Behavioral-variant frontotemporal dementia: diagnosis, clinical staging, and management

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Patients with behavioral-variant frontotemporal dementia (bvFTD) present with insidious changes in personality and interpersonal conduct that indicate progressive disintegration of the neural circuits involved in social cognition, emotion regulation, motivation, and decision making. The underlying pathological changes are heterogeneous and are characterised by various intraneuronal inclusions. Biomarkers to detect these histopathological changes in life are becoming increasingly important with the development of disease-modifying drugs. Gene mutations have been found that collectively account for around 10–20% of cases. Recently, criteria proposed for bvFTD define three levels of diagnostic certainty: possible, probable, and definite. Detailed history taking from family members to elicit behavioral features underpins the diagnostic process, with support from neuropsychological testing designed to detect impairment in decision making, emotion processing, and social cognition. Brain imaging is important for increasing the level of diagnostic certainty. A recently developed staging instrument shows much promise for monitoring patients and evaluating therapies, which at present are aimed at symptom amelioration. Carer education and support remain of paramount importance.

Introduction

Frontotemporal dementia (FTD) is the clinical diagnostic term now preferred to describe patients with a range of progressive dementia syndromes associated with focal atrophy of the orbitomesial frontal and anterior temporal lobes. Epidemiological studies suggest that FTD is the second most common cause of young-onset dementia after Alzheimer’s disease (AD). Two independent studies from the UK revealed a prevalence of around 15 cases per 100 000 population aged 45–64 years (95% CI 8–27 per 100 000). Although thought to be a rare cause of dementia after age 65 years, FTD might be more common than assumed because older adults rarely undergo the types of investigation needed to establish a confident diagnosis in vivo and are not generally followed to autopsy.

Unlike AD, both the clinical profile and the underlying pathological changes are heterogeneous in FTD. Two broad presentations are recognised: progressive deterioration in social function and personality, known as behavioral-variant FTD (bvFTD), and insidious decline in language skills, known as primary progressive aphasia, which can, in turn, be subdivided according to the predominant pattern of language breakdown into progressive non-fluent aphasia and semantic dementia. The syndrome of FTD overlaps with motor neuron disease (MND) both clinically and pathologically, and with some of the extrapyramidal motor disorders. Around 10% of patients with FTD develop clinical and neurophysiological evidence of MND, and, similarly, patients with MND show behavioral and/or language changes that, in some instances, are severe enough to qualify for a diagnosis of FTD. Of the extrapyramidal disorders, corticobasal degeneration and progressive supranuclear palsy show substantial overlap with FTD and share the finding of abnormal tau pathology.

This is a broad and rapidly evolving field; therefore, in this Review, we have focused on the clinical aspects of bvFTD because there have been recent authoritative reviews of the aphasic syndromes. Our aim is to place advances in the diagnosis, staging, and management of bvFTD within the context of recent pathological and genetic discoveries. The assessment of any patient with suspected bvFTD should involve behavioral and neuropsychiatric tests, assessment of everyday abilities, cognitive testing, and neuroimaging. Various blood and CSF biomarkers are under development, but are not yet available for routine clinical application. Genetic testing is advised for those at high risk of a gene mutation (figure 1).

Pathology

The subtypes of underlying pathological changes in patients with FTD are classified on the basis of the pattern of protein accumulation, and are referred to collectively as frontotemporal lobar degeneration (FTLD). At post mortem, cases share, by definition, the finding of bilateral frontotemporal atrophy with neuronal loss, microvacuolation, and a variable degree of astrocytic gliosis. The progression of this atrophy has been examined by mapping the pattern in patients with different disease duration. Initially, mesial and orbital frontal regions bear the brunt of the atrophy, followed by the temporal pole, hippocampal formation, dorsolateral frontal cortex, and the basal ganglia. This pattern of progression of atrophy has been shown to relate to the volume of cortical and subcortical regions, and to the underlying neuron loss. Furthermore, it forms the basis of a useful and quick MRI rating scale described below.

The use of immunohistochemical staining has revolutionised the field of research in FTD. Inclusions of the microtubule-binding protein tau are present in approximately 40% of cases (FTLD-tau). Tau-positive cases include the subset of patients with mutations in the microtubule-associated protein tau (MAPT) gene. Further
Probable bvFTD

Possible bvFTD based on clinical, behavioural, cognitive, and ADL assessments

MRI

Normal

Abnormal

PET

Abnormal

Normal

Possible phenocopy

Probable bvFTD

Strong family history

Yes

Genetic screening

Abnormal

Normal

Figure 1: Possible investigations after the diagnosis of suspected bvFTD based on clinical criteria.

1Presence of neurodegenerative disease and at least three of six behavioural or cognitive core diagnostic criteria are required for diagnosis of the disease.

bvFTD=behavioural-variant frontotemporal dementia. ADL=activities of daily living.

subclassification is based on morphological criteria and the predominance of either tau with three microtubule-binding repeats (3R tau) or four microtubule-binding repeats (4R tau). Most of the remaining cases are tau negative and ubiquitin positive, with one histological variant comprising the 43 kDa TAR DNA-binding protein (TDP-43; FTLD-TDP), but a minority (around 5–10%) are negative for both tau and TDP-43 proteins. Recently, inclusions of the RNA-binding protein fused in sarcoma (FUS) have been found in many of these cases (FTLD-FUS). The search for FUS pathology was initiated after FUS gene mutations were identified in cases of familial MND. Both TDP-43 and FUS are RNA-processing proteins, although the mechanisms leading to TDP-43 and FUS accumulation and resulting neurodegeneration have not yet been elucidated. A small proportion of cases have either no inclusions or show ubiquitin-positive inclusions that are TDP-43 and FUS negative, suggesting that additional protein abnormalities will be found in FTLD.

A major topic of investigation has been to establish the association between clinical phenotypes and molecular pathology. Unlike the progressive aphasic syndromes, which are generally associated more with one histological form of FTLD than another (progressive non-fluent aphasia with FTLD-tau, semantic dementia with FTLD-TDP), in bvFTD any of the histological variants can be found with an approximately 50:50 split between FTLD-tau and FTLD-TDP, and a small proportion of FTLD-FUS cases. With the advent of potential disease-modifying therapies, ascertainment of a pathological diagnosis in vivo will be increasingly important. As yet, no reliable method for detecting these pathological changes in life exists. CSF biomarkers seem to be the most promising in distinguishing FTLD from AD: the ratio of tau to amyloid β1–42 has been found to be lower in FTLD than in AD. Increased concentrations of CSF TDP-43 have also been reported in patients with MND and FTD, but without pathological confirmation of the diagnosis. In addition, the substantial overlap between cases and controls limits the applicability of the assay in clinical practice. Serum progranulin concentrations are exceptionally low in patients with mutations in the granulin gene (GRN), and this assay seems to be a sensitive and specific method of screening for such cases, with suggestions that plasma TDP-43 concentrations could be related to brain pathology.

Genetics

Up to 40% of patients with FTD have a family history of dementia, but the high community prevalence of non-FTD dementia means that many of the elderly family members included in such estimates almost certainly have other causes of dementia. Patients with an autosomal dominant pattern (affected first-degree relatives across two generations) account for only 10% of cases. The strength of family history is highly predictive, in that mutations can now be shown in most patients with two or more first-degree relatives with a dementia syndrome compatible with FTD. Overall, patients with mutations in MAPT and GRN each account for 5–11% of total FTD cases. Mutations in the gene that encodes TDP-43, TARDBP, and in FUS, recognised as a cause of familial amyotrophic lateral sclerosis (ALS), have also been identified in a small number of cases of FTD-ALS, but seem to be rare in uncomplicated FTD. Rare genetic mutations causing FTD include those in the genes encoding valosin-containing protein (VCP) and charged multivesicular body protein 2B (CHMP2B; also known as chromatin-modifying protein 2B). Mutations in VCP cause FTD in association with inclusion body myopathy and Paget’s disease of bone, whereas the CHMP2B gene mutation is mostly confined to a large Danish cohort with FTD. Familial clusters of FTD and MND have been reported. A linkage study of FTD-MND clusters has indicated a common locus in the region of chromosome 9p13.2–21.3, but the causative gene has not yet been identified.

From a practical perspective, a detailed family history should be taken for all patients with suspected FTD, bearing in mind the overlap between MND and FTD, that a diagnosis of FTD or Pick’s disease was rarely made in the past, and the phenotypic variability within families with gene mutations: one member might present with bvFTD, whereas others have a progressive aphasic syndrome or corticobasal syndrome. On the basis of a comprehensive analysis of the frequency of gene mutations according to strength of family history and clinical syndrome in a large clinical cohort, we recommend that patients with one or more first-degree relatives with a disease on the FTD spectrum should be screened for MAPT and GRN gene mutations after appropriate counselling in a clinical genetics setting.
Those with an informative family history that reveals no affected relatives can be confidently reassured and need not undergo gene screening. Of note, the age of onset in patients with MAPT mutations is almost always below 65 years, whereas those with GRN mutations are often older.

**Behavioural features**

Insidious changes in personality, interpersonal conduct, and emotional modulation characterise bvFTD and indicate progressive disintegration of the neural circuits involved in social cognition, emotion regulation, motivation, and decision making. Onset is typically difficult to pinpoint. Since insight is limited, or absent, it is vital that close family members are interviewed alone, and sensitively, to elicit the nature of the early symptoms and their progression. Assessment and diagnosis have been greatly assisted by the development of carer-based questionnaires designed to document the range of symptoms found in the dementia, including the Neuropsychiatric Inventory, Cambridge Behavioural Inventory, and Frontal Behavioural Inventory. All of the features found in bvFTD can occur in other dementias, but their predominance and early emergence typify bvFTD.

Apathy is very common and manifests as inertia, reduced motivation, lack of interest in previous hobbies, and progressive social isolation. Disinhibition often coexists with apathy, and produces impulsive actions leading to overspending, tactless or sexually inappropriate remarks, and a range of socially embarrassing behaviour. New-onset pathological gambling or, more rarely, hyper-religiosity, can be the presenting feature. Repetitive or stereotypic behaviours might be apparent with perseveration and a tendency to repeat phrases, stories, or jokes. Some carers describe excessive hoarding, which results in a state of squalor. Patients often lack empathy and an inappropriately subdued grief reaction is a common early symptom. Mental rigidity is common and patients can have difficulty adapting to new situations or routines. A blunting of affect and reduction in range of emotional expression is frequent and some patients show elevation of mood resembling hypomania. Changes in eating behaviour, with impaired satiety, change in eating preference towards sweet food, and dysregulation of food intake are common and seen across cultures. These alterations in eating have recently been found to be related to pathological changes in the hypothalamus, which is crucial for coordinating metabolic needs, including feeding.

Psychotic symptoms such as delusions, paranoid ideation, and hallucinations are relatively rare in FTD, except in patients with combined MND and in patients with young-onset FTLD-FUS in whom such features are present in up to 50%. Clinically, these patients seem to present with florid behavioural symptoms. In addition, their age of onset is often exceptionally young (≤40 years), and a positive family history seems rare in keeping with the absence of FUS gene mutations in this group.

Patients destined to develop clinical MND who have FTLD-TDP also have a high rate of psychotic features and progress rapidly even before the onset of typically bulbar MND.

Of the features listed above, social disinhibition, euphoria, stereotypical and aberrant motor behaviour, and changes in eating preference most clearly discriminate bvFTD from AD. Variability in the symptom profiles reported across studies might have arisen from the aggregation of patients at different stages of the disease. Increased behavioural changes have been associated with disease severity. Agitation, disinhibition, and irritability also seem to be more frequent in the later stages, whereas restlessness and hyperorality are present throughout the disease. Another important variable is age of disease onset, with apathy being more prominent in late-onset bvFTD, although this finding is not universal.

In summary, behavioural assessment is at the core of assessment in patients with potential bvFTD and seems to be more sensitive in distinguishing bvFTD from AD than standard cognitive testing. Despite a substantial increase in our knowledge of the behavioural changes in bvFTD, which are at the root of so much carer distress (see below), much remains uncertain concerning their specificity, neural basis, and their relation to the underlying pathology.

**bvFTD phenocopy syndrome: implications for diagnostic criteria**

The diagnosis of bvFTD is by no means an easy task in the early stages, and many of the symptoms overlap with those seen in psychiatric disorders and other dementias. It is also increasingly apparent that a subset of patients who present with the clinical features of bvFTD do not progress to frank incapacitating dementia. Such patients are almost always men and they either remain stable over many years or improve. The symptom profile as reported by family members is identical, except that activities of daily living (ADL) are less disrupted. Several features distinguish these non-progressor or phenocopy cases from those with true FTD, notably normal or marginal impairment on neuropsychological tests of executive function, preserved memory and social cognition, a lack of overt atrophy on MRI, and normal metabolic (PET) brain imaging. The aetiology of the phenocopy syndrome is a matter of debate. A proportion of patients seem to have a developmental personality disorder on the Asperger’s spectrum with decompenstation due to altered life circumstances (Hodges J, unpublished). Some might have a chronic low-grade mood disorder, but others remain a mystery.

The phenocopy syndrome has major implications for the current clinical diagnostic criteria for FTD, which require a profile of symptoms compatible with the
diagnosis without imaging or other confirmatory test results. These criteria also present difficulties in their application due to under-specification of some features and were derived by clinical consensus prior to the publication of quantitative studies comparing cohorts with pathologically verified diagnoses. Recently proposed criteria developed by an international FTD research group (panel) \(^{64}\) build on recent work with operationalised definitions that have three levels of diagnostic certainty: possible, probable, and definite bvFTD. Patients qualify for possible bvFTD on the basis of three core behavioural or cognitive features (including social disinhibition, apathy, loss of empathy, stereotypic behaviours or alterations in eating pattern, and neuropsychological deficits indicative of frontal executive dysfunction). A probable diagnosis requires the same clinical features with evidence of progression and unequivocal neuro-imaging abnormalities. The term “definite” is reserved for those with neuropathology or a pathogenic gene mutation. These new criteria (panel) are currently undergoing validation against neuropathological changes by an international consortium of researchers.\(^{64}\)

### Neuropsychology

**Cognition**

Early in the disease process, patients with bvFTD can perform relatively well on formal neuropsychological tests despite the presence of significant personality and behavioural changes.\(^{45}\) The mini mental state examination is insensitive, but the Addenbrooke’s cognitive examination seems to detect at least 90% of cases at presentation.\(^{66}\) The prototypical cognitive profile is one of relatively preserved language and visuospatial/constructive abilities. Whether patients with bvFTD show executive dysfunctions remains contentious;\(^{67,68}\) and has been complicated by the inclusion of phenocopy cases. However, such deficits constitute a central diagnostic feature of the newly proposed clinical diagnostic criteria.\(^{64}\)

Recent evidence suggests that the combination of specific tests (eg, digit span backward task, Hayling test of response inhibition, and the short version of the executive and social cognition battery) might help differentiate these cases, because results are typically abnormal in patients with true bvFTD and normal in phenocopy cases.\(^{69,70}\)

The presence of severe deficits of episodic memory has been used as an exclusion criterion for a clinical diagnosis of bvFTD,\(^{71}\) although a proportion (10–15%) of patients with pathologically confirmed FTLD present with severe amnesia.\(^{72,73}\) A recent report has indicated that deficits in episodic memory are more common than previously reported.\(^{74}\) Carefully selected patients with bvFTD (ie, after excluding phenocopy cases) had similar memory impairments as seen in AD on tests of episodic memory, even after accounting for disease severity.\(^{75}\) The criterion of relative sparing of episodic memory compared with executive functions proposed in the recent international consensus criteria for bvFTD might need to be revisited in the light of current research.\(^{42}\)

The evidence reviewed thus far indicates that no specific cognitive profile seems to be associated with bvFTD early in the disease, although careful cognitive assessment will reveal deficits, generally in the domains of executive function and episodic memory. With disease progression, the atrophy evolves to involve the anterior temporal regions, and the pattern of deficits becomes less distinct from other FTD subtypes, notably semantic dementia.\(^{10}\)

### Panel: International consensus criteria for bvFTD

**Neurodegenerative disease**

Must be present for any FTD clinical syndrome

- Shows progressive deterioration of behaviour and/or cognition by observation or history

**Possible bvFTD**

Three of the features (A–F) must be present; symptoms should occur repeatedly, not just as a single instance:

- A Early (3 years) behavioural disinhibition
- B Early (3 years) apathy or inertia
- C Early (3 years) loss of sympathy or empathy
- D Early (3 years) perseverative, stereotyped, or compulsive/ritualistic behaviour
- E Hyperorality and dietary changes
- F Neuropsychological profile: executive function deficits with relative sparing of memory and visuospatial functions

**Probable bvFTD**

All the following criteria must be present to meet diagnosis:

- A Meets criteria for possible bvFTD
- B Significant functional decline
- C Imaging results consistent with bvFTD (frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)

**Definite bvFTD**

Criteria A and either B or C must be present to meet diagnosis:

- A Meets criteria for possible or probable bvFTD
- B Histopathological evidence of FTLD on biopsy at post mortem
- C Presence of a known pathogenic mutation

**Exclusion criteria for bvFTD**

Criteria A and B must both be answered negatively; 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 non-degenerative nervous system or medical disorders
- B Behavioural disturbance is better accounted for by a psychiatric diagnosis
- C Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process

**Additional features**

- A Presence of motor neuron findings suggestive of motor neuron disease
- B Motor symptoms and signs similar to corticobasal degeneration and progressive supranuclear palsy
- C Impaired word and object knowledge
- D Motor speech deficits
- E Substantial grammatical deficits

Criteria from Rascovsky et al.\(^{64}\) bvFTD=behavioural-variant frontotemporal dementia. FTD=frontotemporal dementia. SPECT=single photon emission computed tomography. FTLD=frontotemporal lobar degeneration.
Emotion recognition and social cognition

A marked impairment in emotion detection and recognition is evident early in the course of bvFTD, and seems to be most pronounced for negative emotions (eg, fear, sadness, anger, and disgust). Disorders of emotion detection and regulation are part of the clinical diagnostic criteria for the disease (ie, early emotional blunting, early decline in social interpersonal conduct). However, such deficits are not limited to this subtype of FTD and are also present in semantic dementia. Difficulties in detecting and understanding emotions are observed with static (photos) or dynamic (films) visual stimuli, voices, or even music. Importantly, physiological responses (eg, skin conductance) to some emotional stimuli are preserved. Deficits have also been observed in detecting more complex emotions, such as embarrassment. These deficits might be amenable to retraining to enhance their recognition and improve interpersonal relationships.

Patients with bvFTD are also impaired on many aspects of social cognition. For example, the often reported feature of lack of empathy and coldness is confirmed on formal testing. Theory of mind is impaired in bvFTD, as exemplified by defective ability to infer intention and mental states in others or to take someone else’s point of view, and impaired detection of social faux pas, discrimination of sincere from sarcastic exchanges, and understanding of situations requiring moral judgment. Whereas most of the tasks described above are used in patients who consistently fail to inhibit the prepotent responses favouring short-term gains leading to long-term loss, and healthy controls. Interestingly, this deficit is not related to performance on other cognitive tasks.

The difficulty in identifying profiles of cognitive deficits specific to bvFTD has led to an interest in aspects of social cognition (theory of mind), emotion recognition and complex problem solving, and the use of naturalistic tasks (ie, tasks indicating cognitive and non-cognitive demands more akin to daily activities). The orbitomesial frontal cortices are crucial for performance in these domains, and lesions within these brain regions have been shown to negatively affect tests measuring these cognitive constructs. The Iowa gambling task of complex decision making requires individuals to inhibit responses that result in short-term high financial gains but long-term losses in favour of responses resulting in small gains in the short term and reduced long-term losses. This task was found to differentiate between patients with bvFTD, who consistently failed to inhibit the prepotent responses favouring short-term gains leading to long-term loss, and healthy controls. Interestingly, this deficit is not related to performance on other cognitive tasks.

Neuroimaging

By use of structural MRI, atrophy of the mesial frontal, orbitofrontal, and anterior insula cortices can be reliably observed on images acquired in the coronal plane (figure 2). A combination of frontal and anterior temporal cortical and basal ganglia atrophy might also be seen at presentation in some patients. This atrophy can be quickly and reliably estimated using relatively simple visual rating scales developed specifically for FTD. However, an apparently normal MRI on visual inspection does not completely exclude a diagnosis of bvFTD, because the changes can be subtle in the early stages.

The development of automated quantitative methods, including voxel-based morphometry and cortical thickness mapping, has been important in revealing selective atrophy of the anterior cingulate and frontal insular cortices early in the course of bvFTD, which is distinct from the pattern seen in other variants of FTD and in AD. The anterior cingulate-frontal insular complex contains a unique population of neurons, the von Economo cells, which are thought to be crucial in the development and maintenance of social cognition and have been shown to be depleted in patients with bvFTD at autopsy. More recently, sophisticated MRI methods of exploring network connectivity have shown significant changes in connectivity among the regions most sensitive to atrophy in bvFTD compared with healthy controls or patients with other dementia syndromes. Patterns of grey matter atrophy might be predictive of the underlying pathological process in bvFTD, with bilateral dorsolateral prefrontal atrophy being suggestive of Pick body inclusions (ie, Pick’s disease), and
asymmetric left and right temporal lobe atrophy being associated with FTLD-TDP and FTLD-tau, respectively.96 Marked atrophy of the caudate nucleus might also be predictive of FTLD-FUS.20,97 However, patterns of atrophy seem to relate more closely to clinical features than to specific pathological changes.98

Brain changes in bvFTD are not limited to the cortex. Atrophy is also present in many subcortical brain regions, including the amygdala, hippocampus, caudate, striatum, putamen, thalamus, and hypothalamus,20,95 accompanied by reduction in connectivity among subcortical structures.95 In addition, atrophy of the amygdala has been proven to be an efficient discriminator between bvFTD and AD.99

By contrast with the well documented cortical grey matter changes, presence and severity of white matter changes in bvFTD have only recently been investigated.103 Frontal lobe white matter volume reduction largely parallels the atrophy in the adjacent grey matter in bvFTD, with different subtypes of FTD showing specific patterns of white matter atrophy.101 Using diffusion tensor imaging, an index of changes in the microstructural organisation of white matter, a study has successfully differentiated bvFTD from AD and other FTD subtypes.102 Patients with bvFTD seem to show a selective reduction in some white matter tracts (superior longitudinal fasciculus, uncinate fasciculus, cingulum tracts, and genu and splenium of the corpus callosum), particularly those within frontal lobe (eg. genu of the corpus callosum) or those connecting frontal and temporal brain regions (eg. uncinate fasciculus).102 Whether these white matter changes are reliable diagnostic markers for bvFTD remains unclear. Patients with the phenocopy syndrome who present with some patients with bvFTD show atrophy similar to those seen in healthy controls (0·3% per year), which might be due to the inclusion of phenocopy cases.103

Serial MRIs show significant atrophy over time in bvFTD. Annual rate of overall brain atrophy can reach 8%, almost twice as severe as that documented in AD, although some patients with bvFTD show atrophy similar to those seen in healthy controls (0·3% per year), which might be due to the inclusion of phenocopy cases.103

Functional neuroimaging techniques, such as [18F]-fluorodeoxyglucose (FDG)-PET are increasingly being used to help with the diagnosis of bvFTD. Frontal hypoperfusion is present on SPECT in bvFTD and differs from the pattern of hypoperfusion observed in AD, which is predominant in the temporoparietal and posterior cingulate cortices.104 Although SPECT seems to be more sensitive than structural MRI in detecting early pathological changes in bvFTD, quantification and specificity of these changes have not been established. Hypometabolism on FDG-PET is detected consistently and reliably in frontal brain regions in patients with bvFTD compared with those with AD, who show posterior cingulate hypometabolism early in the disease process.105 These changes are detected before any changes are visible on structural MRI, making FDG-PET the most sensitive diagnostic tool currently available. FDG-PET is also particularly useful in helping to identify phenocopy cases as these will show preserved frontal metabolism. However, in patients showing clear brain atrophy on structural MRI, little additional diagnostic benefit is gained by doing a PET scan, because focal atrophy is a positive predictive marker of FTD.

A novel PET technique, which uses the amyloid-β-detecting [11C]-Pittsburgh compound B, has shown promising results in discriminating AD and FTD cases,96,106 particularly those presenting with language deficits rather than behavioural changes. Its use as a routine test remains to be established, but its clinical applicability is evident as therapeutic interventions are being developed that are likely to be pathology specific.

In summary, neuroimaging investigations in the diagnosis of bvFTD are powerful tools, which can reliably differentiate bvFTD from other FTD subtypes and from other dementia syndromes, and can corroborate clinical diagnostics based on neuropsychiatric symptoms.

**Functional abilities**

Disability in everyday life is more pronounced in bvFTD than in AD or in the language variants of FTD,65,108,109 even after controlling for length of symptoms or cognitive performance.65,109 Compared with AD, a large proportion of patients with bvFTD are impaired in ADL, and show early impairment in basic ADL at initial assessment.109 Marked changes in driving abilities occur and are associated with the degree of behavioural change,110 which has clear practical implications. A 12-month follow-up study also identified significant changes in ADL, which were associated with general cognitive decline.111 However, these changes were not present in phenocopy cases.

**Disease progression, functional staging, and survival**

Most studies, to date, have used the clinical dementia rating (CDR) scale to measure dementia severity.112 This instrument, which was originally developed for AD, is biased towards memory impairment and most likely underestimates the level of dementia severity in bvFTD. A version adapted for FTD includes language and behavioural domains (FTLD-CDR),112 and the sum-of-boxes score seems to be sensitive to change in most patients with FTD.

Recently, the frontotemporal dementia rating scale (FRS) was developed specifically for FTD.113 This staging tool incorporates changes in behaviour and ADL (table). On the FRS, patients with bvFTD tend to show greater disease severity and a faster progression through the clinical stages than patients with the language variants of FTD, even after adjusting for length of symptoms.114 Importantly, the FRS confirmed that the CDR tends to underestimate dementia severity in bvFTD, with a great proportion of moderate and severe cases on the FRS being rated as “questionable dementia” or “mild” on CDR.
Patients with bvFTD seem to progress faster than patients with AD, with median survival (from first assessment) of about 3–0–4.5 years,\textsuperscript{110,116,117} although this finding has not been universal.\textsuperscript{118} Factors determining reduced survival are associated with MND or ALS and language impairment at diagnosis.\textsuperscript{117} The effect of neuropathological subtype on survival remains contentious.\textsuperscript{116,119}

**Therapeutic intervention and caregiver stress**

Currently, no disease-specific treatment interventions for FTD exist. Consequently, treatment largely remains supportive and involves a combination of non-pharmacological and pharmacological measures aimed at reducing the effect of distressing symptoms.\textsuperscript{120} The role of pharmacological interventions in FTD remains uncertain, and only small and often conflicting treatment trials have been done so far; these studies have not considered the effect on carer stress as a major outcome variable. Selective serotonin reuptake inhibitors have been used to treat disinhibition and challenging behaviours, but evidence for their use remains contradictory.\textsuperscript{121,122} Atypical antipsychotics such as olanzapine have been used for patients with prominent agitation, aggressive behaviour, or psychosis.\textsuperscript{123} Anticholinesterase inhibitors, the mainstay of AD therapy, do not have an established role in the treatment of FTD. One study reported improvement in measures of behavioural disturbance and carer stress with rivastigmine,\textsuperscript{124} although deterioration in neuropsychiatric symptoms without cognitive improvement was shown with donepezil.\textsuperscript{125} Several drugs under development attempt to reduce aggregation of tau or TDP-43 and hence slow the fundamental pathological process in FTD.\textsuperscript{120,126}

Caregiver intervention, which should be the most effective treatment within the context of dementia, has also not been trialled in FTD caregivers. A model for behavioural management has been proposed, whereby a focus on the antecedent–behaviour–consequence model could be applied to different patient situations with recommendations for specific behaviours exhibited in bvFTD,\textsuperscript{110} but research studies are needed to verify their benefits. This would be timely, because caregivers of patients with FTD present with high rates of burden and stress. Recent studies have shown that caregiver burden in FTD is much greater than in AD.\textsuperscript{128–130} Behavioural changes rather than level of disability seem to be correlated with caregiver distress and burden in bvFTD,\textsuperscript{110} although very few studies have been done. Evidence indicates that caregiver health is a major contributor to carer stress, with depression accounting for 58% of the variance of stress scores in FTD caregivers.\textsuperscript{116} The key to reducing caregiver stress seems to lie in increasing their understanding of the symptoms and ways of dealing with challenging behaviours.

Driving and other aspects of capacity in bvFTD are clearly of great practical importance, but have been subject to little systematic research. A single study of driving competence in bvFTD suggested significant problems, even at an early stage of the disease.\textsuperscript{111} On that basis, a driving assessment would seem to be recommended in all cases. In Australia, the UK, and many other countries, an established code of practice exists governing the issue of legal capacity associated with the relevant Mental Capacity Act. Its application is relatively straightforward in patients with advanced bvFTD, but establishing a lack of capacity could be complex in the early stages of the disease. Of note,

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<tr>
<th>Behaviour</th>
<th>Activities of daily living</th>
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<td>Basic</td>
<td>Instrumental</td>
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<td>Mild</td>
<td>Lack of affection</td>
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<td>Agitated, restless</td>
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<td>“Sweet tooth”</td>
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<td>Profound</td>
<td>Does not go to toilet in time (urine)</td>
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<td></td>
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Modified from Mioshi et al.\textsuperscript{115} by permission of Wolters Kluwer Health. bvFTD=behavioural-variant frontotemporal dementia.

Table: Characteristics of each severity stage in the disease progression of bvFTD
capacity is not a global phenomenon but is situation specific. Moreover, unlike in AD, in which capacity can be impaired by amnesia (which is easier to assess), in bvFTD, the key cognitive variables are insight and judgment, which are much harder to assess and quantify. Finally, many useful publications and DVDs are available for caregivers, which can be accessed through the Frontotemporal Dementia Research Group website or the Association for FTDs.

Conclusions and future directions
Knowledge of the clinical presentation of bvFTD and its pathological process has improved substantially over the past 20 years. Clinicians have become more aware of this disabling neurodegenerative condition, which affects individuals who are often still in the workforce or have young children. Careful medical history and information from family members, combined with clinical investigations, neuropsychological testing, and investigations of social cognition, have increased case identification. Sensitivity has also improved with the use of advanced structural and functional neuroimaging techniques. However, the major challenge that remains is to improve the prediction of the underlying neuropathology in patients with bvFTD during life. Efforts to identify potential disease biomarkers for the disease are promising but will require further investigations. This line of research will become particularly relevant as disease-modifying agents are developed.

Contributors
All authors contributed equally to the conception, literature review, and writing of this Review.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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