An Evidence-Based Review of the Psychopathology of Frontotemporal Dementia: A Report of the ANPA Committee on Research

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The Committee on Research of the American Neuropsychiatric Association conducted a review of the noncognitive neuropsychiatric manifestations of frontotemporal dementia. The Committee on Research searched reviews and several online databases for all pertinent publications. Single case reports without pathology were excluded, except for psychosis, where single cases made up much of the literature. The strongest evidence supports an association of frontotemporal dementia with the following behaviors: apathy-abulia; disinhibition-impulsivity; loss of insight and self-referential behavior; decreased emotion and empathy; violation of social and moral norms; changes in dietary or eating behavior; and repetitive behaviors. Frontotemporal dementia is less frequently associated with anxiety and mood disorders, which may be a prodrome or risk factor, and rarely presents with delusions or hallucinations. The results of this review highlight the distinct neuropsychiatric manifestations of frontotemporal dementia and the need to reconsider the current diagnostic criteria for this disorder.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2008; 20:130–149)

Frontotemporal dementia is a neurodegenerative disorder characterized by the development of neuropsychiatric symptoms. These behavioral changes most commonly emerge when patients are in their fifties,[1–3] although the age of onset for frontotemporal dementia can range from the third to the ninth decade.[1,4] Frontotemporal dementia is one of the most common dementias of early onset. Among dementia patients with an age of onset less than 65 years old, frontotemporal dementia accounts for 20%–50% of all cases.[3,5–7]

Frontotemporal dementia results from frontotemporal lobar degeneration. On gross pathology, there is circumscribed and often asymmetric lobar atrophy of the frontal lobes, adjacent anterior temporal regions, or both. On microscopic examination, there are microvacuoles and gliosis with or without inclusion bodies.[8–10] The prior term of "Pick's disease" referred to frontotemporal lobar degeneration with argentophilic, tau-

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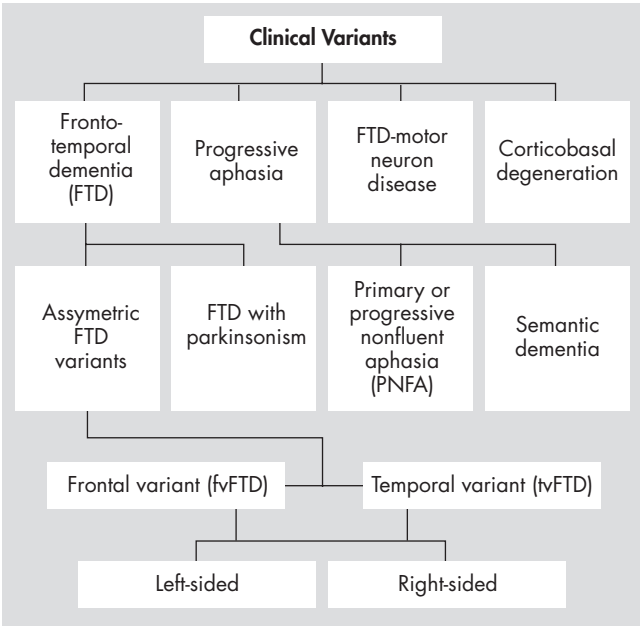
positive intranuclear inclusions (Pick bodies).[11,12] Most patients with frontotemporal dementia and related syndromes, however, lack tau-positive inclusions and may have tau-negative, ubiquitin-positive inclusions with TDP-43 protein.[13,14] Some patients have additional involvement of other areas of the nervous system resulting in parkinsonism, motor neuron disease, or corticobasal degeneration.[4]

Clinically, frontotemporal lobar degenerations reflect the initial distribution of neuropathology and present as several clinical syndromes depending on their predominant presenting symptoms.[9,12] Neuropsychiatric behavioral changes define the clinical syndrome of frontotemporal dementia, which is the most common frontotemporal lobar degeneration.[1] Among 61 patients with pathologically proven frontotemporal lobar degeneration, 90% presented with behavioral disturbances consistent with frontotemporal dementia, including personality and social conduct disorder.[8] This review focuses on the clinical syndrome of frontotemporal dementia. Other frontotemporal lobar degeneration syndromes, such as primary or progressive nonfluent aphasia, semantic dementia, or several movement disorders, are discussed only where they overlap with frontotemporal dementia (Figure 1).[15,16]

This report specifically reviews the noncognitive neuropsychiatric features of frontotemporal dementia. In contrast to Alzheimer's disease, during the first few years after onset, behavioral symptoms in frontotemporal dementia are more prominent and disruptive than memory or other cognitive deficits.[2,5,17–22] In the absence of diagnostic biomarkers, the clinical diagnosis depends on recognizing core, or necessary, behavioral features of frontotemporal dementia.[23] Yet, physicians frequently fail to recognize psychopathology as symptoms and misdiagnose these patients as having a primary psychiatric diagnosis.[23–26] For this and other reasons, this review of the psychopathology of frontotemporal dementia aims to comprehensively review the literature and characterize the psychopathology of this disorder.

FIGURE 1. Schematic Showing the Clinical Variants of Frontotemporal Lobar Degeneration (FTLD)



METHOD

We searched MEDLINE using the strategy: "frontotemporal dementia" OR "Pick's disease" OR "frontotemporal lobar degeneration" OR "frontal dementia" OR "frontal lobe dementia." We also searched PsychInfo with the same strategy. The searches reviewed clinical papers on frontotemporal lobar degeneration if they included frontotemporal dementia or syndromes that overlapped with this disorder. The searches were complete to the end of April 2007 and were not limited to the English language. We also reviewed pertinent sections of selected books and references in our files.

We characterized our reports by type of behavior divided up into changes in personality, anxiety and compulsions, mood disorders, and psychosis. Using all pertinent studies, we summarized the evidence to date. This review focused on the clinical syndrome of frontotemporal dementia and not on the pathological diagnoses. Furthermore, we focused on personality, behavioral, and psychiatric manifestations rather than on memory, language, perceptual, executive, or other cognitive deficits. This review did not include most single case studies except where detailed studies were limited, as in the psychosis section.

Although there were earlier behavioral descriptions, publications on the neuropsychiatric features of frontotemporal dementia did not appear in significant numbers until the early 1990s. The early case reports and papers culminated in the Clinical Consensus Criteria for FTD,[15] published in 1998, which, in effect, summarized the core and supportive behavioral features of frontotemporal dementia up to that date (Table 1). There was

TABLE 1. Consensus Criteria for Frontotemporal Dementia (FTD)[1]

Core Diagnostic Features*	Supportive Behavioral Diagnostic Features
A. Insidious onset and gradual progression	A. Decline in personal hygiene and grooming
B. Early decline in social interpersonal conduct	B. Mental rigidity and inflexibility
C. Early impairment in regulation of personal conduct	C. Distractibility and impersistence
D. Early emotional blunting	D. Hyperorality and dietary changes
E. Early loss of insight	E. Perserverative and stereotyped behavior
	F. Utilization behavior

*All core diagnostic features need to be present for a diagnosis of FTD. Supportive features are only confirmatory.
[1]Neary D, Snowden JS, Gustafson L, et al: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51:1546–1554

still little systematic study of personality and behavior, however, until 2001 when Mychack et al.[27] outlined the need and potential methodologies for investigating the nature of personality and behavior in frontotemporal dementia. The subsequent years yielded a great many papers on the subject, employing a variety of measures and terminology (Table 2). Much of this literature has struggled with the challenge of comparing frontotemporal dementia, a dementia whose criteria emphasize behavioral symptoms, with Alzheimer's disease, a dementia whose criteria emphasizes cognitive deficits.

RESULTS

We obtained 504 citations from MEDLINE and PsychInfo. These citations were then reviewed for studies shedding light specifically on the noncognitive neuropsychiatric aspects of frontotemporal dementia and, with exceptions, not involving just a case report or a genetic kindred. We reviewed and included 192 articles as potentially relevant. After review, the studies were grouped into 10 behavioral categories, additional behaviors with limited literature, and treatment. The findings are summarized below.

Neuropsychiatric Symptoms

Apathy-Abulia Apathy-abulia is the most common initial symptom of frontotemporal dementia and is present in the majority of patients as the disease progresses.[23,28–33] Among frontotemporal dementia patients, clinicians often mistake as depression the presence of apathy, or the lack of feeling or emotion, and abulia, or the loss of volition and initiative.[28,34] Miller et al.[21] initially reported two frontotemporal dementia patients with frontal hypoperfusion on single photon emission tomography (SPECT) who presented with "pseudodepression" attributable to apathy. The following year, Gustafson et al.[35] reviewed several hundred cases of de-

TABLE 2. Terminology

Alzheimer's disease:	The most common dementia; Alzheimer's disease is often used as a comparison group in clinical studies of frontotemporal dementia
Cerebrovascular dementia:	For consistency, the term "vascular dementia" is substituted in this review
Frontal lobe dementia:	For consistency, "frontotemporal dementia" is substituted for this old term
Frontotemporal dementia (behavioral variant):	The most common and main clinical syndrome from frontotemporal lobar degeneration
Frontotemporal lobar degeneration:	The generic term for the underlying neuropathology
Frontal variant frontotemporal dementia (fvFTD):	Refers to frontotemporal dementia with predominant frontal disease on imaging
Pick's disease:	Clinicopathologic term for a frontotemporal lobar degeneration with Pick bodies
Progressive non-fluent aphasia:	A predominant left frontal clinical syndrome from frontotemporal lobar degeneration characterized by non-fluent language difficulty
Primary progressive aphasia:	Often used synonymously with progressive non-fluent aphasia and sometimes used to include semantic dementia
Semantic dementia:	A predominant anterior temporal clinical syndrome from frontotemporal lobar degeneration syndrome with progressive word recognition and other semantic deficits
Temporal variant frontotemporal dementia (tvFTD):	Refers to frontotemporal dementia with predominant anterior temporal disease on imaging. The distinction between semantic dementia and tvFTD is often one of whether semantic deficits are the salient clinical deficits.
Vascular dementia:	Generic term for dementia due to cerebrovascular disease

mentias in a longitudinal prospective clinicopathological study. They identified 30 patients with frontotemporal dementia, all of whom developed apathy with amimia and mutism late in their course. In a careful retrospective review of nine patients with frontotemporal dementia, Galante et al.[36] confirmed that these patients became inactive with decreased behavioral initiation and spontaneity, loss of interest, and, ultimately, frank apathy. Eventually, several large series of outpatients, ranging from 50 to 74 patients, confirmed the presence of apathy-abulia in 62% to 89% of patients with frontotemporal dementia.[23,37–39]

Comparative studies with the Neuropsychiatric Inventory show that apathy-abulia is more common, severe, and pervasive in frontotemporal dementia than in Alzheimer's disease. Investigators developed the Neuropsychiatric Inventory to evaluate patients with Alzheimer's disease on 12 behavioral features including delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities.[40] Levy et al.[41] first used the Neuropsychiatric Inventory to compare 22 patients with frontotemporal dementia with 30 patients with Alzheimer's disease matched for dementia severity and found higher levels of apathy among those with frontotemporal dementia. Subsequently, Neuropsychiatric Inventory investigations reported apathy as one of the most common symptoms of frontotemporal dementia, present in approximately 95% of patients,[42,43] more severe and frequent in frontotemporal dementia compared to Alzheimer's disease,[44–46] and present in both mild and moderate-severe frontotemporal dementia.[47] Furthermore, in a discriminant analysis, Perri et al.[48] combined the Neuropsychiatric Inventory with neuropsychological testing to correctly assign 73.7% of 19 frontotemporal dementia patients and 94.7% of 39 Alzheimer's disease patients based on better Rey's Figure A Copy, worse performance on the Initial Letter Verbal Fluency Test (FAS), and greater Neuropsychiatric Inventory apathy subscale scores among the frontotemporal dementia patients.

Additional scales and measures have further defined the frequency and nature of apathy-abulia in frontotemporal dementia. Bozeat et al.[49] reported apathy among 75% of 33 frontotemporal dementia patients using their own neuropsychiatric caregiver questionnaire. Kertesz et al.[50] confirmed that apathy and aspontaneity distinguish frontotemporal dementia from non-frontotemporal dementia groups using the Frontal Behavior Inventory,[51–52] an instrument that they felt would be more sensitive to frontotemporal dementia than the Neuropsychiatric Inventory.[50] Others found significantly more apathy and negative symptoms in frontotemporal dementia than in Alzheimer's disease, dementia with Lewy bodies, or mixed dementias.[53,54] Rankin and colleagues[55] used the Interpersonal Adjectives Scales, a self-report and caregiver questionnaire, to measure personality change in 16 patients with frontal variant frontotemporal dementia (fvFTD), with greater frontal volume loss, and 13 with temporal variant frontotemporal dementia (tvFTD), with greater anterior temporal volume loss, and in a comparison group of 16 patients with Alzheimer's disease. This, and a subsequent study with the Interpersonal Adjectives Scales, documented that fvFTD patients became aloof and introverted, unassured and socially submissive, and less dominant and assertive.[55,56]

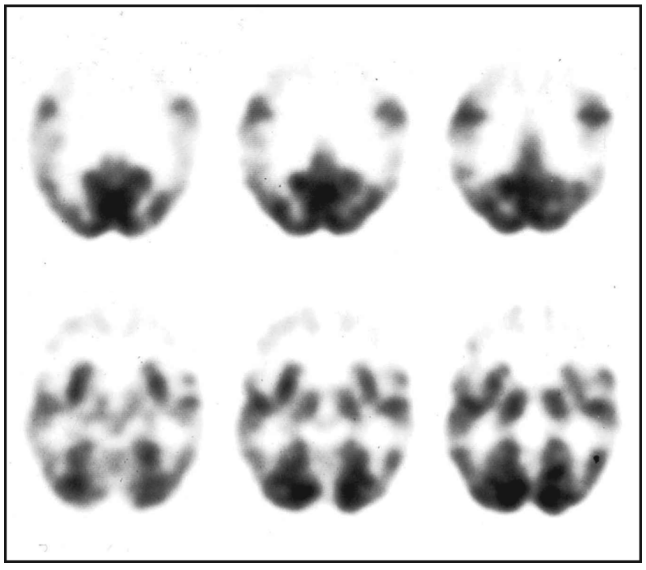
The presence of apathy-abulia in frontotemporal dementia correlates with orbitofrontal disease, extending from Brodmann's area 10 to the anterior cingulate cortex, especially on the right. Liu et al.[57] studied 51 patients with frontotemporal dementia and 20 normal comparison subjects, as well as 22 patients with Alzheimer's disease, using the Neuropsychiatric Inventory and MRI voxel-based morphometry. The fvFTD patients scored higher on apathy compared to the tvFTD patients or the Alzheimer's disease patients. In voxel-based morphometry MRI studies, apathy scores on the Neuropsychiatric Inventory correlated not only with right lateral orbitofrontal atrophy but also with anterior cingulate cortex atrophy and, possibly, caudate head/ventral striatal atrophy.[58,59] In SPECT and positron emission tomography (PET) studies, apathy in frontotemporal dementia correlated with right frontal hypoperfusion or frontal hypometabolism (Figure 2).[30,60] In addition, apathy in fvFTD may be associated with PET hypometabolism in the orbitofrontal cortex and anterior cingulate cortex.[31,61] Investigators further reported orbitofrontal hypometabolism specifically in the right medial Brodmann's area 10 associated with apathy in a range of frontal-predominant disorders.[62]

Disinhibition-Impulsivity Disinhibition-impulsivity is one of two major behavioral subtypes of frontotemporal dementia, along with apathy-abulia.[30–32,34,63] It is unclear from the literature how often disinhibition and impulsivity are dissociable or occur independently in fronto-

temporal dementia. Many clinical and clinicopathological reports describe disinhibition and a decreased ability to restrain impulses as prominent and early symptoms of frontotemporal dementia.[2,21,35,42,61,64–66] Among 63 frontotemporal lobar degeneration patients, Mourik et al.[43] described disinhibition in 52% of the patients on the Neuropsychiatric Inventory administered to their caregivers. Chow et al.[37] described disinhibition throughout the course of frontotemporal dementia among 62 patients evaluated retrospectively. Recently, Liscic et al.[67] reported their results on 48 autopsy-confirmed patients with frontotemporal lobar degeneration compared to 27 autopsy-confirmed patients with Alzheimer's disease. The frontotemporal lobar degeneration patients, most of whom had frontotemporal dementia, had much more disinhibition-impulsivity (23–25 patients; about 50%) compared to the Alzheimer's disease patients (1–3 patients; 4–11%).

Comparative studies using scales and measures show that disinhibition-impulsivity discriminates frontotemporal dementia from other dementias. Multiple investigations using the Neuropsychiatric Inventory to compare frontotemporal dementia with Alzheimer's disease show higher disinhibition scores among the frontotemporal dementia patients, particularly with fvFTD, compared to patients with Alzheimer's disease, dementia with Lewy bodies, and vascular dementia.[41,44,48,57,68,69]

FIGURE 2. PET Images of a Frontotemporal Dementia Patient with Predominant Apathy-Abulia



The PET shows prominent frontal lobe hypometabolism.

Lopez et al.[70] evaluated DSM-III-R diagnoses in 20 patients with frontotemporal dementia and 40 patients with Alzheimer's disease and found disinhibition in six frontotemporal dementia patients (30%) compared to only two Alzheimer's disease patients (5%). Bathgate et al.[71] found greater disinhibition among 30 frontotemporal dementia patients compared to 75 Alzheimer's disease and 34 "cerebrovascular dementia" patients on a semistructured caregiver questionnaire. Bozeat et al.[49] found greater group levels of disinhibition among 33 frontotemporal dementia patients compared to 27 Alzheimer's disease patients using their neuropsychiatric questionnaire.

The presence of disinhibition-impulsivity correlates with right-sided frontotemporal disease. Miller et al.[65] described behavioral disinhibition as one of the dominant, and often first, symptoms in five patients with predominant right frontotemporal involvement, and, in a retrospective comparison of 52 patients with frontotemporal dementia and 101 patients with Alzheimer's disease, Lindau et al.[64] found that disinhibition was greatest in the frontotemporal dementia patients with asymmetric right-sided involvement. In addition, Liu et al.[57] found that disinhibition on the Neuropsychiatric Inventory is associated with decreased right frontal volumes in frontotemporal dementia. In contrast, other investigations have described prominent disinhibited and impulsive behavior or frivolousness and inappropriate humor among frontotemporal dementia patients with bilateral or predominantly right anterior temporal involvement.[60,72–75] Kertesz[28] suggested that the disinhibited subtype of frontotemporal dementia results specifically from both orbitofrontal and anterior temporal involvement. Consistent with this formulation, subsequent PET and voxel-based morphometry studies among disinhibited frontotemporal dementia patients show an interconnected right hemisphere region of involvement extending from the posterior orbitofrontal cortex, subgenu cingulate, to the anterior temporal pole.[1,30,31,59,61] This region may be somewhat more posterior than the region for apathy-abulia, but more research is needed to clarify this difference.

Loss of Insight and Self-Referential Behavior Early in frontotemporal dementia, patients lose awareness of their disability or the consequences of their behavior and cannot see themselves from others' point of view (perspective taking). Since being reported as part of the criteria for this disease,[5,15,38,71,76,77] there have been many clinical

reports on loss of insight in frontotemporal dementia. Among 53 frontotemporal dementia patients, Mendez and Perryman[23] reported loss of insight in 58.5% at onset and in 100% 2 years later. Similarly, Passant et al.[25] found loss of insight in all 19 of their neuropathologically verified cases with frontotemporal dementia. Perrine et al.[78] showed loss of insight in frontotemporal dementia associated with loss of perspective taking (i.e., they cannot show how others see them). More recently, Evers et al.[79] evaluated the decreased insight in five of eight patients with frontotemporal dementia and suggested that there was primarily a loss of "emotional insight" from frontotemporal disease, rather than impairment in "cognitive insight." This loss of emotional insight resembles more of an anosodiaphoria, or indifference towards their illness rather than a true anosognosia, or ignorance of their symptoms.[80]

In comparative studies, the loss of insight or self-awareness is worse in frontotemporal dementia than in other dementia syndromes. Eslinger et al.[81] used the Brock Adaptive Function Inventory and Apathy Evaluation Scale to evaluate 27 frontotemporal lobar degeneration patients, 11 Alzheimer's disease patients, and 11 comparison subjects. Their frontotemporal dementia sample as a whole showed significantly less behavioral self-awareness and self-knowledge than the Alzheimer's disease and healthy comparison samples. Pijnenburg et al.[82] retrospectively reviewed the case notes of 46 patients diagnosed with frontotemporal lobar degeneration (21 with frontotemporal dementia). In contrast to the other patients, the majority of the frontotemporal dementia patients presented without complaints or awareness of symptoms. Moretti et al.[83] compared frontotemporal dementia versus vascular dementia (subcortical) and found that frontotemporal dementia had a total lack of insight, whereas it was more intact in vascular dementia. Finally, O'Keeffe et al.[84] investigated loss of insight in 14 frontotemporal dementia patients compared to 11 corticobasal degeneration and 10 progressive supranuclear palsy patients. Although all groups had decreased insight, the frontotemporal dementia patient group was most impaired in "emergent awareness" or detection of their errors.

The loss of insight in frontotemporal dementia is part of a spectrum of loss of self-referential behaviors such as self-consciousness, self-perception, stable self-concepts, self-criticism or reflection, awareness of personality changes, or self-conscious responses.[56,78,80,81] Snowden et al.[32] characterized frontotemporal dementia patients as lacking self-conscious emotions, and Bathgate et al.[71] characterized frontotemporal dementia patients as selfish. Using an autobiographical memory task, Piolino et al.[85] found a group deficit of autonoetic consciousness (self-perception) in 15 fvFTD patients. In a unique report, Miller et al.[86] showed that stable self-concepts, such as religion and political affiliation, can be altered with the development of frontotemporal dementia. Rankin et al.[56] used the Interpersonal Adjectives Scales to compare self-awareness of personality and personality changes in 12 fvFTD patients, 10 patients with Alzheimer's disease, and 11 comparison subjects. In this and other studies, the frontotemporal dementia patients exaggerated positive qualities, minimized negative ones, and were generally unaware of their personality change (or current personality).[56,81] Finally, Sturm et al.[87] examined the response of 30 frontotemporal lobar degeneration patients and 23 cognitively normal comparison subjects to a loud, unexpected acoustic startle stimulus (115-dB burst of white noise). Results indicated that frontotemporal lobar degeneration patients and comparison subjects had similar responses to the startle except for significantly fewer facial signs of embarrassment or self-conscious responses among the frontotemporal lobar degeneration patients.

The presence of loss of insight and self-referential behavior correlates with right frontal involvement in frontotemporal dementia.[86] On SPECT scans of frontotemporal dementia patients, loss of insight is associated with hypoperfusion in the right hemisphere, particularly the frontal lobe.[60,80] Furthermore, loss of insight was significantly more common with right (54.6%) versus left (13.9%) temporal atrophy;[88] however, involvement of the left temporal lobe may result in anosognosia for their social disability. Sturm et al.'s[87] findings are consistent with neural loss in the medial prefrontal cortex, which may play an important role in the production of self-conscious emotions as self-awareness activates the medial prefrontal cortex during active recollection of one's past and during passive self-reflection.[87] Finally, a recent multi-center study of lack of awareness in frontotemporal dementia compared to Alzheimer's disease suggested that greater loss of awareness in frontotemporal dementia corresponds to the degree of frontally-mediated atrophy.[89]

Decreased Emotion and Empathy In general, frontotemporal dementia patients lack emotional warmth and appear emotionally shallow and indifferent.[32,65,90,91,92] In a

large series, Le Ber et al.[61] document changes in affect and emotional development among patients with frontotemporal dementia, and Snowden et al.[32] found that emotional unresponsiveness, including reduced response to pain, was pervasive among frontotemporal dementia patients. Using the Interpersonal Reactivity Index, a measure of cognitive and emotional empathy, Lough et al.[93] reported decreased empathic concern and decreased perspective taking in frontotemporal dementia, and Eslinger et al.[94] reported decreased self-awareness of empathy. In experiments, the emotional deficit in frontotemporal dementia spares emotional reactivity and the recognition of happiness, but impairs the recognition of negative emotions such as sadness and fear and the experience of self-conscious emotions such as embarrassment and shame.[78,90]

In comparative studies, emotional blunting and loss of empathy are worse in frontotemporal dementia than in Alzheimer's disease and vascular dementia. Among 30 patients with frontotemporal dementia and 30 patients with Alzheimer's disease, Miller et al.[46] reported more patients with emotional unconcern in the frontotemporal dementia group (N = 24, 80.0%) compared to the Alzheimer's disease group (N = 6, 20.0%).[46] Barber et al.[95] found less emotional reaction to handicaps on a retrospective informant questionnaire in 18 subjects with pathologically proven frontotemporal dementia than in 20 subjects with Alzheimer's disease. Likewise, among 30 frontotemporal dementia patients, 75 Alzheimer's disease patients, and 34 vascular dementia patients, Bathgate et al.[71] reported greater loss of emotions among the frontotemporal dementia patients. Two studies that used the Scale for Emotional Blunting recorded higher emotional blunting scores in frontotemporal dementia than in Alzheimer's disease.[53,75] Two other studies using the Interpersonal Reactivity Index reported significantly more impaired cognitive (perspective taking) and emotional (emotional contagion) empathy in frontotemporal dementia compared to other dementia groups.[96,97]

In frontotemporal dementia, decreased empathy is associated with right anterior temporal disease. Case studies or series of tvFTD found loss of empathy, fixed facial expressions unresponsive to situations, and emotional distancing and blunting, particularly with right-sided disease,[72,73,98,99] and the speech of right hemispheric frontotemporal dementia patients was less relevant to emotionally loaded pictures than that of left hemisphere patients.[100] In studies using the Interpersonal Adjectives Scales or the Interpersonal Reactivity Index, Rankin et al.[55] showed that tvFTD patients were particularly prone to interpersonal coldness compared to fvFTD patients and had decreased emotional contagion or emotional response to another's distress.[97] On voxel-based morphometry MRI, empathy correlated with a right medial frontotemporal network, particularly emotional empathy with the right ventromedial and anterior temporal areas.[96,97] Moreover, among artists with predominant right temporal frontotemporal dementia, Mendez and Perryman[101] report decreases in empathy reflected in alterations in their caricatures of others, and, using distorted and morphed face tasks, Mendez and Lim[102] showed that frontotemporal dementia patients with predominant right frontotemporal involvement tended to have decreased empathic awareness.

Violation of Social and Moral Norms Frontotemporal dementia patients have disturbed social and moral behavior. Social changes that differ from the patient's premorbid behavior most commonly include social inadequacy or awkwardness, tactlessness, disagreeableness, decreased propriety and manners, unacceptable physical contact, or improper verbal or physical acts.[15,23,36,64,103] In a retrospective study of 19 neuropathologically verified patients with frontotemporal dementia, Passant et al.[25] found impaired social interactions in all patients, including offensive language in ten, physical aggression in eight, and many traffic violations. Mychack et al.[104] found that 11 of 12 right-sided and two of 19 left-sided frontotemporal dementia patients had socially undesirable behavior, such as criminality or socially deviant acts, as an early presenting symptom of frontotemporal dementia. Frontotemporal dementia patients may engage in minor theft or shoplifting,[76,105] driving violations,[106] inappropriate sexual behavior,[65,107,108] and acts of violence.[76] Miller et al.[109] found antisocial behavior in nearly 50% of patients with frontotemporal dementia, including stealing, hit and run accidents, physical assault, indecent exposure, sexual comments or advances, and public urination. Edwards-Lee et al.[73] described the stealing of small objects in six out of ten tvFTD patients.

Comparative studies indicate that social and moral behavioral changes can differentiate frontotemporal dementia from other dementias. Bozeat et al.[49] found that loss of social awareness helps differentiate frontotemporal dementia from Alzheimer's disease, and Shinagawa et al.[33] found that changes in social behavior were

more common initial symptoms in patients with frontotemporal dementia than in patients with Alzheimer's disease or semantic dementia. A comparison of 21 frontotemporal dementia patients with 11 vascular dementia patients with a dominating frontal lobe syndrome found significantly less social awareness among the frontotemporal dementia patients.[110] Sociopathic acts are also more prominent in frontotemporal dementia compared to Alzheimer's disease or other dementia illnesses.[46,105,108] Mendez et al.[111] reported that 16 frontotemporal dementia patients (57%) had sociopathic behavior, compared to only two Alzheimer's disease patients (7%), and Diehl et al.[105] reported misdemeanor violations in 15 frontotemporal dementia patients (50%), compared to only one Alzheimer's disease patient (3%). Finally, Mendez et al.[112] administered an inventory of moral knowledge and moral dilemmas to 26 patients with fvFTD, 26 patients with Alzheimer's disease, and 26 normal control subjects.[113] Although all groups had knowledge of moral behavior, only the frontotemporal dementia patients were impaired in their ability to make immediate, emotionally based moral judgments.

In frontotemporal dementia, disturbed social and moral behavior correlates with right ventromedial-orbitofrontal-amygdalar disease. Miller et al.[114] suggested that the right hemisphere primarily controls social conduct in frontotemporal dementia, and various investigations have shown greater right-sided changes with social behavioral changes in frontotemporal lobar degeneration.[46,54,71,81,88,98,99,102,111,115,116] Sarazin et al.[62] studied 32 patients with frontal lobe pathologies with PET and found that hypometabolism, predominantly in the right orbitofrontal region, corresponded to an indifference to rules. Decreased agreeableness on the NEO Five-Factor Inventory in frontotemporal dementia also correlates with right orbitofrontal changes.[103] More recently, Nakano et al.[117] correlated antisocial behavior in frontotemporal dementia with decreased blood flow in the orbitofrontal cortex. In sum, frontotemporal dementia affects a socio-moral network that includes the right ventromedial region, which, as previously seen, emotionally tags social and moral situations (reexperiencing previously learned emotional responses in novel situations), the orbitofrontal cortex, which responds to social cues and mitigates impulsive reactions, and the amygdalae, which are necessary for threat detection and moral learning.[78,93,113]

Changes in Dietary or Eating Behavior Early changes in dietary and eating behavior are a common manifestation of frontotemporal dementia and include a spectrum from patients altering their dietary preferences to placing nonfood items in their mouths, consistent with the Klüver-Bucy syndrome.[35,118] Frontotemporal dementia patients develop gluttony, sweets and carbohydrate craving, increased weight, obsessions with particular foods, and occasional alcoholism.

Eating behavior changes occur in almost 80% of frontotemporal dementia patients.[47] Miller et al.[21] suggested that hyperorality was one of the most discriminating aspects of frontotemporal dementia, and, in an early clinicopathological study, Mendez et al.[2] described hyperoral behavior as one of the distinguishing features of frontotemporal dementia. Among 19 neuropathologically verified frontotemporal dementia cases, Passant et al.[25] found that 14 patients had alterations in dietary or oral behavior including two who started to drink alcohol. Other reports on frontotemporal dementia described hyperorality,[39] gluttony and indiscriminate eating,[32,71,119] sweet food preferences,[71,119] and changes in eating behaviors or eating disorders.[45,49] Snowden et al.[32] found that gluttony and early increased appetite, indiscriminate eating, and sweet cravings were the most characteristic dietary or oral symptoms of frontotemporal dementia,[120] whereas patients with semantic dementia were more likely to exhibit food fads or early changes in food preferences.[88,120] Finally, the Klüver-Bucy Syndrome, with generalized and potentially fatal hyperorality, is distinct from the other dietary and oral behaviors and only occurs in a minority of advanced frontotemporal dementia patients with bilateral temporal involvement.[32,118,121]

Comparative studies show that frontotemporal dementia patients have more changes in dietary or eating behavior than patients with Alzheimer's disease or vascular dementia. Miller et al.[122] queried the primary caregivers of 14 patients with frontotemporal dementia and 14 patients with Alzheimer's disease on the occurrence of weight gain and sweet and carbohydrate craving. Weight gain in frontotemporal dementia patients amounted to 64% and carbohydrate craving was 79%, compared to 7% and 0%, respectively, for Alzheimer's disease. Ikeda et al.[120] investigated the frequency of changes in eating behaviors in fvFTD (N = 23), semantic dementia (N = 25), and Alzheimer's disease (N = 43) using a caregiver questionnaire of swallowing problems, appetite change, food preference, eating habits, and other oral behaviors and found that the frequencies of symptoms in all domains except swallowing problems

were higher in fvFTD than in Alzheimer's disease. Srikanth et al.[69] compared 23 frontotemporal dementia patients, 44 Alzheimer's disease patients, and 31 vascular dementia patients on the Neuropsychiatric Inventory and found that mean abnormal scores in the domain of appetite/eating behavior helped differentiate frontotemporal dementia from Alzheimer's disease and vascular dementia. Recently, in Liscic et al.'s[67] clinicopathologic series, the 48 frontotemporal lobar degeneration patients had more hyperorality (N = 6, 12.5%) than the 27 Alzheimer's disease patients (0%).

In frontotemporal dementia, dietary or eating behavioral disturbances correlate with disease affecting lateral orbitofrontal cortex, especially on the right, and adjacent structures, especially the insula. In Neuropsychiatric Inventory studies of frontotemporal dementia, Liu et al.[57] showed that eating disorders correlated with frontal lobe involvement, and Short et al.[123] showed a right rather than a left frontal association with hyperphagia among 59 frontotemporal lobar degeneration patients. Rosen et al.[59] found that eating disorders were more specifically associated with changes in the lateral orbitofrontal cortex, ventral anterior cingulate cortex, and adjacent subfrontal gyrus, caudate head/ventral striatum, and insula. More recently, Whitwell et al.[124] differentiated carbohydrate cravings and hyperphagia in a voxel-based morphometry study of 16 frontotemporal lobar degeneration patients compared to nine normal control subjects. The development of a pathological sweet tooth was associated with gray matter loss in posterior lateral orbitofrontal cortices (Brodmann's area 12/47) and right anterior insula, whereas the development of hyperphagia was associated with gray matter loss in anterolateral orbitofrontal cortices (Brodmann's area 11). Seeley et al.[72] suggested that altered food preferences result from orbitofrontal derailment of satiety centers or from processing of insular disgust signals.

Repetitive Behaviors Investigators have documented a range of repetitive behaviors in frontotemporal dementia.[15,35,41,65,122,125–127] Repetitive behaviors encompass simple repetitive acts and verbal or motor stereotypies such as lip smacking, hand rubbing or clapping, counting aloud, and humming. Repetitive behaviors also encompass complex repetitive motor routines such as counting, checking, cleaning, wandering a fixed route, repetitive trips to the bathroom, collecting and hoarding objects, pathological gambling, and rituals involving touching, grabbing, and superstitious acts.[21,114,126–128] Stereotypies or compulsive acts are often among the earliest and most salient presenting symptom of frontotemporal dementia and can be bizarre and severely disabling.[23,33,65,122]

Similar to dietary and eating behaviors, about 80% of frontotemporal dementia patients eventually have repetitive behaviors,[125] which is more than in other dementias. Miller et al.[21] suggested that the best discriminants for frontotemporal dementia were stereotypical and perseverative behaviors along with hyperorality and loss of hygiene, and these investigators further reported repeated compulsive behaviors in 64% of frontotemporal dementia patients compared to 14% of Alzheimer's disease patients.[122] Gustafson et al.[35] reviewed several hundred clinicopathological cases of dementia and concluded that frontotemporal dementia was a slowly progressive dementia characterized by stereotypy. Mendez et al.[126] evaluated compulsive behaviors as presenting symptoms in 29 patients with frontotemporal dementia compared to 48 patients with Alzheimer's disease. Compulsive behaviors occurred in 11 frontotemporal dementia patients (38%) versus five Alzheimer's disease patients (10%). Other repetitive behaviors reported in frontotemporal dementia include compulsive hoarding, pathological gambling, and self-injurious behaviors such as trichotillomania, picking at fingers to the point of excoriation, and self-biting.[25,129]

The few studies that have used specific behavioral scales for repetitive behaviors have documented motor and verbal stereotypies as well as compulsions in frontotemporal dementia.[34,42,49,52,71,130] Shigenobu et al.[131] developed the Stereotypy Rating Inventory, which evaluates eating and cooking behaviors, roaming, speaking, movements, and daily rhythm; and assessed 26 frontotemporal lobar degeneration patients, 46 Alzheimer's disease patients, 26 vascular dementia patients, and 40 normal controls subjects. The frontotemporal lobar degeneration group scored much higher on this instrument than all the other groups. Nyatsanza et al.[132] used the Stereotypic and Ritualistic Behavior subscale, an addendum to the Neuropsychiatric Inventory, to assess 18 fvFTD, 13 semantic dementia, and 28 Alzheimer's disease patients. Both the fvFTD and the semantic dementia patients scored significantly higher on this subscale than the Alzheimer's disease patients. Mendez et al.[133] used a stereotypy scale to evaluate 18 frontotemporal dementia and 18 Alzheimer's disease patients. Of the frontotemporal dementia patients, eight had stereotyp-

ical behaviors (44.4%), such as frequent rubbing and self-injurious acts, compared to only one of the Alzheimer's disease patients (5.6%). In addition, all of the frontotemporal dementia patients with stereotypical movements had compulsive-like behaviors, suggesting a similar pathophysiological cause.

In frontotemporal lobar degeneration, simple stereotypies correlate with right frontal involvement and complex compulsions with temporal involvement. The occurrence of stereotypies correlates with hypometabolism in the right orbitofrontal region, an area which regulates stimulus reinforcement associated with learning aberrant motor behavior.[62] Rosen et al.[59] further showed that the right lateral orbitofrontal cortex, dorsal anterior cingulate cortex, and insula, along with adjacent motor regions, participate in planning of motor acts in frontotemporal dementia. Consistent with this finding, McMurtray et al.[60] reported that the presence of right frontal hypoperfusion on SPECT predicted stereotyped behaviors in frontotemporal dementia. In contrast to simple verbal or motor stereotypies, frontotemporal lobar degeneration patients with complex compulsive behavior, or intentional and time-consuming repetitive acts, appear to have temporal lobe involvement.[32] Rosso et al.[134] found complex compulsions in 18 of 90 patients with frontotemporal dementia (21%) and an association between temporal lobe atrophy and complex compulsions. Others corroborate an association of prominent rigidity, complex compulsions, and a preoccupation with puzzles among patients with temporal predominant frontotemporal lobar degeneration.[72,88] Finally, some complex compulsions, such as pathological gambling, may require additional disinhibition from involvement in the adjacent orbitofrontal cortex.[135]

Psychotic Symptoms Clinicians can confuse frontotemporal dementia with schizophrenia or atypical psychosis, particularly when frontotemporal dementia occurs at a young age.[9,136–139] Delusional thoughts and hallucinations, however, are uncommon manifestations of frontotemporal dementia, particularly in comparison to Alzheimer's disease.[4] A review of the world's literature found 18 well-documented patients with possible frontotemporal dementia and delusions or hallucinations,[140–146] but only two cases were truly suggestive of this association. Miller et al.[65] and Edwards-Lee et al.[73] reported a 56-year-old woman who believed that she had contracted AIDS through her husband, became depressed, and showed severe hypoperfusion in the right frontal and temporal region and mild left frontotemporal hypoperfusion. Her subsequent course was consistent with frontotemporal dementia, but no pathology was reported. In a strong case for psychosis in frontotemporal dementia, Reischle et al.[147] reported a 53-year-old man with acute auditory and bizarre visual hallucinations with euphoria and self-overstimulation. Remission of the psychotic symptoms unmasked the clinical picture of a rapidly progressive frontotemporal dementia supported by the results of cerebral MRI and PET, but without pathological confirmation.

Although frontotemporal dementia can mimic schizophrenia,[38] the few psychiatric series suggest that frontotemporal dementia rarely manifests as psychosis. Among 68 fvFTD patients, only 5% had delusions and 2% had hallucinations.[61] Using the Comprehensive Psychiatric Rating Scale, Gregory[130] failed to find psychosis among 15 fvFTD patients. Although Gregory and Hodges[24] did not find psychosis in their prospective evaluation of 15 frontotemporal dementia patients, in their retrospective of 12 patients, one had been incorrectly diagnosed with a schizophreniform psychosis. Confirming frequent misdiagnoses during life, Passant et al.[25] found that most of their 19 autopsy-verified frontotemporal dementia patients had had an initial psychiatric diagnosis, including four with psychosis or schizophrenia, but on further review, none of these patients had actually manifested delusions or hallucinations.

In clinical reports, the prevalence of psychosis in frontotemporal dementia is much lower than in Alzheimer's disease and appears overestimated with the Neuropsychiatric Inventory. Levy et al.[41] found delusions on the Neuropsychiatric Inventory in five of 22 frontotemporal dementia patients (23%) and 10 of 30 Alzheimer's disease patients (33%), and Liu et al.[57] found delusions on the Neuropsychiatric Inventory in five of 23 fvFTD patients (22%) and five of 26 tvFTD patients (19%). Levy et al.[41] found hallucinations in none of the frontotemporal dementia patients and two of the Alzheimer's disease patients (7%), and Liu et al.[57] found hallucinations in three of the fvFTD patients (13%) and none of the tvFTD patients. Using the Neuropsychiatric Inventory, Lopez et al.[70] also found much more delusional psychosis in Alzheimer's disease than in frontotemporal dementia, and Hirono et al.[68] confirmed that there were fewer delusions in frontotemporal dementia compared to Alzheimer's disease. Mourik et al.[43] initially reported delusions on the Neuropsychiatric Inventory in eight of 63 frontotemporal dementia patients (12.7%), along with

four with hallucinations (6.3%), but it turned out that none of these patients had true "delusions" when specifically evaluated and queried. Finally, in Liscic et al.'s[67] clinicopathologic series, the 48 frontotemporal lobar degeneration patients had fewer hallucinations than the 27 Alzheimer's disease patients (zero versus four, or 15%). Parenthetically, other investigators suggest that although delusions and hallucinations are rare in frontotemporal dementia, a low B_{12} level may correlate with hallucinations in frontotemporal dementia.[54,148]

Mood Disorders Depressive symptoms occur in frontotemporal dementia. In early studies, Gustafson[107] reviewed the longitudinal course of 20 frontotemporal dementia patients and noted brief depressive reactions, and Miller et al.[21] reported that two of eight patients (25%) presented with depression. In autopsy-confirmed studies, Gustafson[76] found depressive episodes with occasional suicidal ideation and euphoria among 30 cases, and Mendez et al.[2] found depression among two of 21 frontotemporal dementia patients. Using the Comprehensive Psychiatric Rating Scale, Gregory[130] found three fvFTD patients out of 15 who reported sadness, but only one met criteria for DSM-IV major depressive episode. Among 63 frontotemporal dementia patients evaluated with the Neuropsychiatric Inventory, Mourik et al.[43] found depression in 10 cases (16%). Multidimensional scaling revealed a Cluster A was comprised of delusions, hallucinations, irritability, and agitation, and a Cluster B represented depression and anxiety. In some cases, depression may be a prodrome of frontotemporal dementia and a possible familial risk factor.[24,144,149–152]

Depression in frontotemporal dementia has atypical features. Lopez et al.[70] prospectively evaluated DSM-III-R diagnoses in 20 patients with frontotemporal dementia (six autopsy-proven) ascertained by psychiatrists using a structured clinical interview and compared them to 40 patients with Alzheimer's disease. The frontotemporal dementia patients had higher scores on the Hamilton Depression Rating Scale and exhibited significantly more DSM-III-R major depression (N = 5, 25%) than the Alzheimer's disease patients (N = 2, 5%). However, among the frontotemporal dementia patients, only 40% expressed depressed mood, sleep disturbances were found in 30%, appetite changes in 25%, and low self-esteem in 10%, while irritable mood was found in 80% of patients, anergia in 75%, social withdrawal in 70%, psychomotor retardation in 35%, and suicidal ideation in 20%. Swartz et al.,[153] using the Schedule for Clinical Assessment in Neuropsychiatry in a retrospective chart review, found that early episodic lability, sadness, anhedonia, increased appetite, loss of interest, and social withdrawal were common among 19 frontotemporal dementia patients, but hopelessness and suicidal ideation occurred in less than half, and themes of guilt were absent.

The relative prevalence of depression in frontotemporal dementia and Alzheimer's disease may depend upon how depression is ascertained. Using their caregiver questionnaire, Bozeat et al.[49] found that mood changes in general were equally prevalent in frontotemporal dementia and Alzheimer's disease and covaried with disease severity. Other investigations with other means or instruments have shown less depression, and possibly more euphoria, in frontotemporal dementia versus Alzheimer's disease and most other dementias.[41,95,149,154–156] Using caregiver questionnaires and interviews, Barber et al.[95] found that mood changes were significantly more common in 20 Alzheimer's disease than in 18 frontotemporal dementia patients. Snowden et al.[149] summarized their experiences in caring for approximately 200 frontotemporal lobar degeneration patients (40 autopsy-proven), and compared with approximately 400 patients with Alzheimer's disease, depression was less common in frontotemporal dementia. Mendez et al.[154] found positive ratings on the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) affective disturbances subscale in 25% of 29 frontotemporal dementia patients, compared to 38% of 29 Alzheimer's disease patients, and Chiu and colleagues[157] did not find significant differences in the Behavioral Pathology in Alzheimer's Disease affective disturbances subscale between frontotemporal dementia and Alzheimer's disease, vascular dementia, and dementia with Lewy bodies. In two studies using the Neuropsychiatric Inventory (154 patients), Levy et al.[41,156] found that patients with frontotemporal dementia had lower levels of depression or dysphoric mood (39%) than did those with Alzheimer's disease (43%), Parkinson's disease (55%), and Huntington's disease (71%), but not progressive supranuclear palsy (18%). In addition, a neuropsychological study of 40 frontotemporal dementia patients and 40 subcortical vascular dementia patients found milder depressive symptoms in frontotemporal dementia than in vascular dementia.[83]

In addition to depression, euphoria, hypomania, emotional lability, childish excitement, and acquired extroversion can occur in the context of frontotemporal de-

mentia and can mimic bipolar disease.[2,21,46,65,75,158] In a longitudinal series of 20 patients with frontotemporal dementia,[107] euphoria occurred in 35% and ranged between 30% and 36% in two studies that used the Neuropsychiatric Inventory,[41,43] and Levy et al.[41] found that euphoria was more common in frontotemporal dementia (36% of 22 patients) compared to Alzheimer's disease (7% of 30 patients). Although mania has not yet been reported in frontotemporal dementia, McMurtray et al.[60] reported hypomania-like behavior among tvFTD patients, and Thompson et al.[88] found hypomania retrospectively in 2.8% of 36 patients with left-lateralized tvFTD and 9.1% of 11 patients with right-lateralized tvFTD. The hypomanic patient in the latter study appeared to be elated with mild pressured speech and flight of ideas. Emotionalism or lability may occur in some patients with frontotemporal dementia.[15,76,159] Finally, peurile, childish, frivolous, or silly behavior occurs with right temporal, and probably adjacent orbitofrontal, involvement[75] and can be associated with moria, or foolish or silly euphoria, and Witzelsücht, or a tendency to tell inappropriate jokes.[74]

Depression correlates with severe left frontotemporal disease, especially with temporal involvement, whereas other emotional disturbances correlate with early right temporal disease. In the study of Bozeat et al.,[49] depression was present in 45% of their tvFTD patients but only 7% of their fvFTD patients. Similarly, Chow and Mendez[160] found depression in 19% of 16 patients with frontotemporal dementia, compared to 44% of nine patients with semantic dementia. Among tvFTD patients, Edwards-Lee et al.[73] found typical depression (anhedonia, feelings of worthlessness, crying) in two of five left tvFTD patients and none of five right tvFTD patients using the Neuropsychiatric Inventory. In contrast, among 74 frontotemporal dementia patients, McMurtray et al.[60] found hypomanic-like behavior associated with temporal hypoperfusion on SPECT, and Mendez et al.[75] found dysthymia and anxiety associated with right temporal hypoperfusion.

Anxiety, Irritability, and Aggression Anxiety symptoms, usually assessed with the Neuropsychiatric Inventory, may be more frequent among frontotemporal dementia patients than has been previously appreciated. In Lopez et al.'s[70] study, 45% of their 20 frontotemporal dementia patients had anxiety, compared to only 10% of their 40 Alzheimer's disease patients. Neuropsychiatric Inventory studies show more anxiety in patients with fvFTD than those with tvFTD or Alzheimer's disease.[43,57] Porter et al.[161] specifically assessed the prevalence of anxiety among 115 patients with Alzheimer's disease, as compared with 33 patients with frontotemporal dementia, 43 patients with vascular dementia, and 40 normal control subjects. Anxiety was significantly more common in patients with frontotemporal dementia and vascular dementia than in patients with Alzheimer's disease. More recently, Le Ber et al.[61] evaluated 68 frontotemporal dementia patients and reported anxiety symptoms in 15% of them. Among frontotemporal dementia patients, anxiety correlated with right temporal hypoperfusion,[60] and increased neuroticism and personal distress correlated with right temporal atrophy.[99] Finally, several investigators have commented on the presence of hypochondriacal complaints among frontotemporal dementia patients.[15,35,41,65,76,130]

Irritability and aggression are systematically described in only a few publications on frontotemporal dementia. Mendez et al.[154] applied the Behavioral Pathology in Alzheimer's Disease rating scale and found more anger and aggressive outbursts in frontotemporal dementia compared to Alzheimer's disease, and Lopez et al.[70] evaluated DSM-III-R diagnoses and found significantly more irritability and agitation in frontotemporal dementia compared to Alzheimer's disease. Passant et al.[25] reported physical aggression and signs of hostility in eight of their 19 neuropathologically confirmed frontotemporal dementia patients. Edwards-Lee et al.[73] described irritability and aggressive behavior as particularly associated with right temporal involvement, but Thompson et al.[88] indicated that irritability was more common in left than in right temporal frontotemporal lobar degeneration.

Additional Behaviors with Limited Literature Common additional noncognitive behaviors in frontotemporal dementia and related syndromes include declines in hygiene and self-care, behavioral eccentricities, fixed stare and/or smile, aberrant motor behavior, sleep disturbances, and increased artistic creativity. Most of these behaviors are difficult to entirely distinguish from previously discussed neuropsychiatric features of frontotemporal dementia; however, criteria and investigators have specifically referred to these behaviors as characteristic of this disorder. Loss of hygiene and self-care are common in frontotemporal dementia but are difficult to dissociate from apathy-abulia, disinhibition-impulsivity, and loss of insight and self-referential behavior. Sev-

eral investigators have emphasized the eccentric behaviors that can emerge, particularly in right tvFTD, including bizarre alterations in mode of dress and marked changes in religious or political orientation.[73,86] An "alien stare" or peculiar physical bearing (sustained stare or fixed fatuous smile) is associated with right frontotemporal disease.[75] Affect in frontotemporal dementia is sometimes jocular and facial expressions are often fatuous with grinning and inappropriate giggling.[149] Many of the Neuropsychiatric Inventory studies describe aberrant motor behavior in patients with frontotemporal dementia as compared to other conditions,[41,43,44,48,57,68,69] but these can be repetitive stereotypies or compulsions, disinhibition-impulsivity, irritability, or other behaviors. Finally, Liu et al.[57] described sleep disturbances in tvFTD and among 47 semantic dementia patients, and Thompson et al.[88] described those with predominant right-side involvement as more prone to sleep problems.

One of the most interesting and intriguing behavioral changes among frontotemporal dementia patients is an increase in artistic creativity. Several case reports describe an increase in primarily visual artistic performance among well-diagnosed patients with frontotemporal dementia.[162–166] These authors suggest the possibility of a release of perceptual abilities with progressive impairments of language and other left hemisphere functions.

Treatment

There are few studies dedicated to the evaluation of drug treatments in frontotemporal dementia (Table 3).[167] Although there is no specific cure for frontotemporal dementia and related syndromes, symptomatic therapies can be very helpful. Serotonin binding is decreased in frontotemporal dementia,[168] and selective serotonin reuptake inhibitors (SSRIs) can decrease the neuropsychiatric symptoms of frontotemporal dementia.[160] Disinhibition-impulsivity, depressive symptoms, carbohydrate craving, and repetitive behaviors may respond to SSRIs such as sertraline, paroxetine, or fluoxetine[169] and trazodone may help for some of these behaviors.[170] In one study, most frontotemporal dementia patients had a decrease in their stereotypical movements with the administration of sertraline.[133] In another study, four of five frontotemporal dementia patients treated with fluoxetine, sertraline, or paroxetine for a minimum of 3 months had improvement in depressive symptoms.[169] SSRIs, however, may produce side-effects in these patients.[171] For example, treatment of pathological laughter in a 61-year-old man with frontotemporal dementia was complicated by intermittent rhythmic myoclonus, reliably evoked independently by fluoxetine or trazodone.[172] In another example, treatment with paroxetine was associated with impairment on paired associates learning, reversal learning, and delayed pattern recognition.[173] In two patients who failed to respond to SSRIs for depression, preliminary evidence suggested that coadministration of lithium might be helpful,[174] and fluvoxamine helped some patients with compulsions.[175] Frontotemporal dementia is associated with some reduction in dopaminergic function, suggesting an as yet unstudied role for drugs such as selegiline and amantadine.[168] Marked disinhibition, aggressive behavior, or verbal outbursts may respond to small doses of atypical antipsychotics such as risperidone, olanzapine, quetiapine, or aripiprazole. Caution is advised, however, as occasionally, similar to patients with dementia with Lewy bodies, patients with frontotemporal dementia may manifest neuroleptic hypersensitivity and elements of malignant neuroleptic syndrome.[176] Theoretically, carbamazepine, valproate, or lamotrigine may diminish symptoms as well, but no dedicated studies are available. One study has shown some efficacy of a single 40 mg methylphenidate dose in improved decision-making behavior on a gambling task, but not on other behavioral or cognitive measures.[177]

The role of medications used to treat Alzheimer's disease for the treatment of frontotemporal dementia is unclear. Unlike Alzheimer's disease patients, frontotemporal dementia patients have normal cholinergic function.[168] There is questionable benefit from acetylcholinesterase inhibitors such as donepezil, rivastigmine, or galantamine and recent evidence that they may exacerbate disinhibition-impulsivity and repetitive behaviors.[178] Others have suggested improvement among patients with frontotemporal dementia;[179–181] however, those studies probably included significant numbers of Alzheimer's disease patients among those with so-called "FTD." For example, in the largest study to date on acetylcholinesterase inhibitors in frontotemporal dementia, all of the patients uncharacteristically had significant memory, cognitive impairments, and behavioral disorders about 7 months into their disease and were older by about 10 years than the average age of onset for this disease. Antioxidant supplements, such as vitamin E, may be helpful in delaying progression, and the potential role of memantine in frontotemporal lobar

degeneration is currently under active investigation. There is some rationale for the use of this putative neuroprotective agent in patients with frontotemporal dementia.

The nonpharmacological management of patients with frontotemporal dementia focuses on education and behavioral interventions. Clinicians help caregivers by explaining that the neuropsychiatric features have a neurological basis and by designing behavioral management strategies.[160,182] Some behavioral disturbances such as social misconduct and stereotypy might respond to rehabilitation techniques or to retraining via preserved procedural memory.[183,184] When hyperorality is present, dietary and other restrictions may prevent excessive weight gain or the dangerous placement of nonfood items in the mouth.[118] Similarly, other specific interventions should be employed to target other neuropsychiatric behaviors. In general, frontotemporal dementia is very stressful to the caregiver and support for the family, as well as continued advice on the management of disturbed behaviors, is critically important. Depression, anxiety, disinhibition, apathy, agitation, and psychosis should be detected and treated since these are particularly associated with high levels of caregiver distress.[43,44]

DISCUSSION

The current review indicates that frontotemporal dementia patients can develop several noncognitive neuropsychiatric behaviors that are strikingly different from the patient's premorbid behavior. The most common and early indication of frontotemporal dementia is subtle apathy, abulia, or a decreased pursuit of usual activities to the intensity present before. A second major subgroup is first evident when a patient suddenly performs uncharacteristically disinhibited or impulsive acts. Several investigators have suggested that these two presenting subgroups constitute major behavioral subtypes of frontotemporal dementia.[28,32,185] Another characteristic of frontotemporal dementia is an early decrease in self-referential behavior which extends to not only decreases in insight and disease awareness but an inability to see themselves through others' eyes. They cannot rec-

TABLE 3. Treatment of Frontotemporal Dementia

Pharmacological Management

1. Neuropsychiatric symptoms such as disinhibition-impulsivity, depressive symptoms, carbohydrate craving, and repetitive behaviors may respond to selective serotonin reuptake inhibitors such as sertraline, paroxetine, or fluoxetine; fluvoxamine may be particularly useful for compulsions.
2. Coadministration of lithium with SSRIs might be helpful in depression and possibly other conditions.
3. Marked disinhibition-impulsivity or aggressive and disruptive behaviors may respond to small doses of atypical antipsychotics such as risperidone, olanzapine, quetiapine, or aripiprazole.
4. Carbamazepine, valproate, or lamotrigine may diminish long-term emotional fluctuations.
5. Psychostimulants or modafinil may help apathy-abulia, but data are lacking.
6. Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) are of unclear benefit in FTLD and could exacerbate disinhibition-impulsivity and repetitive behaviors.
7. Antioxidants, e.g., vitamin E at 400–2000 IU, may prove to be useful in FTD to delay progression.
8. There may be a role for memantine as a neuroprotective agent in patients with FTD.
9. The role for drugs such as selegiline and amantadine in symptomatic therapy remains to be studied.
10. Sleep aids can help regulate day-night cycle and sleep disturbances.

Non-Pharmacological Management

1. Education-explanation on the nature of the disease and the fact that the neuropsychiatric features have a neurological basis and are not "deliberate" behaviors.
2. Behavioral management strategies and interventions—some behavioral disturbances such as social misconduct and stereotypy might respond to retraining of other strategies.
3. Specific behavioral restrictions—certain behaviors require restructuring the environment or other restrictive measures, e.g., hyperorality, roaming, or compulsions. In particular, FTD patients lack judgment and require monitoring and restriction of decision-making.
4. Attend to the patient's daily quality of life: mood status, social connectedness, ability to communicate, physical activity, and nutritional status.
5. Attend to functional issues: activities of daily living, home environment and safety, transportation and driving, independence vs. alternative living situations, and safe return bracelet.
6. Assure that the patient has a primary medical doctor.
7. Attend to non-medical stressors: financial, legal, and the need for conservatorship.
8. Evaluate the need for genetic counseling, if other family members are affected.
9. Evaluate the need for family or caregiver psychological counseling, if appropriate.
10. Caring for caregiver: support groups, respite, or relief for caregiver including involvement of other family members and referral to community resources, e.g., Family Caregiver Alliance from AD Caregivers Resource Center www.caregiver.org (1-800-445-8106); and the Association for Frontotemporal Dementias; www.ftd-picks.org.

ognize others' feelings, attitudes, or beliefs. Their emotions are blunted, and they become unempathic to the point of not responding to the emotional needs of their family and friends. Perhaps most strikingly there is a decline in social behavior ranging from a loss of a sense of social propriety and manners to frank sociopathic acts. There are major changes in dietary or eating behavior as well, including indiscriminate eating and a craving for sweets or the development of food fads. Frontotemporal dementia patients often manifest a range of repetitive behaviors from simple motor stereotypies to complex compulsions. Other neuropsychiatric manifestations may occur to varying degrees including euphoria and mood lability in about a third of patients; dysphoria or depression, including as a prodrome to frontotemporal dementia; and anxiety, irritability and aggressiveness. However, delusions and hallucinations are rare.

Patients with frontotemporal dementia present with neuropsychiatric features which vary depending on the regions that are involved earliest in the disease.[60,75] In the earliest stages, frontotemporal dementia is associated with significant hemispheric asymmetry as well as a different extent of pathology in frontal and anterior temporal regions.[9] Consequently, the presence of specific regional involvement on functional neuroimaging may suggest which neuropsychiatric features are most likely manifestations of frontotemporal dementia. For example, patients with predominantly frontal frontotemporal dementia may manifest apathy-abulia, decreased social dominance, and aspontaneity,[55,57,104] and those with predominantly temporal frontotemporal dementia may have impairments in emotional processing, complex compulsions, and anxiety or hypomania-like behavior.[55,60,186] Patients with right frontal frontotemporal dementia can violate social and moral norms, manifest disinhibition-impulsivity, lose insight, and have stereotypies and indiscriminate eating.[57,65,73,104,187] Patients with right temporal frontotemporal dementia can have blunted emotions and nonempathic affect and interpersonal coldness. These and other neuropsychiatric-neuroimaging correlations are useful in the early diagnosis of frontotemporal dementia.

In sum, frontotemporal dementia is a devastating neurodegenerative disease, and the early diagnosis of this disorder is critical for developing management strategies and interventions for these patients. Within the first few years after onset, the neuropsychiatric behaviors reviewed here usually precede or overshadow any cognitive disabilities.[2,5,21,22,73] In the absence of a biomarker, however, frontotemporal dementia remains difficult to diagnose and may be confused with other neurological or psychiatric disorders.[2,23,25,188–190] During the first 2 years of their disease, these patients may see many different doctors and undergo extensive evaluations with significant delays in diagnosis of 3–4 years or more.[8,25,190] Moreover, clinicopathologic studies report a wide range (0%–71%) of clinical accuracy for diagnosing frontotemporal dementia.[2,3,6,8,12,13,188,189] Even at tertiary centers, the diagnostic rate for frontotemporal dementia reaches only about 80%–85% by the time of death.[13,191,192] Recognizing these noncognitive neuropsychiatric symptoms of frontotemporal dementia is critical to recognizing the clinical disease.

Directions for Future Research

Clinical investigators still have far to go in defining the neuropsychiatric features of frontotemporal dementia and arriving at better diagnostic criteria. First, as new and better diagnostic criteria are developed, investigators need to specifically include the neuropsychiatric behaviors reviewed here. In the absence of biomarkers for frontotemporal dementia and related disorders, clinicians rely on behavioral criteria for diagnosis during life. Second, the neuropsychiatric features need to undergo more rigorous examination. The current literature is often confounded by a lack of systematic assessment of specific behavioral disorders using valid and reliable criteria and by a lack of uniform assessment methodology. Many studies are retrospective investigations that do not use a gold standard technique for diagnosing frontotemporal dementia and rely on chart notes for documentation of behavioral disturbances. Some studies appear to use strictly clinical impressions without defining behavioral criteria. Others use behavioral scales, such as the Neuropsychiatric Inventory, rather than formal diagnostic criteria for psychiatric symptoms. There is a clear need for the systematic assessment of neuropsychiatric behaviors using valid and reliable diagnostic criteria with a view toward defining their prevalences, correlates (neurological, functional, imaging, prognostic, pathological), and treatment outcomes. Finally, there is a striking lack of clinical drug trials for the frontotemporal lobar degenerations. Both therapeutic and symptomatic drug trials are desperately needed in frontotemporal dementia. These trials should employ well-diagnosed patients and conditions and utilize adequate outcome measures. Nevertheless, the exponen-

tial increase in research studies in frontotemporal dementia in recent years is an indication that the future promises to reveal much more about the neuropsychiatry of frontotemporal dementia and its treatment.

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