Assessment of Behavioral Variant Frontotemporal Dementia

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Behavioral variant frontotemporal dementia (bvFTD) is one of the three neurodegenerative syndromes collectively referred to as frontotemporal dementia (FTD). Initially thought to be rare, we now know that it is equally as common as Alzheimer's disease in individuals under the age of 65 [1] and is the third most common dementia after Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) [2]. Precise estimation of the prevalence of FTD has been difficult as disease frequency is low and accurate diagnosis depends on expert evaluation. However, population-based studies in both the United States and United Kingdom estimate a sporadic occurrence at around 3.3–3.5/100,000 in individuals between 45 and 65 years of age [3, 4]. Age of onset is typically in midlife, though onset ranges considerably, from the 30s to 90s [1, 5, 6]. Survival rates vary depending on clinical phenotype, from 3 to 14 years [7]; however, median survival for all variants from diagnosis to death has been estimated to be approximately 7–13 years [8].

Clinically, FTD is expressed as three main variants [9]. BvFTD is characterized by profound and early changes in personality and behavior [9]. This phenotype is most common and accounts for approximately 70% of the clinical expression of the disease [10]. As such, bvFTD will be the focus of this chapter. The other two variants are subtypes of the Primary Progressive Aphasia (PPA) syndromes. The semantic variant (svPPA) is associated with the loss of word knowledge (e.g., semantic structure of language), while the nonfluent variant (nfPPA) is characterized by early disturbances in motor speech output and loss of syntax (e.g., grammatical structure of language) [9, 11]. These two variants account for approximately 15% and 10% of the phenotypic expression of the disease, respectively [10]. While some studies suggest that a gender distribution bias occurs by clinical syndrome (e.g., male bias in bvFTD and svPPA; female bias in nfPPA [1, 5, 6]), a recent review examining the prevalence and incidence of FTD suggests that males and females were equally as likely to be affected with FTD across all variants [12].

Earliest Signs of bvFTD

The earliest signs of disease in bvFTD are frequently subtle personality and behavioral changes that become increasingly pronounced as time goes on. These symptoms often include apathy or disinhibition, reduced emotional response, changes in personality or beliefs [13], poor

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judgment, and impairment in personal and social awareness [14–17]. These changes are often dramatic, resulting in the dissolution of the individual's former self, such that partners and families no longer recognize their loved ones [13]. For example, individuals may begin to make impulsive decisions or actions, including such behaviors as shoplifting, driving recklessly, or physically assaulting others [14, 16, 18, 19]. They might violate social norms by making inappropriate sexual comments [20] or become emotionally cold and self-centered such that they no longer respond to others' emotional needs or pain [21]. These changes often exist in sharp contrast to their cognitive ability, which may remain relatively intact for some time.

Diagnostic Criteria for bvFTD

In the past, diagnosis of bvFTD was most often made using the revised version of the Lund–Manchester criteria, which were then reformulated by a consensus of specialists in 1998 [9]. However, considerable advancements in our understanding of this disease over the last two decades has led to the development of new criteria, published in 2011 by the International bvFTD Criteria Consortium [22] (Table 33.1). With these criteria, diagnosis of possible bvFTD is based solely on clinical presentation. Patients must meet at least three of the six following criteria: (1) early behavioral disinhibition; (2) early apathy/inertia; (3) early loss of sympathy or empathy; (4) early perseverative, stereotyped, or compulsive behaviors; (5) hyperorality or dietary changes; and (6) a neuropsychological profile suggesting deficits on tasks of executive function with *relative* sparing of memory and visuospatial function. To meet the criteria for probable bvFTD, a patient must meet the criteria for possible bvFTD, exhibit significant functional decline, and show evidence of frontal and/or temporal atrophy on structural MRI or CT or hypometabolism on positron emission tomography (PET). Sensitivity of the new criteria has been demonstrated via retrospective chart review of pathologically confirmed cases in a multisite study, and findings suggest that the new criteria have greater sensitivity to the diagnosis of bvFTD, compared to the previous criteria (0.85 vs. 0.52, respectively) [22]. In addition, a study by LaMarre and colleagues has shown that the criteria demonstrate excellent inter-rater reliability for the diagnosis of both possible and probable bvFTD [23].

Neuroanatomy and Pathology of bvFTD

The hallmark symptoms of bvFTD strongly reflect initial areas of neurodegeneration. Structural neuroimaging analysis in patients in the earliest stages of bvFTD (Clinical Dementia Rating (CDR) scale = 0.5; mild dementia) suggests that initial degeneration occurs primarily in paralimbic structures such as the anterior cingulate cortex, frontoinsular region, dorsal anterior insula, and lateral orbitofrontal cortex [24], and disease staging of autopsy-confirmed cases of bvFTD are consistent with this finding [25]. These structures have been widely implicated in human social function and awareness of the self [26] and are part of a neural network thought to play a role in decoding the emotional salience (visceral, homeostatic, hedonic value) of a stimulus in order to facilitate appropriate action, i.e., "salience network" [27]. As the disease progresses, neurodegeneration occurs in widespread areas of the frontal and temporal lobes [28–32].

BvFTD is caused by abnormal aggregation of protein in the brain, referred to collectively as frontotemporal lobar degeneration (FTLD). The two most common pathologies associated with bvFTD are FTLD with tau-positive inclusions (FTLD-tau) and FTLD with TDP-43 positive inclusions (FTLD-TDP) [2, 33], with a handful of additional proteins accounting for approximately 10% of bvFTD cases [33]. Under normal conditions, both tau and TDP-43 play important roles in neuronal cell structure and function [34, 35]. Under pathologic conditions, however, these proteins aggregate and accumulate in the cytoplasm of neurons and glial cells and are associated with neuronal death and atrophy [2, 33].

Table 33.1 International consensus criteria for bvFTD [22]

I. Neurodegenerative disease
The following symptom must be present for any FTD clinical syndrome:
A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)
II. Possible bvFTD
Three of the following behavioral/cognitive symptoms [A–F] must be present to meet criteria. These symptoms should occur repeatedly, not just as a single instance
A. Early behavioral disinhibition
(a). Socially inappropriate behavior (b). Loss of manners or decorum (c). Impulsive, rash, or careless actions
B. Early apathy or inertia
(a). Apathy: Loss of interest, drive, or motivation (b). Inertia: Decreased initiation of behavior
C. Early loss of sympathy or empathy
(a). Diminished response to other people's needs or feelings: Positive rating should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings (b). Diminished social interest, interrelatedness, or personal warmth: General decrease in social engagement
D. Early perseverative, stereotyped, or compulsive/ritualistic behavior
(a). Simple repetitive movements (b). Complex, compulsive, or ritualistic behaviors (c). Stereotypy of speech
E. Hyperorality and dietary changes
(a). Altered food preferences (b). Binge eating, increased consumption of alcohol or cigarettes (c). Oral exploration or consumption of inedible objects
F. Neuropsychological profile: Executive/generation deficits with relative sparing of memory and visuospatial functions
(a). Deficits in executive tasks (b). Relative sparing of episodic memory (compared to degree of executive dysfunction) (c). Relative sparing of visuospatial skills (compared to degree of executive dysfunction)
III. Probable bvFTD
A. Meets criteria for possible bvFTD B. Exhibits significant functional decline (by caregiver report or as evidenced by CDR or FAQ scores) C. Imaging results consistent with bvFTD
(a). Frontal and/or anterior temporal atrophy on CT or MRI (b). Frontal hypoperfusion or hypometabolism on SPECT or PET
IV. bvFTD with definite FTLD pathology
Criterion A and either criterion B or C must be present to meet criteria
A. Meets criteria for possible bvFTD B. Histopathological evidence of FTLD on biopsy or at postmortem C. The presence of known pathogenic mutation
V. Exclusion criteria for bvFTD
Criteria A and B must both be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD
A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders, e.g., delirium, cerebrovascular disease, cerebellar disorder, systemic disorders (e.g., hypothyroidism), or substance-induced conditions B. Behavioral disturbance is better accounted for by a psychiatric diagnosis, e.g., depression, bipolar disorder, schizophrenia, preexisting personality disorder C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process (e.g., genetic mutations, extensive PIB finding, CSF markers)

Advancements in our understanding of the underlying pathology of FTD over the past 15 years have also demonstrated links with diseases not historically believed to be associated with changes in cognition and behavior [36–38]. For example, FTLD-tau includes cases fulfilling pathological diagnostic criteria for not only Pick's disease and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) but also for motor disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [39, 40]. Similarly, cases found to have FTLD-TDP may present alone or in combination with motor neuron disease (e.g., amyotrophic lateral sclerosis (ALS)) [41, 42]. There is also a growing consensus that the behavioral syndrome of bvFTD can manifest in patients with PSP, CBD, and ALS [43–45].

Genetics

While sporadic cases are common in bvFTD, at least 30–40% of all cases appear to be genetic in nature [46], with rates of autosomal dominant pattern of inheritance ranging from 10% to 30% [47, 48]. At this time, genetic mutations known to cause familial FTD have been found on three different chromosomes (3, 9, 17) [49–51]. The first gene was discovered in 1998 and was found to be caused by mutations in the microtubule-associated protein ("MAPT") gene [52]. It is now known that *MAPT* codes for the protein tau, which as mentioned above, is a major pathological subtype of FTD [53]. Several years later, linkage analysis in the same region of chromosome 17 found that mutations in the gene coding for the growth factor progranulin also cause FTD (*PGRN*; [54]). Unlike *MAPT*, these cases display TDP-43 inclusions rather than tau [55]. Most recently, it was discovered that the most common cause of inherited FTD (and ALS) was caused by a GGGGCC hexanucleotide repeat expansion within the noncoding region of the chromosome 9 open reading frame 72 (i.e., *C9orf72* gene) [50]. While the minimum repeat length to confer risk is unknown, individuals with bvFTD and/or ALS can have anywhere from 100 to several thousand copies of the repeat expansion. Similar to *PGRN*, pathology typically shows TDP-43 inclusions [56]. Interestingly, any of the three clinical variants of FTD may occur in familial forms of the disease; however, certain variants are more likely to be expressed than others [10, 56, 57]. For example, *PGRN* mutation carriers tend to develop symptoms characteristic of bvFTD or nfPPA [58].[1]

Differential Diagnosis

Despite significant advancements in the field, diagnosis of bvFTD remains clinically challenging. Unsurprisingly, bvFTD is commonly misdiagnosed as early-onset AD. Many symptoms of the two diseases overlap, including neuropsychiatric disturbance and executive dysfunction [59, 60]. Patients with neurodegenerative motor syndromes may also exhibit symptoms consistent with a diagnosis of bvFTD (or an aphasia variant) [43–45]. As such, having a concomitant syndrome such as PSP or ALS should not be considered exclusionary for a diagnosis of bvFTD. Huntington's disease may also mimic many of the behavioral and psychiatric disturbances seen in bvFTD [61].

Patients with bvFTD may also be misdiagnosed with a late-onset psychiatric disturbance. Symptoms of disinhibition, euphoria, and poor judgment can mimic those of mania, while profound apathy and eating disturbance might be misconstrued as depression. Wooley and colleagues [62] completed a retrospective chart review of 252 patients with neurodegenerative disease presenting to an academic medical center specialty clinic. Of the patients with bvFTD, 51% of patients had received a prior diagnosis of a psychiatric disorder (e.g., major depression, bipolar disorder, schizophrenia) compared to 23% of patients with Alzheimer's disease (e.g., major depression, anxiety), suggesting that the symptoms of bvFTD may be misunderstood by mental health-care providers. That said, certain

[1] For a recent review on the genetics of FTD, please read Pottier et al. [56].

forms of the disease may actually cause outright psychiatric symptoms. For example, carriers of *C9ORF72* mutations frequently display psychiatric symptoms at disease onset, including those seen in psychotic, bipolar, and compulsive disorders [63–66]. As such, neurodegenerative disease should always be considered on the differential when new-onset psychiatric disturbance is present in older individuals.

A small subset of patients diagnosed with bvFTD have been characterized as "nonprogressive" or "bvFTD phenocopies" due to the presence of a behavioral disturbance in the context of lack of notable atrophy on imaging or cognitive decline over time [67–69]. The etiology of this syndrome remains unclear. For example, it has been demonstrated that some cases may actually represent psychiatric or personality disorders [70], while other cases may be due to a slowly progressive genetic form of the disease [71]. The importance of accurate differential diagnosis cannot be overstated. Treatments meant for a different diagnosis, such as AD, can potentially exacerbate bvFTD symptoms (Table 33.2).

Efforts to develop specific, disease-modifying therapies for FTLD are advancing rapidly, focusing on the major proteins currently known to be involved in the pathogenesis of the disease. Clinical trials aimed at manipulating tau, TDP-43, and PGRN levels have already begun. Testing the efficacy of these medications greatly depends on our ability to ensure homogenous samples in clinical trials. As there are currently no definitive methods for determining FTLD pathology prior to autopsy, predicting pathology antemortem remains a key challenge. Researchers are actively working to better understand the clinicopathologic correlations relevant to each protein currently believed to be involved in the development of FTLD.

Table 33.2 Disorders that may present with similar neurobehavioral features to bvFTD

Neurodegenerative diseases	Progressive supranuclear palsy
	Corticobasal syndrome
	Amyotrophic lateral sclerosis
	Alzheimer's disease
	Semantic variant primary progressive aphasia
	Huntington's disease
	Lewy body dementia
Psychiatric disorders	Bipolar disorder
	Major depression
	Psychosis
	FTD phenocopy
	Psychopathy
Neurologic disorders	Cerebrovascular accident
	Traumatic brain injury

Review of Neuropsychological Literature

Despite obvious impairment in the patient's behavior and judgment, researchers seeking to characterize a neuropsychological profile specific to bvFTD have not been highly successful. Research is plagued with a number of significant issues that likely contribute to discrepancies in the data, including lack of universally applied diagnostic criteria, variability in diagnostic terminology, lumping together of all three clinical variants of the disease, small sample sizes, and lack of reporting of disease severity or symptom duration [72]. Issues can also arise due to test selection and interpretation issues, including the possibility that impaired performance on tests are due to factors that are beyond what the test is meant to measure. For example, a study examining qualitative features of performance on neuropsychological testing in bvFTD and AD found that patients with bvFTD tend to perform poorly on tasks of visuoconstructive ability, not due to deficits in visual perceptive ability, but rather, due to perseverations and deficits in organizational ability [73]. Moreover, behavioral manifestations of the disease itself, including poor motivation and distractibility, may contribute to variability in cognitive performance scores.

Our current understanding of the neuropsychology of bvFTD lies largely within the context of research seeking to improve differential diagnosis between neurodegenerative diseases. In most cases, the cognitive profiles of individuals with bvFTD and AD are compared, though efforts to delineate specific tasks or cognitive facets that

will reliably differentiate the two have been unsuccessful. As such, *relative test score patterns* between domains appear to be most informative to differential diagnosis.

Memory

Compared to patients with AD who exhibit severe verbal and visuospatial episodic memory deficits [74–77], patients with bvFTD demonstrate a *relative* preservation in their episodic memory [73, 78–80], at least in the early stages of the disease [81]. The pattern is typically one of attenuated learning with a disorganized or inefficient approach. For example, Glosser and colleagues found that difficulty with serial-order recall was more common in individuals with bvFTD than in those with AD and svPPA [82]. Perhaps the most salient difference between bvFTD and AD is that bvFTD patients tend to retain information over delays, while AD patients exhibit rapid forgetting. Indeed, a recent study by Mansoor and colleagues found that individuals with pathology-confirmed bvFTD demonstrated significantly better consolidation of information over delays on a list-learning task when compared to individuals with AD [83]. Visual memory also appears to be relatively spared in bvFTD [78–81]. When both visual and verbal memory are within normal expectations, this may help strengthen diagnostic certainty that the patient does not have Alzheimer's disease.

These patterns of memory performance, however, are not specific to bvFTD. Disorders with frontal–subcortical involvement such as Parkinson's disease and PSP may also demonstrate similar patterns [84, 85]. Moreover, Ranasinghe and colleagues demonstrated that episodic memory declines longitudinally in both bvFTD and AD though mean scores at baseline were significantly different [81]. Nevertheless, relative preservation of episodic memory in bvFTD compared to AD remains one of the most reliable differences between these diseases.

Language

While individuals with bvFTD do not exhibit the same aphasia patterns that accompany PPA variants of FTD, notable declines in speech and language ability can occur. There are often reductions in spontaneous speech and decreased verbal output (single words or decreased phrase length) that can potentially progress to complete mutism [9, 86–88]. Reiterative speech disorders can also occur, such as palilalia, echolalia, verbal stereotypies, and automatic speech [9]. Despite these changes in verbal output, examination of semantic and syntactical knowledge using measures of confrontation naming, word/picture matching, and sentence comprehension suggests that these aspects of language remain relatively intact in bvFTD [73, 79, 89, 90].

There have been few studies that have directly examined differential language patterns between bvFTD and other diseases [87, 90, 91]. Rascovsky and colleagues [91] studied verbal fluency in pathology-confirmed cases of FTD and AD who were matched on age, education, and dementia severity. When converted to *z*-scores based on an age-matched control sample, scores on semantic fluency in the AD group were significantly lower than their scores on phonemic fluency, while the FTD patients performed poorly on both semantic and phonemic fluency.

Visuospatial

Although several studies have found that patients with bvFTD have visuoconstructional deficits on par with AD when the figure is very complex [78, 92, 93], the vast majority of research indicates that visuoconstruction and visual perceptual skills are better preserved in patients with bvFTD relative to AD [73, 86, 94–96]. Difficulties can arise for bvFTD patients when the task relies heavily on top-down control of spatial processing. For example, Possin and colleagues [97] demonstrated that figure copy performance was significantly correlated with right parietal cortex volume in patients with AD, but not with right

dorsolateral prefrontal cortex (DLPFC) volume. The opposite relationship was demonstrated in patients with bvFTD.

Attention/Executive Functions in bvFTD

While intuitive, the claim that attention and executive functions are broadly and disproportionately impacted in bvFTD lacks strong empirical support. Investigation of this domain using "traditional" tasks of executive function has led to largely conflicting findings. While some studies find impairments in this domain [79, 98–100], others do not [101–103]. One reason for this discrepancy likely relates to stage of disease at which patients are assessed. As neurodegeneration begins in the ventromedial aspect of the frontal lobe and moves dorsolaterally with disease progression [24, 27, 28, 104, 105], we would not expect to see executive deficits manifest until later in the disease. Moreover, some pathological subtypes of bvFTD do not necessarily exhibit significant DLPFC degeneration (e.g., TDP-43, Type II) [106]; as such, one might hypothesize that patients with this type of pathology will be less likely to demonstrate executive function deficits.

Another reason why findings have been inconsistent may be due to the fact that executive functions are a poorly defined construct that encompass heterogeneous facets of cognition such as working memory, inhibition, and set shifting [77, 107, 108]. Moreover, they depend heavily on lower-order aspects of cognition such as processing speed and visual perception. It appears that any number of tasks may be subsumed under this umbrella term and are often discussed as if interchangeable. Within the bvFTD neuropsychological literature, there is little consistency regarding which component of executive function might be particularly impaired in bvFTD (working memory vs. inhibition), or in the type of task chosen (e.g., Trail Making Test vs. Digit Span).

Overall, it appears that "traditional" clinical measures of executive function are not particularly sensitive early in the disease process. It is possible, however, that experimental measures of executive function may be more sensitive to subtle declines. For example, Krueger et al. [100] administered traditional tasks of executive function, as well as a computerized Flanker task (measuring cognitive control) to patients with bvFTD and healthy control subjects. Patients were dichotomized into those who scored within normal limits on standard tasks of executive function and those who did not, and their scores on the Flanker task were compared. Interestingly, *both* bvFTD patient groups showed a significantly larger congruency effect (e.g., longer latency on incongruent vs. congruent trials) compared to the normal control subjects [100]. These results suggest that even those patients who perform well on standard tasks of executive function may still have subtle yet perceptible deficits in cognitive control if measured by the appropriate method.

Another approach to measuring executive functioning in bvFTD has been to measure process-oriented features of performance such as errors. Kramer et al. found that overall error scores on tasks of executive function discriminated between patients with bvFTD and AD [79]. Rule violation errors may also be helpful in discriminating between AD and bvFTD. Carey and colleagues [109] found that despite similar achievement scores on the Delis–Kaplan Executive Function System Tower Task, patients with bvFTD made significantly more rule violations compared to patients with AD and normal controls. Similarly, Possin et al. (2012) have shown that despite similar scores on total number of correct designs generated, patients with bvFTD make a greater number of repetition errors compared to patients with AD [110]. Poor "online" detection of errors has also been shown to distinguish between bvFTD, CBS, and PSP [111].

Thompson et al. qualitatively analyzed error types between patients with AD and bvFTD on multiple tasks from several different domains of cognition, including language, memory, visuospatial, and executive function. While several tests were significantly different between the two groups, overall, differences in the types of errors

made were best able to distinguish between AD and bvFTD on regression analysis (e.g., spatial errors vs. perseverations on a drawing task) [73].

Examining errors is also important given that some researchers have found that patients with bvFTD often perform faster on measures of executive function (e.g., Stroop inhibition) than patients with AD but also make significantly more errors, indicating an imbalance in their ability to accurately make speed/error trade-offs [102, 103].

Social Behavior and Personality

The dorsolateral prefrontal cortex (DLPFC) degenerates in both AD and bvFTD, though this may occur at different stages in disease course [104]. This likely explains why large group differences in executive functioning are not regularly demonstrated between the two diseases [101, 112, 113]. Investigations into social and emotional function have produced more consistent results, likely due to the fact that they are mediated by more anterior and ventral aspects of the prefrontal cortex [114–117], areas selectively involved in bvFTD relative to other neurodegenerative disorders.

Studies examining social behavior in bvFTD have found that these individuals tend to demonstrate flat affect, reduced initiative, and more perseveration than patients with other neurodegenerative diseases [118]. Other studies have also found deficits in social pragmatics during conversation [87], worse judgment regarding social norms compared to patients with AD [119], and poor social judgment compared to patients with primary progressive aphasia [120]. Changes in personality facets related to interpersonal function have also been noted to occur in bvFTD. For example, Rankin et al. demonstrated that agreeableness (one of the Big Five personality traits) was not only decreased in bvFTD but also significantly related to right orbitofrontal cortex volumes [121].

Several researchers have found that patients with bvFTD have significantly less self-awareness regarding their current personality and behavioral deficits [21, 122–124] compared to patients with other neurodegenerative diseases, such as AD. This lack of awareness or concern may be due, in part, to the emotion-processing deficits that have been documented in bvFTD. While basic emotion processing such as the startle reflex has been shown to remain intact in patients with bvFTD [125], there are deficits in more complex forms of emotion such as self-conscious emotion, including embarrassment, [125, 126], emotional down-regulation [127], recognition of emotions in others [21, 128–131], and ability to empathize with others [120, 123, 132].

Complex Learning and Decision-Making

The ventral and orbital medial regions of the prefrontal cortex are also thought to be involved in self-advantageous decision-making and adaptive responses to changing emotional or social demands in the environment [115, 116]. Researchers have begun to create experimental paradigms which are thought to tap these processes, including tasks which measure risk taking via computerized gambling programs (e.g., Iowa Gambling Task) [133] and reversal learning tasks focused on reward and punishment [115]. Several studies have demonstrated impairments on these tasks in patients with bvFTD [98, 134–136]; however, these studies did not directly compare the performance of bvFTD to patients with other neurodegenerative diseases. More recently, several studies have demonstrated their utility in the differential diagnosis of bvFTD versus AD [137, 138]. Further research into the discriminatory ability of these tasks between different disease groups is warranted.

Summary of Neuropsychology Literature

While the "classic" pattern of impaired attention and executive function with relative sparing of memory, language, and visuospatial function can occur in bvFTD, this pattern is not

a constant and is just one of the six symptoms that define bvFTD (the other five being social or behavioral). As such, it is imperative that practitioners *do not* use evidence of this neuropsychological pattern as justification for diagnosis of the disease in the absence of other symptoms outlined in the International Diagnostic Criteria [22].

Clinical Assessment of bvFTD

A comprehensive evaluation of bvFTD should include a clinical interview, neuropsychological assessment, assessment of social and emotional function, and informant-based measures. Given that cognition can be relatively preserved in the early stages of the disease, the history, informant report, and observable behavior seen throughout the assessment will likely be the most helpful information you gather.

Interview

A well-structured clinical interview with a collateral source is critical. Patients typically lack insight into the social, emotional, or behavioral issues that are most germane to their caregivers and tend to deny problems. If the informant does not feel comfortable speaking frankly in front of the patient, one should consider conducting a separate interview. During the interview, important areas to cover include:

Onset and Progression

Has the onset been slow and insidious, or abrupt and explicit? Behavioral variant FTD is an insidious disease that may begin many years before changes become obvious. Moreover, because the age of onset of bvFTD tends to be in the late 50s, the personality and behavior changes are often misinterpreted as "midlife" troubles. While insidious change is common to most neurodegenerative diseases, abrupt onset changes in personality and behavior are less likely to be bvFTD.

Nature of Change

As evidenced in the International Criteria for bvFTD [22], changes in personality, emotionality, and social behavior are the most salient symptoms of bvFTD, and the six major symptoms of the International criteria can be used to structure the interview:

1. *Early behavioral disinhibition*. Has the person become socially, behaviorally, or cognitively disinhibited? Do they make inappropriate comments or engage in socially unacceptable behaviors (e.g., flatulence, nose picking)? Do they approach strangers and engage them in conversations or have new-onset gambling or stealing?
2. *Early apathy/inertia*. Does the patient demonstrate a significant loss of interest, drive, or initiation of behavior? For example, those patients who were once hardworking and spontaneous may become passive and indifferent to the surrounding environment. They may also become disengaged in others around them and show little interest in initiating or maintaining conversations.
3. *Early loss of empathy/sympathy*. Does the patient make hurtful or insensitive comments to others (e.g., make disparaging remarks about other's weight or looks), or seem not to notice the pain or distress of others, or lack emotional warmth?
4. *New-onset compulsive/stereotyped behaviors*. Patients with bvFTD can manifest complex compulsions, such as counting or checking rituals or hoarding of useless items such as paper napkins. They may also display simple motor or vocal stereotypies such as tapping, picking, lip smacking, and repeating nonsensical phrases.
5. *Hyperorality or dietary changes*. Changes in eating or hyperorality may occur as well, such that a person may begin to consume alcohol in large quantities, take up smoking cigarettes, or prefer to eat only fast food or sweets. Indeed, significant weight gain is common in bvFTD. Eating behaviors can also take on a

compulsive or rigid quality such as binge eating, eating only certain foods, or needing to be served meals at a particular time.

6. *Neuropsychological profile* (*executive deficits with relative preservation of memory and visuospatial function*). Does the patient seem to have trouble completing complex tasks, or doing two things at once, but can still drive, navigate around town, or remember conversations that occurred a few days earlier? As many patients will not have undergone neuropsychological testing prior to your assessment, pointed "real-world" questions regarding attention/executive functions vs. memory and visuospatial function can help get a better understanding of their cognitive profile.

Family History

Approximately 30–40% of all individuals with bvFTD have a strong family history of the disease. Unfortunately, clear family histories are often difficult to elicit. There may be vague recollections that one of their grandparents was "senile" or had been diagnosed with a psychiatric disorder later in life. However, if a history reveals family members who exhibited significant changes in personality and social behavior after the fifth decade or who had symptoms of motor disorder (e.g., ALS, PSP, CBS), these are potential clues that the individual may have a genetic form of the disease.

Neuroimaging

If the patient has had neuroimaging, it will be helpful to obtain the report or review the scan with a neuroradiologist or neurologist. Atrophy is often asymmetric (right > left) and, in the early to middle stages, confined to the medial frontal and anterior temporal lobes. With increasing disease severity, more diffuse areas of these brain regions degenerate, and more posterior areas including the parietal cortex become involved [25, 104, 105]. Of note, atrophy of the hippocampus also occurs in bvFTD [24, 25]; therefore, this finding should not be used to support a diagnosis of AD rather than bvFTD. Clinically, structural magnetic resonance imaging (MRI) is best for reviewing these findings, though positron emission tomography (PET) scans may also reveal hypometabolism of the frontal and temporal lobes. PET imaging that utilizes Pittsburgh Compound B (PIB), a radioligand which binds to amyloid in the brain, has been shown to be negative in bvFTD [104].

Cognitive Assessment

In general, tests of global cognition such as Folstein's Mini Mental Examination (MMSE; [139]), the Blessed-Roth Dementia Rating Scale [140], or the Montreal Cognitive Assessment (MoCA; [141]) can be insensitive to the subtle cognitive changes that occur early in bvFTD. Indeed, some bvFTD patients in our clinic score 30/30 on the MMSE, despite significant behavioral and social deficits. Nevertheless, inclusion of a measure of global cognition is standard practice in dementia assessment. With its greater focus on verbal fluency and executive functions, the MoCA may be better able to pick up on subtle deficits in bvFTD and is our measure of choice in this population.

We find that a short battery (approximately 1–1.5 h) that examines all major cognitive domains is a quick and useful way to help aid differential diagnosis without overtaxing the patient. While by no means invariable, the relative neuropsychological profile of a patient with bvFTD tends to be one of spared visuospatial and language function and relatively better performance than patients with AD on tests of episodic and semantic memory. Categorical verbal fluency is relatively better than phonemic fluency (though both may be attenuated due to economy of speech). We also recommend executive function tests that elicit and quantify performance errors such as rule violations, perseveration, environmental dependency, impulsivity, and distractibility since achievement scores have not been shown to reliably differentiate between bvFTD and AD.

Behavioral Observations

After neuropsychological evaluation, examiners at our center complete a brief behavior rating scale where patients are rated on a scale ranging from none, mild, moderate, to severe on the following observable behaviors: agitation, stimulus boundedness, perseverations, decreased initiation, motor stereotypies, distractibility, lack of social/emotional engagement, impulsivity, socially inappropriate behavior, and impaired or fluctuating levels of attention. Data from our center suggest that perseverative and inappropriate behaviors and lack of social engagement significantly discriminate between patients with bvFTD and AD. In addition to providing important diagnostic information, quantifying behaviors systematically can also be helpful in interpreting the neuropsychological data (e.g., Did the patient fully attend to the task, or were they distracted and disinhibited?).

Informant-Based Measures

The inclusion of informant-based measures in your assessment can yield important information which, for one reason or another, was not elicited on interview. These scales can provide invaluable information regarding social and emotional deficits experienced by the patient.

Neuropsychiatric Inventory [142]

The Neuropsychiatric Inventory (NPI) is a screening measure that is administered to the patient's informant by the clinician and is a well-validated measure of neuropsychiatric symptoms common in neurodegenerative disease. It was developed as a way to quickly and accurately assess the frequency and severity of 12 different neuropsychiatric behaviors that may occur in the context of dementia (e.g., anxiety, apathy, disinhibition, aberrant motor behavior). The informant is also asked to rate their level of distress by each symptom, which can be useful in helping structure feedback with the family. Extensive research investigating neuropsychiatric symptoms in dementia has been completed with the NPI [142]. Patients with bvFTD tend to have higher overall total scores on the NPI compared to AD, and the domains of apathy, disinhibition, aberrant motor behavior, and appetite/eating changes appear to best differentiate between bvFTD and AD [143–145].

Revised Self-Monitoring Scale [146]

This 13-item questionnaire measures an individual's sensitivity and responsiveness to social cues. While the measure was initially designed for self-report, this questionnaire is easily adapted to an informant-based questionnaire.

Interpersonal Reactivity Index [147]

The empathic concern (EC) and perspective taking (PT) subscales of the Interpersonal Reactivity Index (IRI) were designed to evaluate an individual's ability to empathize with others. The 7-item EC scale specifically measures an individual's emotional response which results from the perception of another's emotional state. The 7-item PT subscale measures an individual's tendency to spontaneously employ perspective taking in their typical social interactions. A recent paper by Dermody and colleagues (2016) demonstrated that while both AD and bvFTD patients displayed significantly worse scores on the Perspective Taking subscale of the IRI compared with healthy control participants, only patients with bvFTD displayed significantly worse scores on the Empathic Concern subscale, thus identifying a dissociation between AD and FTD patients in terms of cognitive versus affective facets of empathy [148].

Experimental Measures of Emotional/Social Function

There are a number of commercially available measures of emotional and social function that have been used to study deficits in bvFTD, but many of these tasks are too demanding for patients and do not provide reliable information. The following two measures were developed by Dr. Katherine Rankin at the University of

California, San Francisco (UCSF; krankin@memory.ucsf.edu). They are well tolerated by patients and provide diagnostically valuable information. If you would like to obtain copies, please contact Dr. Rankin.

Dynamic Affect Recognition Test

This test was designed to assess emotion recognition using dynamic, ecologically valid stimuli. Individuals are asked to watch 12 brief (20 s) vignettes of actors depicting one of the six basic emotions (happy, surprised, sad, angry, fearful, and disgusted) with a semantically neutral script and choose the correct emotion. Comparison of performance between patients with AD and bvFTD suggests that those with AD perform comparably to normal controls, while those with bvFTD have significant deficits in their ability to accurately recognize emotions [149].

Social Norms Questionnaire

This simple, 22-item yes/no questionnaire was developed as a way to determine the degree to which patients understand and can accurately identify implicit but widely accepted social boundaries dominant in the US culture. The social norms questionnaire (SNQ22) includes both inappropriate (e.g., "Cut in line if you are in a hurry," "Pick your nose in public," and "Wear the same shirt every day") and generally acceptable behaviors (e.g., "Tell a coworker your age," "Blow your nose in public," and "Eat ribs with your fingers"). Research suggests that compared to patients with AD, those with bvFTD rate many behaviors as appropriate that normal adults would say are inappropriate [119].

Case History

History of Presenting Illness

Mr. R is a 63-year-old, right-handed, retired policeman presenting for evaluation of personality and behavioral changes. While Mr. R denies any changes in his cognition or behavior, his wife and son provided additional clinical history.

Mr. R's symptoms began insidiously around the age of 58. Previously kind and even tempered, Mr. R became progressively more negative, sarcastic, and critical of others. He started to tell off-color jokes in mixed company and made loud derogatory remarks about overweight individuals standing nearby. He was more irritable and impatient when driving, lashing out verbally against other drivers for perceived infractions. There were no reported incidents of aggressive or violent behaviors. His family reported an overall emotional blunting, social withdrawal, and detachment from his family, losing all interest in their lives. The patient's wife reported that if she did not plan activities, Mr. R would stand and stare out the window all day. His son noted that his previously strong interest in the upkeep of his car had dissipated over the past 2 years. In addition, his diet drastically changed from healthy, low-fat foods to primarily junk food, candy, and large quantities of coffee. His family reported a weight gain of over 20 pounds in the past 5 years.

Mr. R's family also reported a significant decline in function, such that he became unable to follow through with paying bills, instead just leaving paperwork in piles around the house. His wife was not aware of this issue until they began receiving a series of notices. While previously handy around the home, Mr. R became unable to complete familiar projects, such as hanging doors, instead starting the job but then leaving it midstream. His family was also aware that Mr. R's job category at the police station changed once or twice in the 2 years before retirement for reasons that were unclear to them but which they now believe may have had to do with his impairments.

The patient's family noted that Mr. R had begun to engage in compulsive behaviors including emptying the recycling bin at home several times a day, checking the lint trap in the dryer repeatedly, and collecting paper napkins from restaurants. He also engaged in repetitive behaviors such as whistling and tapping his hands on

the table for prolonged periods of time. He compulsively scratches himself but no rash has been noted. He continues to display loss of empathy and will laugh when other people get hurt. He will often say repeatedly throughout the day, "everyone has lost their sense of humor!" or "where has your sense of humor gone?" He is restless and often wants to go somewhere; however, upon arriving at a new destination, he then wants to go back home. The family did not endorse any significant declines in his episodic memory, language, visuospatial, or motor function.

Mr. R's typical day consists of getting up, showering, and getting dressed. He requires reminders to bathe and groom. He will stand at a window for long periods of time and report that his son has gone by or that he is waiting for somebody to arrive. He appears insatiable and will eat for extended periods of time if he is not stopped.

Social/Medical History

Mr. R has been married to his wife for 44 years. They have four adult children. He completed a Master's Degree in Sociology. He worked in law enforcement for 30 years. According to his family, he performed his job in a professional manner and was well respected.

Past medical history is significant for a history of hypercholesterolemia. He has never been hospitalized nor had any surgery. He has no history of head trauma, severe febrile illness, or thyroid disease.

Family history is significant for a mother who developed signs of significant cognitive dysfunction around age 85 which was characterized mainly by memory loss and hallucinations. She died in 2007 with a diagnosis of dementia. His father died at age 59 of a heart attack. There is no other known family history of dementia, neurological or neuromuscular disorders, or psychiatric illness.

Neuropsychological Test Summary

Please see Table 33.3.

Neuropsychiatric Symptom Assessment

Examination of the NPI subscales indicates that the patient's wife endorsed frequent symptoms of agitation, apathy, disinhibition, aberrant motor behavior, and changes in appetite/eating behavior that cause her significant distress (NPI Total Score: 60).

Functional Evaluation

The patient's Clinical Dementia Rating Scale (CDR) total score was 1.0. His most significant impairments occurred in the domains of judgment and problem-solving, home and hobbies, and personal care.

Imaging Results (Fig. 33.1)

Impressions and Formulation

Mr. R is a 63-year-old, retired policeman with a 5-year history of significant personality and behavior changes marked by disinhibited and socially inappropriate behavior, irritability, apathy and social withdrawal, poor executive functioning, obsessive–compulsive activities, and hyperorality with a 20-pound weight gain in the past 5 years.

On neuropsychological testing, his affect was notable for emotional blunting and mild irritability. Overall, Mr. R demonstrated below-average performance on free recall measures of verbal and visual episodic memory. Verbal and visual recognition memory was within normal limits. His performance on measures of executive functioning varied, ranging from impaired to average.

Table 33.3 Neuropsychological test summary

Domain	Test	Raw score	Range
Global	MMSE	29/30	Within normal limits (WNL)
Attention/working memory	Longest digit span forward	7	WNL
	Longest digit span backward	5	WNL
Memory	CVLT-II-SF trial 1–4 total	23/36	Below average
	CVLT-II-SF 10-min delay	6/9	Below average
	CVLT-II-SF cued recall	7/9	Below average
	CVLT-II-SF recognition	9/9; 1 false positive	WNL
	Figure copy recall	10/17	Below average
	Figure copy recognition	YES	WNL
Language	Abbreviated BNT total	15/15	WNL
	Syntax comprehension	5/5	WNL
	Repetition	5/5	WNL
Visuospatial	Figure copy	15/17	WNL
	Object–number location matching	10/10	WNL
	Face perception	12/12	WNL
	Calculations	4/5	Below average
Executive function	Modified Trail making test (time)	64/120	Below average
	Modified Trail making test errors	4	–
	Design fluency	11	Average
	Design fluency errors	4	–
	"D" word fluency (60)	3	Impaired
	"D" word errors	3	–
	Animal fluency (60)	14	Below average
	Animal fluency errors	2	–
	Stroop interference total	54	Average
	Stroop interference errors	9	–
	Affect naming	9/16	Impaired

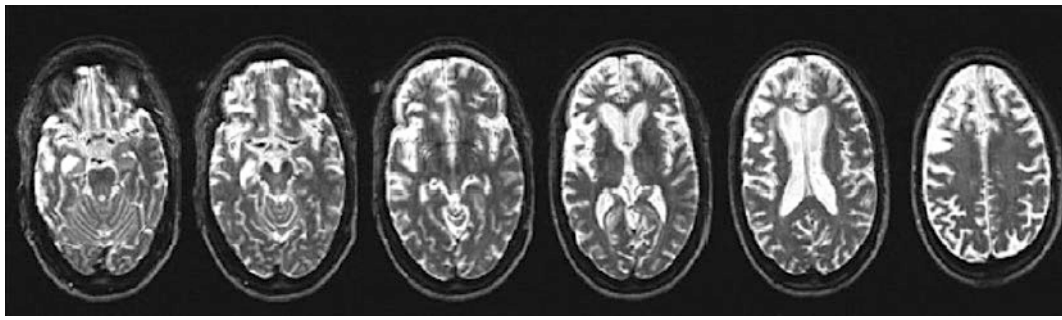

Fig. 33.1 T2-weighted structural magnetic resonance imaging (MRI) of Mr. R's brain. Note the significant volume loss in the frontal and temporal lobes bilaterally, worse on the right compared to left. (image is oriented according to radiological convention; e.g., left = right, right = left)

Of note, he made a total of 22 errors, which is well above average compared to others in his age range. Global cognition, attention/working memory, language, and visuospatial function remain largely intact.

Given his history of significant emotional and behavioral changes, error-prone pattern of performance on measures of executive function and neuroimaging findings of right > left degeneration of paralimbic frontal, temporal, and insular structures, his pattern of findings is most suggestive of a diagnosis of behavioral variant frontotemporal dementia.

In terms of treatment, Mr. R's primary care physician may want to consider prescribing treatment with a selective-serotonin reuptake inhibitor (SSRI) in order to target his obsessive–compulsive behaviors and irritability. However, anticholinesterase agents should not be prescribed, as these have been known to exacerbate the irritability seen in frontotemporal dementia. I also recommend that Mr. R begin a program of vigorous physical activity, as exercise has been shown to have neuroprotective properties. His entire family may want to consider attending a FTD caregiver support group. Finally, despite intact attention and visuospatial skills, it is strongly recommended that Mr. R discontinue driving.

Clinical Pearls

- FTD is first and foremost a disease that disrupts behavior and social function.
- Compared to AD, patients with bvFTD tend to have little insight into their condition and are more flat, perseverative, inappropriate, and emotionally dysregulated.
- Due to its pathological heterogeneity, bvFTD can present alone or in combination with other diseases such as PSP, CBD, and ALS.
- BvFTD is often misdiagnosed as late-onset psychiatric disease or early-onset AD.
- The presence of executive dysfunction in the absence of other major cognitive impairments is not specific to bvFTD.
- Neuropsychological testing should focus on *relative patterns* of performance vs. domain impairments.
- In the early stages of disease, process-oriented features of performance such as rule violations and errors appear to best discriminate between bvFTD and AD.
- Integration of history, behavioral observations, imaging, social/emotional function, informant questionnaires, and relative test scores in keeping with the disease are most important in coming to an accurate diagnosis.
- A multidisciplinary team approach, working with a neurologist and other health-care professionals, is most helpful in diagnosing this elusive disease.

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