects: 45 Alzheimer's disease (National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association research criteria); 40 frontotemporal dementia, 21 semantic dementia, and 13 progressive nonfluent aphasia (Neary research criteria); 14 corticobasal degeneration and 21 progressive supranuclear palsy (Litvan research criteria); 37 dementia with Lewy bodies (McKeith research criteria); 16 vascular dementia (Ischemic Vascular Disease research criteria); 29 mixed vascular and Alzheimer's disease (Alzheimer's Disease Diagnostic and Treatment Centers criteria); and 35 primary psychiatric disorder (DSM-IV) patients and 17 normal older controls. The study was conducted from March 2002 to January 2005.

Results: Statistical item analyses demonstrated specific patterns of social behavior that differentiated both frontotemporal dementia and semantic dementia patients from (1) nondementing older adults, (2) nondementing individuals with psychiatric conditions, (3) individuals with cerebrovascular disease, and (4) individuals with other neurodegenerative disorders. Semantic dementia patients verbally and physically interrupted evaluations, spoke perseveratively and tangentially, and resisted clinician redirection. Frontotemporal dementia patients were apathetic or disinhibited and were unconcerned about meeting clinician expectations.

Conclusion: Specific, abnormal, interpersonal behaviors can alert nonexperts to the need for specialized dementia referral.

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An alarming 4.5 million people were diagnosed with Alzheimer's disease in the United States as of the year 2000,[1] and the number of individuals diagnosed with the disease is predicted to triple by 2050. Alzheimer's disease is the most common and well-known subtype of dementia; however, it typically accounts for only 50% to 70% of dementia cases, while the rest can be attributed to other neurodegenerative diseases such as vascular dementia, frontotemporal lobar degeneration (FTLD), corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies. As distinct treatment regimens develop for each of these dementias, it becomes increasingly imperative that they are recognized early and are referred to dementia specialists for specialized treatment and inclusion in clinical trials.

Diseases such as progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies characteristically have early motor signs that accompany any cognitive or behavioral symptoms, and which can serve as a red flag to primary care clinicians to initiate a neurologic referral.[2–4] Similarly, variants of FTLD such as the left-temporal predominant type of semantic dementia and progressive nonfluent aphasia cause easily-observed speech and language deficits that can signal the need for specialty referral.[5] However, patients with 2 subtypes of FTLD, specifically the frontotemporal dementia subtype and patients with the right temporal predominant variety of semantic dementia, can present with

TAKE-HOME POINTS

- A significant subset of patients with dementia initially present with aberrant social behavior in the context of completely normal cognition and motor skills.
- Patients in the early stages of frontotemporal lobar degeneration may demonstrate specific patterns of aberrant social behavior that can be observed during routine medical visits without specialized testing.
- Patients above the age of 40 years who interrupt and control the clinical interaction and are resistant to redirection, or who show no self-consciousness or concern about their failure to meet the clinician's expectations, may require referral to dementia specialists for further evaluation.

no appreciable motor, language, memory, or other cognitive symptoms[6,7] yet may already be experiencing severe frontal or temporal neurodegeneration. Because the only symptoms many of these patients display early in the disease process are altered personality and social behavior, they are frequently misdiagnosed as having a psychiatric condition,[8,9] or the disease is missed entirely by nonexperts who believe the patient is merely difficult or odd, but neurologically normal.[10] Misdiagnoses are even more likely because semantic dementia and frontotemporal dementia appear at a significantly younger age than classic dementias such as Alzheimer's disease and vascular dementia, with an average age at onset in the mid-60s and cases commonly beginning as early as the 30s and 40s.[11] Even when a neurodegenerative condition is suspected in an FTLD patient, it is often mistaken for Alzheimer's disease or vascular dementia.[9,12] As a result, physicians often fail to refer the patient to a specialty clinic, and may administer incorrect treatments. For example, the current standard pharmaceutical treatment of Alzheimer's disease and vascular dementia is an acetylcholinesterase inhibitor, but this treatment can often exacerbate FTLD symptoms rather than relieve them.[13] Particularly in managed care settings, primary care clinicians lack the time and resources needed to provide specialized dementia examinations for their patients, and they will not perform a separate dementia screen unless they already suspect there is a problem.[14,15] Alternatively, FTLD patients may first present in a mental health setting, where neurologic disease may be low on the diagnostic differential.

The magnitude and nature of FTLD behavior deficits, along with the fact that many of these patients are young and still have school-age children, combine to have a more devastating impact on family and caregivers than the burden caused by other dementias.[16] Early, accurate education about disease course and typical expected symptoms, as well as FTLD-specific support mechanisms for the caregiver, can significantly alleviate this burden, but only if the patient is properly diagnosed. Quick, simple, but sensitive mechanisms must be developed to allow mental health and primary care clinicians to screen for these behavioral dementias. We hypothesized that patients with different neurodegenerative diseases would spontaneously display objective social behavior deficits during routine clinical interactions. In particular, we hypothesized that the presence and pattern of unsolicited social behaviors would distinguish (1) frontotemporal dementia and semantic dementia patients from healthy older adults; (2) frontotemporal dementia and semantic dementia patients from patients with psychiatric features; (3) frontotemporal dementia and semantic dementia patients from patients with vascular dementia, who sometimes also exhibit inappropriate social behaviors and personality changes[17,18]; and (4) frontotemporal dementia and semantic dementia patients from patients with all other major dementias, including Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies.

METHOD

Participants

All subjects were recruited over a 3-year period after being referred to a university hospital neurology clinic specializing in neurodegenerative disorders. The study was conducted from March 2002 to January 2005. Two hundred eighty-eight patients (157 male, 131 female) were included in this study because they met established research criteria for one of 11 diagnoses. These groups included 45 Alzheimer's disease patients (meeting National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[19] research criteria); 40 frontotemporal dementia, 21 semantic dementia and 13 progressive nonfluent aphasia patients (meeting the Neary[5] research criteria for FTLD); 21 progressive supranuclear palsy patients (meeting Litvan[3] research criteria); 37 patients with dementia with Lewy bodies (meeting McKeith[4] research criteria); 16 vascular dementia patients (meeting Ischemic Vascular Disease research criteria[20]); 29 patients with mixed Alzheimer's disease and vascular disease (Alzheimer's Disease Diagnostic and Treatment Centers crite-

Table 1. Demographics and Summary Scores After 1 Hour of Cognitive Testing, Across All Diagnostic Groups

Characteristic	Overall Test Statistic	Overall p Value	Alzheimer's Disease (N = 45)	Frontotemporal Dementia (N = 40)	Semantic Dementia (N = 21)	Progressive Nonfluent Aphasia (N = 13)
Sex, male/female, N/N	$\chi^2 = 30.84$	.0006	22/23	29/11	14/7	1/12
Age, mean (± SD), y	F = 30.53[a]	< .0001	75 (9.5)*	59.7 (7.1)	65.9 (7.3)	64.8 (11.4)
Education, mean (± SD), y	F = 1.26	NS	15.5 (3.0)	16.4 (2.4)	16.3 (2.1)	16.1 (2.9)
MMSE score, mean (± SD)	F = 24.06[a]	< .0001	22.7 (3.6)*	24.3 (6.1)*	18.2 (8.1)*	24.9 (4.5)
IMP total score, mean (± SD)	F = 6.81	< .0001	19.2 (2.3)	22.1 (4.8)**	24.7 (6.2)***	18.4 (1.0)
IMP no. items checked, mean (± SD)	F = 4.49	< .0001	0.6 (1.4)	1.2 (1.9)	2.7 (2.4)***	0.0 (0.0)

[a]F and p values derived from Welch's analysis of variance statistic due to a positive Levine's test for inhomogeneous variances.
*p < .05 compared to normal controls (Dunnett's post hoc test).
**p < .05 compared to normal controls (Dunnett-Hsu post hoc test controlling for sex, age, and MMSE score).
***p < .01 compared to normal controls (Dunnett-Hsu post hoc test controlling for sex, age, and MMSE score).
Abbreviations: AD/VD = mixed Alzheimer's disease and vascular disease, IMP = Interpersonal Measure of Psychopathy, MMSE = Mini-Mental State Examination, NS = not significant.

ria[20]); and 14 corticobasal degeneration patients (Litvan Criteria[21]). Patients were included in the psychiatric group (N = 35) if (1) the expert diagnostic team determined that no neurodegenerative disease was present to account for the patient's cognitive or behavior symptoms and (2) evaluation by a geriatric psychiatrist, a psychologist, or a neurologist determined that the patient had a current or past history of bipolar disorder, clinically significant current levels of anxiety or depression, psychotic features not associated with a dementia, or personality pathology consistent with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) Axis II disorder. However, patients with clinical paranoia may have been more likely to decline participation in the study, thus it is possible that they were underrepresented in the psychiatric disorder group compared to the initial clinic subject pool. Alzheimer's disease patients were included in the pure Alzheimer's disease group only if they met criteria for probable Alzheimer's disease and no other comorbid conditions were suspected to be present (e.g., psychiatric features, vascular disease, metabolic conditions). Though many Alzheimer's disease patients meeting these criteria were seen during the 3-year course of the study, only the first 45 eligible patients were included in order to limit the disparity between cell sizes across dementia groups. All other diagnostic groups included all eligible, consenting subjects available during the study period.

Normal control subjects (N = 17) were recruited from the San Francisco Bay Area, Calif., through advertisements in local newspapers and recruitment talks at local senior community centers. Interested individuals underwent telephone screening for a history of problems with their physical or psychiatric health or a substance abuse history. Information about their current medication status was obtained, and their fluency in English was verified at this time. Individuals were accepted only if they had an informant available who had close contact with the subject for more than 5 years and was willing to answer questions about the subject to corroborate their clinical history. Participants who passed the telephone screen then underwent a 1-hour neuropsychological evaluation, routine labs, and a brain magnetic resonance imaging (MRI) scan. Following this initial evaluation, a multidisciplinary team consisting of a neurologist, a neuropsychologist, and a nurse reviewed the data to determine if the patient met criteria to be a healthy control subject.

For inclusion as a healthy control subject for this study, subjects must have had a normal neurologic exam, a Clinical Dementia Rating Scale score = 0, a Mini-Mental State Examination (MMSE) score equal to or greater than 28/30, and delayed memory performance equal to or greater than the 25th percentile in both verbal and visuospatial domains.

This research was subject to approval by the University of California, San Francisco, Committee for Human Resources Independent Review Board. Because data were initially collected as part of a clinical evaluation, subjects' data were included only if they later signed a consent form stating that the collected data could be used for research purposes. In all cases, informed consent and assent were gained from both the patient and the primary caregiver.

Participants' ages ranged from 33 to 94 years, with a mean of 68.2 (SD = 11.9). The majority of the participants were white (87.1%), followed by Chinese (11%), Latino/Hispanic (7%), African American (6%), Japanese (4%), Filipino (3%), Asian Indian (3%), and unknown (2%). The mean level of education was 15.8 (SD = 2.8) years. The mean MMSE score across the patient groups was 23.2 (SD = 6.0), and MMSE scores ranged from 0 to 30 (Table 1).

Procedures

All patients presented to a neurology clinic at a university hospital to undergo clinical screening for dementia. Before they underwent neurologic examination or any diagnostic evaluation was performed, cognitive testers

Corticobasal Degeneration (N = 14)	Progressive Supranuclear Palsy (N = 21)	Dementia With Lewy Bodies (N = 37)	Vascular Dementia (N = 16)	AD/VD (N = 29)	Psychiatric Disorder (N = 35)	Patient Total (N = 271)	Normal Controls (N = 17)
6/8	14/7	27/10	7/9	16/13	15/20	151/120	6/11
62.4 (5.9)	68.6 (7.6)*	74.9 (7.7)*	74.6 (11.1)*	81.5 (5.6)*	56.5 (11.5)	68.7 (11.8)	60.7 (12.0)
14.1 (2.1)	16 (3.2)	16 (3.7)	14.5 (2.9)	15.4 (2.1)	16.3 (2.7)	15.8 (2.8)	16.4 (2.1)
19.6 (7.4)*	25.3 (4.2)	22.2 (6.3)*	23.5 (5.5)*	20.0 (6.0)*	28.6 (1.7)	23.2 (6.0)	29.3 (1.3)
18.5 (0.8)	18.9 (4.2)	18.9 (1.7)	20.1 (4.1)	20.0 (4.5)	18.9 (1.4)	20.0 (3.7)	18.8 (2.4)
0.1 (0.3)	0.2 (0.5)	0.5 (0.8)	0.9 (1.8)	1.0 (1.8)	0.3 (0.8)	0.8 (1.5)	0.6 (1.9)

blind to patient history performed 1 hour of testing with patients. These testers included clinical research assistants with a bachelor's degree but no graduate study (36%), psychology postdoctoral students (24%), neuroscientists (19%), or neuropsychologists (21%). Immediately after the conclusion of this cognitive testing session, examiners filled out the Interpersonal Measure of Psychopathy (IMP) behavior checklist (see "Measures") describing the patient. After the cognitive testing session, the patient immediately underwent a medical examination conducted by a neurology or psychiatry resident or fellow. This evaluation included a full clinical history as well as a neurologic examination, and family members and caregivers were asked to be present to provide corroboration and increase the reliability of information obtained about the patient. A nurse also interviewed family members and caregivers separately from the patient to obtain additional corroborative information and an assessment of the patient's functional status. After each of these examinations was performed, a clinical conference was held in order to make a diagnostic determination based on the neurologic examination, history and physical, cognitive testing, and functional evaluation as well as any existing medical records, computed tomography or MRI data, or laboratory values that may have been available. Clinicians at these diagnostic conferences included senior neurologists who specialize in neurodegenerative disease, geriatric psychiatrists, neuropsychologists, pharmacists, nurses, and neurology and neuropsychology fellows. The results of the IMP were not used as part of the diagnostic determination, though the cognitive data from the hour-long evaluation were used. If consensus was not reached about patient diagnosis at this time, additional laboratory work or a structural MRI scan was obtained within 1 month, after which another diagnostic conference was held. Patients were also typically seen at least once a year for clinical follow-up visits to monitor disease progression and reevaluate diagnosis. The potential for involvement in research was discussed with patients and their caregivers either at the end of their first evaluation day or during a follow-up visit at the clinic, at which time informed consent to use their data for research purposes was obtained and both the patient and his or her caregiver signed the consent form. All subjects from whom IMP data were initially collected, but who did not consent to involvement in research, were excluded from analysis.

Measures

Because dementia-related behavior change has been described as "acquired sociopathy,"[22] we wished to use an established behavior instrument designed to assess observed sociopathic behaviors. One factor analysis of sociopathy suggests that it can be divided into 2 factors, one corresponding to criminal behavior, and the other describing a tendency toward interpersonal coldness and lack of empathy that can lead to subtly inappropriate interpersonal behaviors.[23] The IMP[24] was initially developed with a forensic population and was designed to assess this second, "coldness," factor by operationalizing this construct to be represented by a list of objectively observed behaviors. We chose to use a behavioral checklist instead of a subjective assessment of sociopathy, which could vary significantly depending on the rapport between the patient and the evaluator. We were particularly interested in determining if a brief clinical interaction would be adequate time to observe objective behaviors that would significantly correspond with real-life sociopathy, particularly in cases in which the clinician had never met the patient and had no previous knowledge of his or her typical social behavior.

The IMP (version 1) contains 18 items on which raters are asked to identify the degree to which a behavior typified the patient (1 = not at all, 2 = somewhat, 3 = very well, 4 = perfectly), e.g., "ignores professional boundaries." In addition to the primary items, the IMP also has 32 checklist behaviors that could be endorsed if the patient engaged in them at any time during the assessment period (e.g., "touched interviewer"), which are scored in a

Table 2. Interpersonal Measure of Psychopathy (IMP) Behavioral Descriptor Ratings (Mean [SD]) Across Collapsed Diagnostic Groups

IMP Descriptor	Semantic Dementia (N = 21)	Frontotemporal Dementia (N = 40)	Any Vascular[f] (N = 45)	Psychiatric Disorder (N = 35)	Other Dementia[g] (N = 130)	Normal Controls (N = 17)	Overall F Value[h]	p Value
1 Interrupts	1.9 (0.9)[a,b,c,d]	1.4 (0.6)[d]	1.3 (0.8)	1.1 (0.3)	1.1 (0.4)	1.1 (0.2)	6.60	< .0001
2 Refuses to tolerate interruption	1.6 (1.0)[a,b,c,d,e]	1.2 (0.5)[d]	1.1 (0.3)	1.0 (0.0)	1.0 (0.2)	1.1 (0.2)	9.61	< .0001
3 Ignores professional boundaries	1.2 (0.6)	1.3 (0.8)[b,d]	1.1 (0.3)	1.0 (0.0)	1.0 (0.2)	1.0 (0.0)	3.81	.0024
4 Ignores personal boundaries	1.4 (1.0)[d]	1.4 (0.8)[b,c,d]	1.1 (0.4)	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)	5.76	< .0001
5 Tests examiner	1.0 (0.0)	1.1 (0.3)	1.0 (0.3)	1.0 (0.0)	1.0 (0.2)	1.0 (0.0)	0.66	NS
6 Makes personal comments	1.2 (0.5)	1.3 (0.7)[d]	1.2 (0.5)	1.1 (0.3)	1.1 (0.3)	1.0 (0.0)	2.77	.0186
7 Makes requests of examiner	1.2 (0.7)	1.2 (0.5)	1.1 (0.5)	1.1 (0.2)	1.0 (0.2)	1.0 (0.0)	1.55	NS
8 Tends to be tangential	2.1 (1.1)[a,b,c,d,e]	1.3 (0.5)	1.3 (0.7)	1.2 (0.4)	1.1 (0.5)	1.2 (0.7)	8.02	< .0001
9 Fills in dead space	1.7 (1.0)[a,b,c,d,e]	1.3 (0.5)	1.1 (0.4)	1.1 (0.3)	1.1 (0.2)	1.2 (0.7)	7.11	< .0001
10 Exhibits unusual calmness or ease	1.4 (0.8)[b,d]	1.5 (0.8)[a,b,c,d]	1.0 (0.1)	1.0 (0.0)	1.1 (0.3)	1.1 (0.2)	7.81	< .0001
11 Becomes frustrated with argument avoidance	1.2 (0.7)[d]	1.1 (0.2)	1.0 (0.2)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	2.40	.0374
12 Perseverates	1.9 (1.0)[a,d]	1.5 (0.9)[a,d]	1.4 (0.8)	1.1 (0.3)	1.1 (0.4)	1.0 (0.0)	7.35	< .0001
13 Expresses ethical superiority	1.0 (0.0)	1.0 (0.2)	1.0 (0.0)	1.0 (0.0)	1.0 (0.1)	1.0 (0.0)	0.49	NS
14 Expresses narcissism	1.3 (0.8)[c,d]	1.3 (0.6)[d]	1.1 (0.3)	1.0 (0.2)	1.0 (0.1)	1.2 (0.6)	5.29	.0001
15 Incorporates examiner into personal stories	1.1 (0.3)	1.1 (0.2)	1.1 (0.4)	1.0 (0.2)	1.0 (0.0)	1.0 (0.0)	1.25	NS
16 Seeks alliance with examiner	1.1 (0.3)	1.2 (0.5)[d]	1.1 (0.3)	1.1 (0.3)	1.0 (0.2)	1.0 (0.0)	2.78	.0182
17 Displays showmanship	1.1 (0.5)	1.1 (0.4)	1.0 (0.0)	1.0 (0.2)	1.0 (0.1)	1.0 (0.0)	1.72	NS
18 Is angry	1.2 (0.7)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)	1.0 (0.0)	0.49	NS
IMP descriptor total	24.7 (6.2)[a,b,c,d]	22.1 (4.8)[a,b,c,d]	20.0 (4.0)	18.9 (1.4)	18.9 (1.9)	18.8 (2.4)	13.87	<.0001

[a]Significantly different from the normal control group ($p < .05$ Tukey-Kramer post hoc test).
[b]Significantly different from the psychiatric disorder group ($p < .05$ Tukey-Kramer post hoc test).
[c]Significantly different from the any vascular group ($p < .05$ Tukey-Kramer post hoc test).
[d]Significantly different from the other dementia group ($p < .05$ Tukey-Kramer post hoc test).
[e]Significantly different from the frontotemporal dementia group ($p < .05$ Tukey-Kramer post hoc test).
[f]Any vascular = vascular dementia and mixed Alzheimer's disease and vascular disease.
[g]Other dementia = Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies.
[h]Omnibus F statistic for effect of diagnosis across all 6 groups, controlling for age, sex, and MMSE score.
Abbreviations: MMSE = Mini-Mental State Examination, NS = not significant.

binary manner (0 = no, 1 = yes). All items can be seen in Tables 2 and 3.

RESULTS

IMP Summary Scores

Interpersonal Measure of Psychopathy total scores ranged from 18 to 40, with a mean of 19.9 (SD = 3.7) for all patients and controls combined; and IMP total items checked scores ranged from 0 to 8, with a mean of 0.8 (SD = 1.6) (Table 1). These low numbers suggest that across the whole sample, the behaviors assessed by the IMP were not frequently endorsed. Data analysis was performed using a GLM procedure in SAS (SAS Institute Inc., Cary, N.C.) to derive analysis of covariance statistics, controlling for sex, age, and MMSE total score. Patients diagnosed with frontotemporal dementia (mean ± SD IMP total score = 22.1 ± 4.8, $p < .05$) and semantic dementia (24.7 ± 6.2, $p < .01$) had significantly more item endorsements than normal control subjects (18.8 ± 2.4) using a Dunnett-Hsu test, controlling for age, sex, and MMSE score, for post hoc comparisons. Only semantic dementia patients showed significantly higher numbers of IMP items checked (2.7 ± 2.4) compared to the normal control group (0.6 ± 1.9) at $p < .01$.

IMP Item Analysis

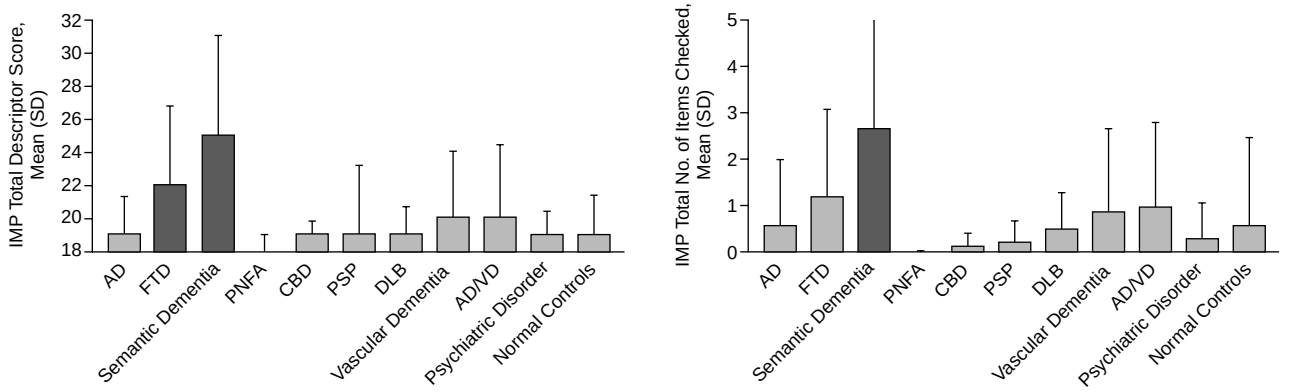
Patient groups were collapsed for the item analysis to answer the questions posed by the 4 group-comparison hypotheses. The third and fourth highest levels of total item endorsement were in the vascular and the mixed vascular/Alzheimer's groups, so these were collapsed together into an "any vascular" group. Patients in the psychiatric disorder group were kept as a separate group for analysis. The other dementia groups (Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, dementia with Lewy bodies) were collapsed into an "other dementia" group. The semantic dementia, frontotemporal dementia, psychiatric disorder, any vascular, other dementia, and normal control groups were then compared to determine if there were significant differences in item endorsement by clinicians. For the 18 descriptor items, SAS GLM procedures controlling for age, sex, and MMSE score were followed by post hoc Tukey-Kramer tests to compare the 6 groups, and a $p < .05$ level of significance was accepted.

Table 3. Percentage of Each Diagnostic Category Exhibiting Interpersonal Measure of Psychopathy (IMP) Behavior Checklist Items

IMP Checklist Item	Semantic Dementia (N = 21), %	Frontotemporal Dementia (N = 40), %	Psychiatric Disorder (N = 35), %	Any Vascular[f] (N = 45), %	Other Dementia[g] (N = 130), %	Normal Controls (N = 17), %	Overall Fisher Exact p Value
1A Interrupted exam	47.6[a,b,c,d]	10.0	2.9	15.6	11.5	5.9	< .0001
1B Interrupted examiner	28.6[b,c,d]	17.5[b,d]	0.0	6.7[d]	0.8	5.9	< .0001
3A Called examiner by first name	0.0	5.0	0.0	0.0	1.5	0.0	.0233
3B Asked for something examiner had in their possession	0.0	2.5	0.0	0.0	0.0	0.0	NS
4A Touched examiner	14.3[d]	7.5[d]	2.9	4.4[d]	0.0	0.0	< .0001
4B Leaned very far forward	4.8	7.5[d]	0.0	4.4	0.8	5.9	< .0001
5A Asked about examiner's credentials	0.0	2.5	0.0	2.2	2.3	0.0	.0404
5B Asked examiner general psychology or other questions	0.0	0.0	2.9	0.0	0.8	0.0	NS
5C Asked to see identification	0.0	2.5	0.0	0.0	0.0	0.0	NS
6A Insulted examiner's dress or manner	0.0	5.0	0.0	0.0	0.8	0.0	.0257
6B Commented on examiner's dress or manner	4.8	7.5	5.7	11.1[d]	2.3	0.0	< .0001
8A Provided very lengthy answers	28.6[b,d]	7.5	5.7	11.1	6.2	5.9	< .0001
8B Changed answer in middle of explanation	23.8[a,b,c,d]	2.5	2.9	6.7	2.3	0.0	< .0001
10A Put feet up	4.8	0.0	0.0	0.0	0.0	0.0	NS
10B Stretched often	0.0	0.0	0.0	0.0	0.8	5.9	NS
10C Moved about the room	9.5[c,d]	7.5[d]	0.0	0.0	0.0[a]	5.9	< .0001
11A Repeatedly tried to begin an argument with examiner	0.0	2.5	0.0	4.4[d]	0.0	0.0	.0101
11B Became angry or frustrated when examiner agreed with subject	0.0	0.0	0.0	0.0	0.0	0.0	…
12A Returned often to one event	28.6[a,b,c,d]	2.5	2.9	4.4	2.3	0.0	< .0001
12B Returned often to one theme (eg, winning, intelligence)	19.1[b,d]	5.0	2.9	15.6[d]	2.3	0.0	< .0001
13A Expressed overt desire to help others	0.0	2.5	0.0	2.2	0.0	0.0	.0436
13B Made references to own truthfulness	0.0	0.0	0.0	0.0	0.0	0.0	…
13C Indicated that others are "not as good" as subject is	0.0	0.0	0.0	0.0	0.8	0.0	NS
14A Expressed personal superiority	4.8[d]	2.5	0.0	2.2	0.0[a]	5.9	.0023
14B Displayed grandiosity	4.8[d]	2.5	0.0[a]	2.2	0.0[a]	11.8	< .0001
14C Discussed personal uniqueness	19.1[c,d]	7.5[d]	5.7[d]	0.0[a]	0.0[a]	11.8	< .0001
16A Excessive smiling	4.8	2.5	0.0	0.0	0.8	0.0	.0278
16B Verbal expression of communality	4.8	0.0	0.0	2.2	0.8	0.0	.0313
16C Sought interviewer's agreement of subject's views	0.0	2.5	0.0	2.2	0.0	0.0	.0439
17A Displayed large gestures	4.8[d]	2.5	0.0	0.0	0.0	0.0	.0205
17B Used voice inflection to emphasize points	4.8[d]	2.5	0.0	0.0	0.0	0.0	.0205
17C Used dramatic language	4.8[d]	2.5	0.0	0.0	0.0	0.0	.0205
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
IMP total no. checked	2.7 (2.4)[a,b,c,d,e]	1.2 (1.9)[d]	0.3 (0.8)	1.0 (1.8)	0.4 (1.0)	0.6 (1.8)	< .0001

[a]Significantly different from the normal control group ($p < .05$).
[b]Significantly different from the psychiatric disorder group ($p < .05$).
[c]Significantly different from the any vascular group ($p < .05$).
[d]Significantly different from the other dementia group ($p < .05$).
[e]Significantly different from the frontotemporal dementia group ($p < .05$).
[f]Any vascular = vascular dementia and mixed Alzheimer's disease and vascular disease.
[g]Other dementia = Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies.
Abbreviation: NS = not significant.
Symbol: … = not applicable.

Figure 1. Clinician Ratings of Collapsed Patient Groups on Interpersonal Measure of Psychopathy (IMP) Descriptor Item Total Score and Number of IMP Checklist Items Endorsed[a]



[a]Patient groups showing significantly higher rates of a behavior compared to normal controls are marked with black bars; groups with no significant difference from normal controls are marked with grey bars.
Abbreviations: AD = Alzheimer's disease, AD/VD = mixed Alzheimer's disease and vascular disease, CBD = corticobasal degeneration, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, PNFA = progressive nonfluent aphasia, PSP = progressive supranuclear palsy.

The descriptor item results can be found in Table 2 and in Figures 1 and 2. Checklist items were scored as yes-no items, and the frequency with which they were endorsed by clinicians across the 6 groups was analyzed using a Fisher exact test. The checklist item results are in Table 3 and in Figure 1.

Hypothesis 1: Frontotemporal dementia and semantic dementia vs. normal control subjects. Both frontotemporal dementia and semantic dementia groups had significantly higher clinician ratings than normal controls on the descriptor "perseverates," but no checklist items significantly differentiated both groups from controls.

Semantic dementia patients also differed from the normal control group by demonstrating significantly higher levels of clinician endorsement of the descriptors "interrupts," "refuses to tolerate interruption," "tends to be tangential," and "fills in dead space." Compared to controls, the semantic dementia group was also significantly more likely to spontaneously engage in the checklist behaviors, "interrupted exam" (48% of semantic dementia patients, compared to 6% of normal controls), "changed answer in middle of explanation" (semantic dementia = 24%; normal controls = 0%), and "returned often to one event" (semantic dementia = 29%; normal controls = 0%).

Frontotemporal dementia subjects rated higher than normal control subjects on the descriptor, "exhibits unusual calmness or ease"; however, frontotemporal dementia subjects did not significantly differ from normal controls on frequency of endorsement of any checklist items.

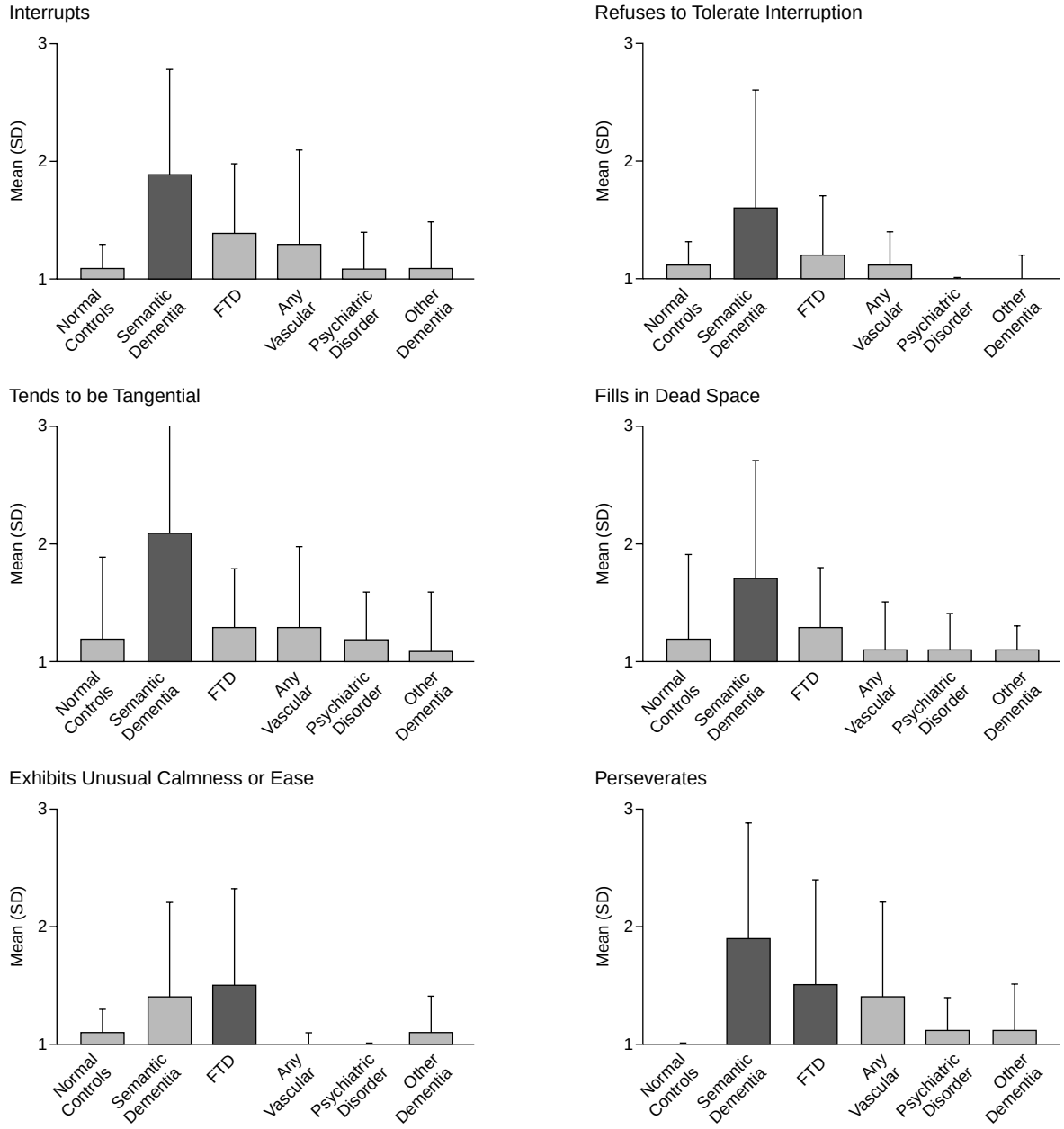
Hypothesis 2: Frontotemporal dementia and semantic dementia vs. psychiatric disorder subjects. Clinicians rated both frontotemporal dementia and semantic dementia subjects as significantly higher than psychiatric disorder subjects on the descriptor, "exhibits unusual calmness or ease." Both frontotemporal dementia and semantic dementia subjects were also significantly more likely to engage in the checklist behavior, "interrupted examiner" (semantic dementia = 29%; frontotemporal dementia = 18%; psychiatric disorder = 0%).

Semantic dementia subjects also were rated significantly higher than psychiatric disorder subjects on the descriptors, "interrupts," "refuses to tolerate interruption," "tends to be tangential," and "fills in dead space." Semantic dementia subjects were more likely than psychiatric disorder subjects to engage in the checklist behaviors, "interrupted exam" (semantic dementia = 48%; psychiatric disorder = 3%), "provided very lengthy answers" (semantic dementia = 29%; psychiatric disorder = 6%), "changed answer in middle of explanation" (semantic dementia = 24%; psychiatric disorder = 3%), "returned often to one event" (semantic dementia = 29%; psychiatric disorder = 3%), and "returned often to one theme" (semantic dementia = 19%; psychiatric disorder = 3%).

Frontotemporal dementia subjects were significantly more likely than psychiatric disorder subjects to cause clinicians to endorse the descriptors, "ignores professional boundaries" and "ignores personal boundaries." No additional checklist items differentiated frontotemporal dementia and psychiatric disorder subjects.

Hypothesis 3: Frontotemporal dementia and semantic dementia vs. any vascular subjects. No single IMP item successfully differentiated both the semantic dementia and frontotemporal dementia groups from the any vascular group.

Figure 2. Clinician Ratings of Collapsed Patient Groups on 6 Interpersonal Measure of Psychopathy (IMP) Descriptor Items[a,b]



[a]Patient groups showing significantly higher rates of a behavior compared to normal controls are marked with black bars; groups with no significant difference from normal controls are marked with grey bars.
[b]The other dementia group includes Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies. The any vascular group includes vascular dementia and mixed Alzheimer's disease and vascular disease.
Abbreviation: FTD = frontotemporal dementia.

However, semantic dementia subjects scored higher than those in the any vascular group on the descriptor items, "interrupts," "refuses to tolerate interruption," "tends to be tangential," "fills in dead space," and "expresses narcissism." Additionally, the semantic dementia group was significantly more likely to spontaneously engage in the checklist behaviors, "interrupted exam" (semantic dementia = 48%; any vascular = 16%), "interrupted examiner" (semantic dementia = 29%; any vascular = 7%), "changed answer in middle of explanation" (semantic dementia = 24%; any vascular = 7%), "moved about the room" (semantic dementia = 10%; any vascular = 0%), "returned often to one event" (semantic dementia = 29%; any vascular = 4%), and "discussed

personal uniqueness" (semantic dementia = 19%; any vascular = 0%).

Frontotemporal dementia subjects had significantly higher endorsement rates of the descriptors, "ignores personal boundaries" and "exhibits unusual calmness or ease" than any vascular subjects. However, the frontotemporal dementia group did not differ significantly from the any vascular group on any checklist items.

Hypothesis 4: Frontotemporal dementia and semantic dementia vs. other dementia subjects. The IMP showed the greatest discriminative power when differentiating the behavior of frontotemporal dementia and semantic dementia subjects from subjects with nonvascular dementias (Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies). Both semantic dementia and frontotemporal dementia subjects showed significantly higher rates of clinician endorsement of many descriptors, including "interrupts," "refuses to tolerate interruption," "ignores personal boundaries," "exhibits unusual calmness or ease," "perseverates," and "expresses narcissism." Both frontotemporal dementia and semantic dementia subjects were more likely than other dementia subjects to have a clinician endorse the checklist items, "interrupted examiner" (semantic dementia = 29%; frontotemporal dementia = 18%; other dementia = 1%), "touched examiner" (semantic dementia = 14%; frontotemporal dementia = 8%; other dementia =0%), "moved about the room" (semantic dementia = 10%; frontotemporal dementia = 8%; other dementia = 0%), and "discussed personal uniqueness" (semantic dementia = 19%; frontotemporal dementia = 8%; other dementia = 0%).

In addition, semantic dementia subjects showed significantly higher ratings than other dementia subjects on the descriptors, "tends to be tangential," "fills in dead space," and "becomes frustrated with argument avoidance." Compared to other dementia patients, the semantic dementia group was significantly more likely to spontaneously engage in the checklist behaviors, "interrupted exam" (semantic dementia = 48%; other dementia = 12%), "provided very lengthy answers" (semantic dementia = 29%; other dementia = 6%), "changed answer in middle of explanation" (semantic dementia = 24%; other dementia = 2%), "returned often to one event" (semantic dementia = 29%; other dementia = 2%), "returned often to one theme" (semantic dementia = 19%; other dementia = 2%), as well as low-frequency checklist behaviors such as "expressed personal superiority" (semantic dementia = 5%; other dementia = 0%), "displayed grandiosity" (semantic dementia = 5%; other dementia = 0%), "displayed large gestures" (semantic dementia = 5%; other dementia = 0%), "used voice inflection to emphasize points" (semantic dementia = 5%, other dementia = 0%), and "used dramatic language" (semantic dementia = 5%; other dementia = 0%).

Frontotemporal dementia subjects significantly differed from other dementia subjects by showing higher scores on the descriptors, "ignores professional boundaries," "makes personal comments," and "seeks alliance with examiner." The frontotemporal dementia patients also were more likely than other dementia patients to engage in the low-frequency checklist behavior, "very far forward" (frontotemporal dementia = 8%; other dementia = 1%).

Additional comparisons. Semantic dementia patients could also be significantly discriminated from frontotemporal dementia patients based on higher clinician endorsement of the descriptors, "refuses to tolerate interruption," "tends to be tangential," and "fills in dead space."

Psychiatric disorder patients were significantly less likely than normal controls to show the checklist behavior, "displayed grandiosity" (psychiatric disorder = 0%; normal control = 12%) but were more likely than other dementia patients to engage in the behavior, "discussed personal uniqueness" (psychiatric disorder = 6%; other dementia = 0%).

The any vascular group was significantly less likely than normal controls to engage in the checklist behavior, "discussed personal uniqueness" (any vascular = 0%; normal control = 12%). They were also more likely than the other dementia group to engage in the behaviors, "interrupted examiner" (any vascular = 7%; other dementia = 1%), "touched examiner" (any vascular = 4%; other dementia = 0%), "commented on examiner's dress or manner" (any vascular = 11%; other dementia = 2%), "repeatedly tried to begin an argument with examiner" (any vascular = 4%; other dementia = 0%), and "returned often to one theme" (any vascular = 16%; other dementia = 2%).

Other dementia patients were less likely than normal controls to engage in the checklist behaviors, "moved about the room" (other dementia = 0%; normal control = 6%), "expressed personal superiority" (other dementia = 0%; normal control = 6%), "displayed grandiosity" (other dementia = 0%; normal control = 12%), and "discussed personal uniqueness" (other dementia = 0%; normal control = 12%).

DISCUSSION

The primary finding of our study was that patients with frontotemporal dementia and semantic dementia spontaneously demonstrate specific social behaviors during clinical interactions that can be used to differentiate them from (1) nondementing older adults, (2) nondementing individuals with psychiatric conditions, (3) individuals with a dementing condition caused by vascular disease or a combination of vascular disease and Alzheimer's disease, and (4) individuals with other major dementias, including Alzheimer's disease, progressive nonfluent aphasia, pro-

gressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies. These behavioral features may be used by clinicians who do not specialize in atypical dementias to screen their patients for dementia specialty referral, increasing the chance of early and accurate differential diagnosis of dementias causing primarily behavioral symptoms. This study also found additional results that are more relevant to differential diagnosis in a specialized setting: (1) that certain social behaviors help discriminate frontotemporal dementia from the behavioral variant of semantic dementia and (2) specific behaviors may help identify the presence of vascular disease in patients with other, nonbehavioral dementias.

Behavioral Dementia as a New Paradigm

Dementia is classically considered to be a disorder of cognition. Recent challenges to this characterization have been posed by the atypical dementias but have been slow to reach the primary care and mental health clinicians who are the first to see these patients. While patients presenting with memory, language, or motor symptoms have a greater chance of being appropriately referred to a clinic specializing in dementia diagnosis and treatment, dementia is rarely part of the differential diagnosis for patients with a behavioral presentation in either primary care or mental health settings.

Behavior symptoms are central to the diagnosis of the frontotemporal dementia subtype of FTLD. Standard research criteria for frontotemporal dementia allow a diagnosis based on (1) insidious onset and gradual progression, (2) early decline in social interpersonal conduct, (3) early impairment in regulation of personal conduct, (4) early emotional blunting, and (5) early loss of insight.[5] This disease initially causes neuropathologic changes in the orbitofrontal cortex, the anterior cingulate, and the insula,[25] areas directly involved in social and emotional processing, but the dorsolateral frontal cortex remains unaffected until later. Thus, the frontal-executive cognitive symptoms that result from dorsolateral damage may not appear until years after disease onset, while florid social behavior symptoms will have already disrupted the patient's capacity to function in work, social, and family relationships.

The semantic dementia subtype of FTLD is primarily considered to be a language disorder, the hallmark of which is early neurodegeneration in the left anterior temporal lobe causing a loss of semantic meaning for words and everyday objects. However, as this disease has been more carefully characterized in recent years, it has become apparent that a large proportion of patients with this disease also have prominent behavior symptoms.[26–28] In addition to left temporal atrophy, the orbitofrontal cortex, anterior cingulate, and insula areas involved in emotional behavior are damaged early in semantic dementia, just as they are in frontotemporal dementia.[29] The majority of patients with left anterior temporal atrophy also eventually evidence neurodegeneration of the right temporal lobe and amygdala, areas which are directly responsible for social and emotional processing.[30–32] Making diagnosis even more difficult, this right temporal lobe damage occurs first in a subset of semantic dementia patients, so the left-sided damage that would normally cause telltale language symptoms is subtle or absent. Of all FTLD patients, it is this group of patients that is most likely to be misdiagnosed in primary care settings and referred for mental health treatment of their late-onset, bizarre personality and behavior changes. Dementia specialty clinics currently see more than 3 left-temporal predominant semantic dementia patients for every 1 that is right-temporal predominant,[33] and many experts suspect that this is partly due to a referral bias in which these patients are never recognized as having a dementia and instead undergo long-term psychiatric hospitalizations or live as deteriorating, treatment-resistant social recluses.

Our study found that when taken as a whole, the semantic dementia group demonstrated more dramatic and broad behavior changes even than the frontotemporal dementia group, which is consistent with other studies showing poorer emotion recognition[34] and more pervasive loss of empathy[27] in semantic dementia than in frontotemporal dementia. However, it is likely that the semantic dementia group's high IMP scores were generated by the subset of semantic dementia patients with right temporal damage, and the wide standard deviations seen in this group suggest that it included some patients, probably with left-temporal predominant disease, who did not show behavioral symptoms during this clinical visit.

Recognizing FTLD Behaviors as Abnormal

The first challenge of primary care and mental health clinicians is to recognize that a patient with a behavioral form of dementia is not simply an "odd" or "difficult" individual who is otherwise neurologically normal. Thus, our first goal was to differentiate frontotemporal dementia and semantic dementia patients' spontaneous behavior from what could be expected from healthy, nondementing older adults. Clinicians in our study were more likely to use the term "perseverates" to describe both FTLD subtypes, meaning that the patients tended to become fixated on one idea or stimulus and failed to allow the clinical interaction to proceed fluidly to the next idea. This trait was further elucidated by the comparison between controls and semantic dementia subjects, whose uniquely characteristic pattern of behaviors involved derailing the clinical examination process. Fully one half of semantic dementia patients in this study interrupted the clinician or the process of the examination itself, even to the point of standing up and attempting to leave the room prematurely. Approximately one quarter of them spoke

in a tangential, rambling manner that shifted to irrelevant topics, and they were more likely to resist the clinician's attempts to redirect them back to the exam. Semantic dementia subjects rated higher on both perseverative and tangential speech because they tended to repeatedly shift the discussion to 1 or 2 pet topics that were neither initiated by the clinician nor relevant to the exam, then insisted on completing their train of discourse, despite the clinician's protests that they have already heard about it. These same behaviors were seen in only 0% to 6% of control subjects, and, taken together, should be considered abnormal social behavior.

This pattern of behavior may be directly linked to the right temporal damage common to this dementia subtype. The implicit social expectation conveyed in the context of a medical or psychological evaluation assumes the clinician is "in charge" and will determine the course and pace of the interaction. The failure of such a large proportion of semantic dementia subjects to recognize this power differential and appropriately defer to this expectation, even when the clinician explicitly reminds them of it by openly interrupting the patient's perseverative or tangential thought process, demonstrates a loss of sensitivity to social signals. The right temporal lobe is involved in many aspects of basic social perception, ranging from identifying emotions in faces, voices, and gestures,[32,35,36] to higher social processes such as empathy.[37] The controlling, insensitive behavior of these semantic dementia subjects may be the practical manifestation of this breakdown of social cognition.

When compared to healthy aging controls, subjects with frontotemporal dementia did not demonstrate this particular set of abnormal social behaviors as a whole, though some patients did engage in 1 or 2 of these same behaviors. Though frontotemporal dementia subjects were described as perseverative, they were less likely than semantic dementia subjects to interrupt or be tangential. However, they were described as "exhibiting unusual calmness or ease." This behavior was initially included in the development of the IMP to measure the almost unnatural lack of anxiety seen in many developmental sociopaths. However, in this context, clinicians endorsing this symptom described a subset of frontotemporal dementia patients as qualitatively flat, unresponsive, and lacking normal initiative. Apathy is one of the primary clinical symptoms of frontotemporal dementia[38] and has been directly associated with the medial frontal damage characteristic of this disease.[39] Our study suggests that in a subset of cases, this apathy is observable in the course of a typical clinical interaction and may provide a red flag for referral. However, it is important for clinicians to note that apathy characterizes only one subset of frontotemporal dementia patients, while others with this diagnosis present with positive symptoms such as disinhibition, hyperkinesis, and logorrhea.

Distinguishing FTLD From a Psychiatric Condition

In everyday clinical practice, behavioral-predominant dementias are routinely mistaken for psychiatric disorders; however, our study suggests that FTLD patients' spontaneous behavior is very different from that of patients with psychiatric conditions. Our group of psychiatric patients was diverse and somewhat atypical, in that it was comprised of patients that presented to a memory clinic complaining of cognitive symptoms, which were subsequently determined to originate in a psychiatric disorder rather than a primary neurodegenerative condition. Diagnoses within this group included anxiety, bipolar and unipolar depression, psychotic disorders, and Axis II personality pathology. However, this group was rated by clinicians as seldom engaging in any of the behaviors measured by the IMP. They did not differ from controls on any descriptor items and were actually significantly less likely than controls to behave in a grandiose manner.

Semantic dementia and frontotemporal dementia patients differed from the psychiatric disorder group for many of the same reasons they differed from controls. The semantic dementia group's pattern of derailing the course of the clinical interaction, described above, also differentiated them from the psychiatric disorder group, who did not engage in this cluster of behaviors. Both semantic dementia and frontotemporal dementia subjects were also considered by clinicians to be significantly more likely than psychiatric disorder patients to "exhibit unusual calmness or ease." Paradoxically, frontotemporal dementia patients were also more likely than psychiatric disorder patients to ignore professional and personal boundaries, though these behaviors were probably seen in patients exhibiting the disinhibited rather than apathetic phenotype of frontotemporal dementia. These data highlight one of the primary clinical factors that distinguish FTLD from psychiatric disease. The core neuroanatomy of frontotemporal dementia and semantic dementia, in which orbitofrontal, anterior cingulate, and insular cortex are damaged, causes an early decrease in emotional reactivity and sensitivity, along with a loss of self-awareness and impression management. Whether they were apathetic or disinhibited, these patients were observed to be unfazed by the evaluative context of the cognitive exam, often not caring whether or not they made mistakes; they showed little emotional reactivity; and they did not show a tendency to "check in" with the examiner either verbally or via eye contact to obtain social feedback. In contrast, patients with psychiatric disorders were more likely to be anxious or self-critical, and often required reassurance and feedback from the examiner. Psychiatric disorder patients as a group made an appreciable effort to defer to the examiner, meet expectations, and remain task-focused, in a pattern of behavior opposite to that of the semantic dementia patients.

Is Cerebrovascular Disease a Behavioral Dementia?

Particularly in cases in which patients exhibit some cognitive symptoms such as memory loss or executive deficits, FTLD is misdiagnosed as vascular disease.[7] Both conditions eventually cause a frontally-predominant pattern of cognitive deficits, and both can cause behavioral impulsivity and poor social judgment. One of the most common forms of vascular disease in aging adults does not involve obvious focal strokes, but creates a pattern of leukoencephalopathy, or white matter disease, that interferes with frontal-subcortical circuits and effectively "disconnects" the frontal lobes.[40] Our study found that patients with clinically significant vascular disease, diagnosed alone or mixed with Alzheimer's disease pathology, were more likely than any other non-FTLD patient group to spontaneously exhibit problematic social behaviors during our clinical evaluations. These cerebrovascular patients' scores on IMP items were not significantly different from those of healthy aging control subjects. However, a subset of vascular dementia subjects was more likely than patients with other dementias (Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies) to engage in behaviors such as interrupting the examiner while they were speaking, touching the examiner, commenting on the examiner's dress or manner, attempting to argue with the examiner, or returning to the same theme in conversation (4%–16% of the group for each behavior).

Despite this increased base rate of behavioral irregularities in vascular patients, they could be discriminated from both semantic dementia and frontotemporal dementia patients on the basis of numerous behavior differences. Importantly, the cluster of interrupting/controlling behaviors demonstrated by a large proportion of the semantic dementia group did not appear in the vascular patients, with the exception that 16% of vascular patients verbally interrupted the examination (compared to almost half of the semantic dementia patients, many of whom actually stood up to leave the room). An additional discriminating factor was that semantic dementia patients were more likely to behave in a narcissistic manner, with one fifth of them explicitly raising the topic of their personal uniqueness, while none of the vascular patients did this. The pathologic lack of social responsiveness that discriminated frontotemporal dementia subjects from healthy controls and psychiatric patients also significantly differentiated them from vascular patients. In addition, clinicians rated frontotemporal dementia patients as significantly more likely than vascular disease patients to ignore personal boundaries. Overall, discrimination between FTLD and vascular patients may be based on the fact that despite occasionally irritable, impulsive behaviors on the part of some vascular patients, they remain capable of self-reflection and retain a greater sensitivity to the social and emotional context of the clinical interaction than FTLD patients do.

FTLD Behavior Is Highly Divergent From Other Dementias

Our results also showed that the spontaneous behaviors more common in FTLD patients than in controls, psychiatric patients, and vascular patients are not merely a result of "dementia" in general. Frontotemporal lobar degeneration patients act quite different from patients with other dementias such as Alzheimer's disease, progressive nonfluent aphasia, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies. None of these dementia groups showed a distinctive pattern of social behavior during the evaluation. In fact, the overall trend was that non-FTLD dementia patients were less spontaneously active, thus were less likely to evidence the positive behaviors of the IMP than either FTLD patients or healthy aging controls. For example, despite the fact that the combined other dementia group numbered 130 patients, not a single person was observed to move around the room or speak in a narcissistic, "personally superior" manner, while 6% to 10% of the normal subjects and even more FTLD patients did these things. Fewer than 3% of other dementia patients interrupted the examiner or spoke in the perseverative, tangential manner we observed in approximately one quarter of FTLD patients. In practical terms, however, using behavior to differentiate FTLD patients from those with other types of dementia may be less useful in a typical primary care or mental health setting, because these other dementias should have telltale memory, language, or motor symptoms that indicate the need for neurologic referral.

Study Limitations

There are some methodological considerations specific to our study that may limit the generalizability of our findings. One issue is the possible circularity of performing behavior ratings on patients who are diagnosed, in part, based on behavioral criteria. This study was performed at a neurology specialty clinic by clinicians who are exposed to dementia patients more frequently than typical primary care or mental health professionals. However, almost 40% of the ratings were performed by bachelor's degree–level research assistants with no formal medical or psychological education, which was done purposely to reduce the chance raters would correctly recognize the patient's disease before they had filled out the IMP. We also specifically selected a measure with an objective behavior–checklist component to reduce the likelihood that the rater's "guess" about patient diagnosis would influence their ratings.

This study was designed to identify FTLD-specific behaviors likely to occur spontaneously in primary care or mental health settings; however, these ratings were per-

formed by clinicians who had been one-on-one with the patient for 1 hour performing cognitive testing. Important behaviors that might be seen in a more naturalistic clinical interview setting may have either been elicited or suppressed by the cognitive testing context. Also, the typical primary care visit is only 15 minutes in duration, reducing the time in which important patient behaviors might be observed. In mental health settings such as therapy, the clinician does spend 45 minutes to an hour one-on-one with the patient; however, the social dynamic of talk therapy is different from what is seen in other, more goal-directed contexts like a physician's visit or a structured cognitive exam. Some of the behaviors this study suggests are specifically associated with behavioral dementias, such as perseverative, tangential, or narcissistic discourse, may fall within the limits of normal behavior in a therapy session. Clinicians should be careful to recognize context in their interpretation of patient behavior.

The behavior checklist used in this study was not developed for use with dementia patients, thus it was not comprised of a comprehensive list of all behaviors that might be expected from FTLD patients. Despite our use of an imprecise instrument, however, we still found that many spontaneous social behaviors do differentiate FTLD patients from other patients during brief clinical interactions, which suggests that future research with a behavioral checklist tailored to FTLD might show even better results. The behaviors we found that were useful discriminators occurred in no more than half of our patients, which suggests that though these behaviors are fairly specific, they are not highly sensitive. Research to discover additional behaviors that occur in a larger proportion of FTLD patients will allow more of them to be recognized by medical gatekeepers and appropriately referred.

CONCLUSION

Primary care and mental health professionals are likely to be the first clinicians to recognize that FTLD patients require a referral for a dementia evaluation, thus these clinicians must be able to recognize salient behaviors without needing to perform specialized evaluations. This study demonstrated that FTLD patients are likely to spontaneously exhibit specific patterns of aberrant social behavior that can be objectively observed by nonexperts in a time-limited, problem-focused clinical context. These behaviors are not typical of normal aging and are not common in psychiatric or cerebrovascular disease, and thus they should be seen by clinicians as red flags for behavioral dementias.

The most powerful discriminator of the semantic dementia subtype of FTLD was a pattern of behavior in which the patient derails the course of the clinical interaction by verbally and physically interrupting the evaluation, speaking at length and repeatedly about 1 or 2 irrelevant topics, and resisting the clinician's attempts to interrupt and redirect them. The frontotemporal dementia subtype of FTLD showed no self-consciousness or concern about meeting the clinician's expectations, though they displayed this behavior in the context of 2 different phenotypes: they either displayed an abnormally flat, apathetic demeanor or were socially disinhibited, readily crossing personal and professional boundaries. When observed in a primary care or mental health context, these symptoms may indicate the need for referral to a dementia specialist for further evaluation.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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Gender Differences in 2 Clinical Trials of Adults With Attention-Deficit/Hyperactivity Disorder: A Retrospective Data Analysis

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