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REVIEW ARTICLE

Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders

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The behavioural variant of frontotemporal dementia (bvFTD) is a frequent cause of early-onset dementia. The diagnosis of bvFTD remains challenging because of the limited accuracy of neuroimaging in the early disease stages and the absence of molecular biomarkers, and therefore relies predominantly on clinical assessment. BvFTD shows significant symptomatic overlap with non-degenerative primary psychiatric disorders including major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, autism spectrum disorders and even personality disorders. To date, ~50% of patients with bvFTD receive a prior psychiatric diagnosis, and average diagnostic delay is up to 5–6 years from symptom onset. It is also not uncommon for patients with primary psychiatric disorders to be wrongly diagnosed with bvFTD. The Neuropsychiatric International Consortium for Frontotemporal Dementia was recently established to determine the current best clinical practice and set up an international collaboration to share a common dataset for future research. The goal of the present paper was to review the existing literature on the diagnosis of bvFTD and its differential diagnosis with primary psychiatric disorders to provide consensus recommendations on the clinical assessment. A systematic literature search with a narrative review was performed to determine all bvFTD-related diagnostic evidence for the following topics: bvFTD history taking, psychiatric assessment, clinical scales, physical and neurological examination, bedside cognitive tests, neuropsychological assessment, social cognition, structural neuroimaging, functional neuroimaging, CSF and genetic testing. For each topic, responsible team members proposed a set of minimal requirements, optimal clinical recommendations, and tools requiring further research or those that should be developed. Recommendations were listed if they reached a $\geqslant 85\%$ expert consensus based on an online survey among all consortium participants. New recommendations include performing at least one formal social cognition test in the standard neuropsychological battery for bvFTD. We emphasize the importance of 3D-T_1 brain MRI with a standardized review protocol including validated visual atrophy rating scales, and to consider volumetric analyses if available. We clarify the role of ^{18}F-fluorodeoxyglucose PET for the exclusion of bvFTD when normal, whereas non-specific regional metabolism abnormalities should not be over-interpreted in the case of a psychiatric differential diagnosis. We highlight the potential role of serum or CSF neurofilament light chain to differentiate bvFTD from primary psychiatric disorders. Finally, based on the increasing literature and clinical experience, the consortium determined that screening

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for *C9orf72* mutation should be performed in all possible/probable bvFTD cases or suspected cases with strong psychiatric features.

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Abbreviations: ALS = amyotrophic lateral sclerosis; bvFTD = behavioural variant of frontotemporal dementia; FTLD = frontotemporal lobar degeneration; NfL = neurofilament light chain; PPD = primary psychiatric disorders

Introduction

Frontotemporal dementia (FTD) is one of the most common forms of early-onset dementia (Ratnavalli *et al.*, 2002; Onyike and Diehl-Schmid, 2013). Most cases are sporadic, with ~20% having an autosomal-dominant genetic mutation [hexanucleotide repeat expansions near the chromosome 9 open reading frame gene (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*), being the most common causative genes]

(Rademakers *et al.*, 2012). Whereas the diagnosis of Alzheimer's disease has become easier with the use of amyloid ligands for PET and CSF biomarkers that can identify underlying Alzheimer's disease pathology (McKhann *et al.*, 2011), the diagnosis of behavioural variant FTD (bvFTD) remains challenging because of the absence of such molecular biomarkers, and therefore relies predominantly on clinical assessment. Moreover, the symptomatic overlap with non-degenerative primary psychiatric disorders (PPD) including major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, autism spectrum disorders and even personality disorders (Ducharme *et al.*, 2015) means that PPD often constitute the main differential diagnosis of bvFTD (Krudop *et al.*, 2017). Around 50% of patients with bvFTD receive a prior psychiatric diagnosis (most frequently major depression), and average diagnostic delay is up to 5–6 years from symptom onset (Woolley *et al.*, 2011; van Vliet *et al.*, 2013; Ducharme *et al.*, 2017). It is also common for patients with PPD to be wrongly diagnosed with bvFTD, particularly in community settings (Shinagawa *et al.*, 2016), preventing patients from accessing evidence-based psychiatric treatments. While part of the diagnostic confusion between bvFTD and PPD stems from a lack of expertise in behavioural neurology and neuropsychiatry, some cases are diagnostically ambiguous even for experts.

Expert clinicians around the world have developed various approaches to identify bvFTD among individuals presenting with late-onset behavioural changes (>40 years of age) or with pre-existing chronic psychiatric disorders, but there is no consensus approach, and evidence suggests a low rate of diagnostic accuracy. Indeed, the Late-Onset Frontal (LOF) lobe study (Krudop *et al.*, 2014) demonstrated that in a cohort of mixed neuropsychiatric cases (i.e. representative of clinical practice) the application of current diagnostic criteria for possible bvFTD has poor specificity (27%) (Vijverberg *et al.*, 2016*b*; Krudop *et al.*, 2017). In addition, while the presence of predominant frontal and/or anterior temporal atrophy on structural imaging has good diagnostic specificity, the sensitivity of standard MRI was found to be insufficient in the LOF study (70%), while the specificity of ^{18}F-fluorodeoxyglucose-PET (FDG-PET) was low (68%) because of frequent non-specific abnormal findings in patients with PPD (Vijverberg *et al.*, 2016*a*). Moreover, neuropsychological tests were found to poorly differentiate bvFTD from PPD (Vijverberg *et al.*, 2017*c*). Adding to the complexity, patients with FTD secondary to the *C9orf72* mutation can present with heterogeneous neuropsychiatric phenotypes (such as late-onset psychosis or mania) without family history, sometimes several years prior to onset of more typical bvFTD features (Ducharme *et al.*, 2017).

Distinguishing patients with bvFTD from patients with PPD is crucial because of the drastically different prognosis, differences in patient management, family counselling and caregiver education, and the necessity to accurately identify patients with bvFTD in the early stages for future clinical trials. Family members of patients with bvFTD identify delayed and incorrect diagnoses as the biggest problems they faced (Chow *et al.*, 2011*b*). A few approaches have shown potential to improve diagnostic accuracy in small scale studies, including the systematic application of clinical scales (Krudop *et al.*, 2015), neuropsychiatric consultation (Krudop *et al.*, 2017), social cognitive batteries (Bertoux *et al.*, 2012), CSF markers (Vijverberg *et al.*, 2017*a*), and morphometric image processing (Moller *et al.*, 2016).

The Neuropsychiatric International Consortium for Frontotemporal Dementia (NIC-FTD) was established to determine the current best clinical practice and set up an international collaboration to share a common dataset for future research. The goal of the present paper was to review the existing literature on the diagnosis of bvFTD and its differential diagnosis with PPD. We aimed to create a list of clinical recommendations for the assessment of bvFTD in patients with late-onset behavioural changes based on evidence from the literature, as well as consensus expert opinions.

Research methods

A systematic literature search was performed to determine all bvFTD-related diagnostic evidence for the following topics: bvFTD history taking, psychiatric assessment, clinical scales, physical and neurological examination, bedside cognitive tests, neuropsychological assessment, social cognition, structural neuroimaging, functional neuroimaging, CSF and genetic testing. Two databases, Medline (PubMed) and Embase, were used to perform a search evaluating the diagnostic accuracy of clinical practice for bvFTD by using key indicators and relevant terms. The systematic search was completed in September 2017 and articles between 1992 and 2017 were retrieved. For each section, authors were allowed to include relevant references published after the systematic review. A similar method was followed for all topics. We did the search by using Medical Subject Heading (MeSH) terms including FTD, keywords for the topic, and diagnostic keywords. For example, for the structural imaging section: 'Frontotemporal Dementia' [MeSH], 'Tomography, X-Ray Computed' [MeSH], OR 'Magnetic Resonance Imaging' [MeSH], 'Sensitivity and Specificity' [MeSH] and 'Predictive Value of Tests' [MeSH]. Details of the search strategies for each topic are provided in Supplementary Figs 1–8).

Each topic was assigned to two to three members of the NIC-FTD, based on specific expertise. Teams reviewed all abstracts to identify articles relevant for the diagnostic assessment process. For each topic, except 'FTD history taking', responsible team members proposed a set of minimal requirements, clinical recommendations, and tools requiring further research or tools that should be developed. Minimal requirements include well-validated diagnostic approaches that should be available and used in any setting when diagnosing bvFTD in cases with PPD as a

differential diagnosis. Clinical recommendations refer to validated practices and tools that should ideally be used in specialized bvFTD clinics, or that clinics should aim to add to their arsenal if not already available. Tools requiring further research include methods that have not been studied sufficiently to be recommended but have shown promise. An in-person meeting of members of the NIC-FTD was held in Sydney, Australia on 13 November 2018 to review preliminary recommendations. This was followed by two rounds of draft review and teleconferences to finalize them. The final consensus was obtained through an online survey of all co-authors, establishing $\geqslant 85\%$ approval as the threshold to include recommendations.

Results

Behavioural variant frontotemporal dementia history taking

A good clinical assessment should always start by obtaining a detailed history to establish a probabilistic differential diagnosis that will guide investigations (Ducharme and Dickerson, 2015). History should include all the sections of the standard medical and psychiatric assessment, including current medication, overt and covert substance use, and vascular risk factors. Several elements of the history taking are particularly important in the assessment of bvFTD and late-onset behavioural changes more widely (Ducharme *et al.*, 2015; Dols *et al.*, 2016). Given the impaired insight that is almost always present in bvFTD, a caregiver-based history is essential. As the history may be complex or biased by the caregiver's perception or relational tensions, an additional history taken from an independent relative or friend can be helpful.

The first element is to establish a clear timeline of symptoms including the age at onset, predominant early symptoms (e.g. behaviour, language, memory, mood), relationship to life events (e.g. interpersonal conflicts, psychosocial stressors) and progression over time. Major PPD tend to have their onset in late adolescence or early adulthood. While the onset of behavioural changes in middle to late adulthood is a known risk factor for progression to dementia including FTD (Taragano *et al.*, 2009) and therefore deserves a more thorough investigation, later-onset idiopathic mood or psychotic disorders can start around the same age range as typical bvFTD (ages 40–70) (Howard *et al.*, 2000; Depp and Jeste, 2004). In bvFTD, an insidious onset with some degree of progression over time (albeit sometimes slowly over years) is expected as opposed to abrupt onset or fluctuating courses. Given the wide differential diagnosis, it is crucial to explore both neurological and psychiatric symptoms. Symptoms of particular interest include features that are strongly associated with other types of dementia and or with other frontotemporal lobar degeneration (FTLD)-spectrum syndromes [e.g. alien-limb phenomenon (corticobasal degeneration), falls (progressive supranuclear palsy), and dysphagia (amyotrophic lateral sclerosis, ALS)]. History of psychiatric symptoms must include depressive symptoms, anxiety, apathy, (hypo-)manic symptoms, delusions and hallucinations, obsessive-compulsive disorder symptoms and personality traits, as well as characteristics of autism spectrum disorders. A comprehensive developmental and educational history is important, to establish the presence of premorbid learning difficulties and personality vulnerabilities. Past history of neuropsychiatric disorders should be reviewed, including exposure to traumatic brain injuries, both as a general dementia risk factor and to help exclude chronic traumatic encephalopathy. A positive history of psychiatric illness is associated with a higher likelihood of PPD; however, clinicians should remain vigilant for emerging signs of bvFTD in patients with chronic mental illnesses. It is also crucial to elicit a detailed family history of first and second-degree relatives (see 'Genetic testing' section). Of note though, a positive family psychiatric history has been shown to bias towards missing bvFTD diagnoses (Woolley *et al.*, 2011).

Frontotemporal dementia-specific clinical scales

In past decades, the literature about clinical diagnostic scales in bvFTD has mainly focused on the differentiation between bvFTD and other types of dementia (>150 studies). Fewer studies have explored the validity of FTD symptom scales to differentiate bvFTD from PPD. The Frontal Behavioral Inventory (FBI) has been suggested as a suitable neurobehavioural tool to distinguish bvFTD from other types of dementia, but it has been shown that the overall score does not distinguish bvFTD from PPD (Kertesz *et al.*, 2000; Alberici *et al.*, 2007; Milan *et al.*, 2008; Krudop *et al.*, 2015; Dols *et al.*, 2016; Suhonen *et al.*, 2017). However, a score >12 on the positive FBI-subscale was indicative of a bvFTD diagnosis in patients with late-onset behavioural changes (Krudop *et al.*, 2015). The specific sub-items of the FBI that have been found to support bvFTD more than an idiopathic psychiatric state are 'aphasia and verbal apraxia, indifference/emotional flatness, alien hand and apraxia, and inappropriateness' whereas 'irritability' is more indicative of a PPD (Kertesz *et al.*, 2000; Dols *et al.*, 2016). The Stereotypy Rating Inventory (SRI) (Shigenobu *et al.*, 2002) is another scale that has shown interesting discriminatory features, as stereotypies were shown to be more commonly present in bvFTD than in patients with similar presenting symptoms but with a final diagnosis of PPD (Krudop *et al.*, 2015; Dols *et al.*, 2016). DAPHNE, a recently developed informant-based behavioural inventory with 10 items based on the 2011 bvFTD international consensus diagnostic criteria, demonstrated an ability to distinguish bvFTD from bipolar disorder (Boutoleau-Bretonniere *et al.*, 2015). The

Box 1 Assessment recommendations for clinical scales

Clinical scales		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Clinically assess for behavioural abnormalities according to the bvFTD international consensus diagnostic criteria via history and clinical observation.	Minimal requirements + • Systematic use of a behavioural clinical scale (e.g. FBI, SRI)	• FTD versus PPD checklist. • Development of composite scales specifically for discriminating bvFTD from PPD.

FBI = Frontal Behavioral Inventory; SRI = Stereotypy Rating Inventory.

Cambridge Behavioural Inventory (CBI) (Wear *et al.*, 2008; Wedderburn *et al.*, 2008) is of qualitative use in the management of behavioural symptoms in bvFTD, especially with regard to symptom profile, and has also been suggested as a useful outcome measure in clinical trials (Hancock and Larner, 2008; Wear *et al.*, 2008; Wedderburn *et al.*, 2008); however, there are no studies documenting its performance against PPD. Measuring apathy has value as it is common in bvFTD; however, it is unknown if apathy scales have benefit for the differential diagnosis with PPD. Finally, the Frontotemporal Dementia versus Primary Psychiatric Disorder (FTD versus PPD) Checklist is a recently developed tool to standardize the assessment of simple clinical factors that have value for the distinction between bvFTD and PPD (Ducharme *et al.*, 2019). Items were selected based on literature review and clinical expertise, and subsequently reduced to 17 items based on statistical analyses in two clinical cohorts. The FTD versus PPD Checklist proved to have good diagnostic accuracy in samples of 29 and 137 patients, respectively; however, further prospective validation is needed (Ducharme *et al.*, 2019). For a summary, see Box 1.

Psychiatric assessment

While multiple neuropsychiatric symptoms such as apathy, disinhibition and compulsions overlap between bvFTD and PPD, some clinical features can help to distinguish these disorders in clinical practice (Ducharme *et al.*, 2015; Dols *et al.*, 2016). Indeed, careful clinical phenotyping of cases suspected for bvFTD revealed that those patients most often do not fulfil formal DSM-5 criteria for another mental disorder (Gossink *et al.*, 2016*b*). This supports the importance of multidisciplinary work, including consultation with a psychiatrist with expertise in FTD who can rigorously apply DSM-5 criteria combined with expert clinical judgement to identify specific psychiatric diagnoses in clinics led by neurologists or geriatricians. In terms of key differentiating clinical features, the emotional distress that characterizes most psychiatric disorders is usually absent in patients with bvFTD, who present with prominent emotional blunting and show lower than expected mood and/or subjective distress symptoms (although some patients show restlessness or agitation that may be over-interpreted or attributed as anxiety) (Cheran *et al.*, 2018). Another potential discriminator is the degree of concern, which is often present in many PPD (as opposed to marked lack of insight in bvFTD), except in severe psychotic disorders and mania. Furthermore, while psychotic symptoms are possible in bvFTD (especially in *C9orf72* mutations), they are more commonly associated with PPD, and therefore the presence of such symptoms should lead to a psychiatric evaluation (Gossink *et al.*, 2017). The Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) is frequently used to evaluate psychiatric symptoms in dementia, but is not sufficient in itself to rule PPD in or out. Indeed, the clinical assessment should go beyond the simple identification of psychiatric symptoms as a general category (e.g. psychosis) and provide a more detailed phenomenological description of symptoms that can have diagnostic value, such as the high prevalence of somatic delusions in *C9orf72* carriers (potentially related to altered body schema) (Downey *et al.*, 2014).

The value of structured psychiatric symptom rating scales in differentiating bvFTD from PPD has not been systematically studied. The usefulness of self-report psychiatric scales in bvFTD is minimal due to patients' impaired insight. However, clinician-rated symptom scales could have value in increasing diagnostic consistency. Specific scales for mood symptoms [e.g. Montgomery and Asberg Depression Rating Scale (MADRS), and Hamilton Depression Rating Scale (HAM-D)] can be applied in suspected bvFTD cases to systematically assess differentiating features (e.g. depressed mood, suicidal thoughts) (Blass and Rabins, 2009; Vijverberg *et al.*, 2017*b*). The Mild Behavioral Impairment Checklist is a more specific tool to measure later-life behavioural changes that can be the harbinger of dementia (Ismail *et al.*, 2017); however, it does not facilitate the differentiation of PPD from bvFTD.

Experienced clinicians also identify more subtle features in the psychiatric assessment that point towards PPD versus bvFTD. This includes aspects of the history content (e.g. fluctuating symptoms, patient's understanding of bvFTD), but also about the interview process (e.g. who initiated the consultation process, whether the patient is over or under-emphasizing the severity of disability). Indeed, lack of insight is especially common in bvFTD, more so than in PPD.

Box 2 Assessment recommendations for the psychiatric assessment

Psychiatric assessment		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Evaluation by one or more clinicians with expertise in neurocognitive disorders and psychiatry to evaluate patients in which primary PPD are on the differential diagnosis. • Application of DSM-5 clinical criteria to identify specific PPD and psychiatric comorbidities to bvFTD. • Access to neurological consultations in clinics led by psychiatrists.	Minimal requirements + • Multi-disciplinary environment with psychiatric and neurologic diagnostic expertise in FTD in cases in which PPD is on the differential diagnosis.	• Systematic use of a depression scale (e.g. MADRS). • Structured psychiatric diagnostic interview (e.g. Structured Clinical Interview for DSM-5 disorders).

MADRS = Montgomery–Åsberg Depression Rating Scale.

Behavioural scales that can capture this lack of insight, as well as other clinical information has been shown to improve early differentiation between bvFTD and PPD (Ducharme *et al.*, 2019). Using tests that objectively quantify insight and meta-cognitive awareness (O'Keeffe *et al.*, 2007; Hutchings *et al.*, 2015) may also be helpful in this regard.

Of note, psychiatric symptoms may not only present as a differential diagnosis, but also constitute co-morbidity and even a prodrome prior to the emergence of bvFTD features several years later. In particular, *C9orf72* repeat expansion carriers can present with psychiatric symptoms and form a diagnostic challenge given their slow progressive course and atypical findings in neuroimaging (see 'Genetic testing' section) (Khan *et al.*, 2012; Solje *et al.*, 2015; Ducharme *et al.*, 2017). For a summary, see Box 2.

Physical and neurological examination

A comprehensive clinical examination including vital signs, basic cardiovascular exam and basic neurological examination helps inform the appropriate investigations or explore alternative diagnoses. The neurological examination also aims to identify motor signs that may be associated with FTD or FTD-related disorders, such as parkinsonism, oculomotor disorders or ALS. Those types of findings on examination strongly point towards subtypes of FTLD as opposed to PPD.

The frequency of parkinsonism varies between 25% and 80% in structured clinical studies of FTD (Diehl-Schmid *et al.*, 2007*b*; Padovani *et al.*, 2007; Park *et al.*, 2017). Bradykinesia/akinesia, parkinsonian gait/posture and rigidity were found to be the most common, with tremor being less common. Asymmetric rigidity, alien hand, and apraxia raise the possibility of corticobasal syndrome, whereas vertical gaze palsy (or in early stages, absence of normal optokinetic nystagmus or slowing of down saccades) and postural instability are suggestive of progressive supranuclear palsy. In genetic cases of bvFTD, parkinsonism is relatively frequent (Snowden *et al.*, 2012; Siuda *et al.*, 2014). It should be taken into account that symmetric bradykinesia, rigidity, and tremor can also be part of drug-induced parkinsonism in patients with a PPD.

In the neurological examination of patients with bvFTD, signs of degeneration of both upper and lower motor neurons can be found. Upper motor neuron signs raising concerns for a motor neuron disease are hyperreflexia, hypertonia or spasticity, as well as Babinski and Hoffmann signs. Upper motor neuron signs also include less specific primitive reflexes (frontal release signs) such as grasp, suck or palmomental (as mentioned in the Lund and Manchester criteria for bvFTD) (Englund *et al.*, 1994). Of note, mild motor abnormalities ('neurological soft signs') can also be found in PPD, particularly in schizophrenia (Griffiths *et al.*, 1998). Signs of lower motor neuron degeneration include weakness, atrophy, fasciculations or hyporeflexia. In particular, a careful tongue exam should be performed, looking for atrophy and fasciculations. Dysarthria and dysphagia suggest bulbar involvement and may also be associated with ALS, as well as pseudobulbar involvement in progressive supranuclear palsy. Overall, the finding of motor neuron dysfunction in patients with behavioural changes strongly points to a neurodegenerative disorder (ALS or bvFTD) and is associated with a poor prognosis. For a summary, see Box 3.

Bedside cognitive tests

A bedside cognitive screening assessment is an essential component of the initial assessment, and several instruments are commonly used including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Examination (ACE). A normal-range MMSE score is often seen in clinically suspected bvFTD (Hutchinson and Mathias, 2007) at early stages and the MMSE is therefore unsuccessful in the discrimination between bvFTD and PPD (Krudop *et al.*, 2015). With a classification accuracy of 88% (78% sensitivity and 98% specificity), the MoCA appears to be a better instrument than the MMSE for brief cognitive

Box 3 Assessment recommendations for the physical and neurological examinations

Physical/neurological examination		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Global physical and neurological examination including: (i) Testing for parkinsonism: bradykinesia/akinesia, parkinsonian gait/posture or rigidity. (ii) Testing for motor neuron signs and non-specific primitive reflexes such as the grasp reflex. (iii) Test smooth pursuit and saccadic eye movements for vertical eye-gaze palsy (downward > upward). • Refer for EMG in the presence of unexplained upper and/or lower motor neuron signs.	Minimal requirements + • Detailed neurological examination including additional signs such as: (i) Decreased velocity of saccades[a]. (ii) Test/observe for unilateral dystonia, stimulus-sensitive myoclonus, cortical sensory deficits, ideomotor apraxia and alien limb phenomenon[b]. (iii) Evaluate for absence of optokinetic nystagmus vertically[a].	• Automated eye-tracking for FTD and FTD-ALS.

[a]Clinical features that are found in progressive supranuclear palsy.

screening of patients with suspected bvFTD (Freitas *et al.*, 2012); however, its value to differentiate bvFTD from PPD is uncertain. The ACE includes items that overlap with the MMSE, but provides additional language, semantic memory, and visuospatial components (Mathuranath *et al.*, 2000). Many studies have supported its use in differentiating between FTD and Alzheimer's disease, but it has been less studied for the differential with PPD (Mathuranath *et al.*, 2000; Dudas *et al.*, 2005; Hodges, 2012; Hsieh *et al.*, 2015). The most recent version (ACE-III) showed excellent sensitivity and specificity for detecting early-onset dementia, but the lowest sensitivity was observed in bvFTD (Elamin *et al.*, 2016). One study showed that a total score of $\leqslant 88$ on the ACE was associated with an underlying neurodegenerative disorder (including FTD) rather than major depression (Dudas *et al.*, 2005); however, it is unclear if this would also apply to early-stage patients when the differential problem with PPD is most acute. Finally, the *Dépistage Cognitif de Québec* (DCQ; www.dcqtest.org) (Laforce *et al.*, 2018), which takes into account the cognitive profiles of non-memory Alzheimer phenotypes, primary progressive aphasia and the FTLD spectrum, showed a predictive power of 79% to distinguish between typical and atypical dementia, superior to the MoCA (Sellami *et al.*, 2018). While its performance to differentiate bvFTD from PPD is unknown, the DCQ is the only screening cognitive test that also includes a behavioural index.

One of the limitations of traditional cognitive screening tools is their inability to detect subtle changes in executive functioning. Screening tools of executive functions such as The Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000) and The Institute of Cognitive Neurology Frontal Screening (IFS) (Torralva *et al.*, 2009) can provide information on executive capacities in neurodegenerative and psychiatric conditions. However, the FAB did not differentiate bvFTD from PPD in one study (Krudop *et al.*, 2015). On the IFS, however, patients with bvFTD scored significantly worse on several sub-items than subjects with major depression and bipolar disorder (Fiorentino *et al.*, 2013). Therefore, the IFS might have discriminatory power to distinguish bvFTD from PPD. Recently, the Frontier Executive Screen (FES) showed a sensitivity of 71% at a specificity of 73% to differentiate bvFTD from Alzheimer's disease (Leslie *et al.*, 2016), but has not yet been applied in the differential diagnosis with PPD. Of note, while this is less evidence-based than standardized screening instruments, clinicians can complement their bedside examination with a variety of simple tests for executive functions (e.g. Luria motor sequence and loops, Go/No-Go). For a summary, see Box 4.

Neuropsychological examination

While bedside cognitive tests can help provide a quick overview of a patient's deficits, formal neuropsychological testing provides a comprehensive profile, particularly in patients with mild or questionable cognitive deficits or in those with high premorbid intellect. Major deficits in attention (Kipps *et al.*, 2008) and executive functions (Kipps *et al.*, 2008; Harciarek and Cosentino, 2013) are often reported; however, these are not specific to bvFTD (Jenner *et al.*, 2006). The letter verbal fluency, Hayling Sentence Completion Test, Digit Span Backwards, Stroop Test and the Trail-Making Test – Part B are of particular use in the differential diagnosis of bvFTD (Braaten *et al.*, 2006; Hornberger *et al.*, 2008). As a caveat, symptomatic PPD subjects were shown to have worse performance on formal neuropsychological testing compared to bvFTD in one study (Vijverberg *et al.*, 2017*c*). While executive functions are also significantly affected in PPD (Ziauddeen *et al.*, 2011; Chan *et al.*, 2014; Vijverberg *et al.*, 2017*c*), persistent and progressive executive dysfunction over time despite improvement in psychiatric symptoms should raise suspicion for bvFTD. Therefore, serial/longitudinal

Box 4 Assessment recommendations for bedside cognitive tests, neuropsychological examination, and social cognition tests

Bedside cognitive tests, neuropsychological examination and social cognition		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• General bedside screening tests using either MoCA, ACE-III or DCQ. • If no abnormalities on general screening, add an executive function test, such as IFS or FES, ± bedside executive function tests (e.g. Luria motor sequence and loops) • Distinction between bvFTD and PPD should not be based on global cognitive screening test score only. • Screen social cognition by informant-based history[a].	Minimal requirements + • In diagnostically ambiguous cases, bedside screening tests plus neuropsychological examination testing all domains: (i) Attention (e.g. Digits Forwards, Trail Making Test – Part A); (ii) Language (e.g. expressive and receptive); (iii) Memory (e.g. episodic verbal and non-verbal) (iv) Working memory, (e.g. Digits Backwards); (v) Visuoperceptual tasks (e.g. VOSP); (vi) Executive tasks (e.g. Stroop Test, Trail Making Test Part B, Hayling Sentence Completion Test); (vii) Extensive language testing including assessment of semantic associations. • Perform at least one structured test of social cognition, (e.g. Ekman 60 Faces Test, SEA or Mini-SEA). • Integrate qualitative evidence to inform the interpretation of the neuropsychological assessment.	• Action words naming. • Cross disorder phenotyping of social cognition in bvFTD and primary psychiatric disorders mimicking bvFTD. • Clinical and transcultural validation of research social cognitive instruments. • Validation and sensitivity/specificity of additional social cognition tests (e.g. TASIT, ToM cartoons and stories, Abraham's Cognitive-Affective Judgement of Preference Test).

[a]Examples of screening questions: How does she/he behave in social situations? Does she/he have difficulty understanding how others feel? Is he/she less empathetic or less appropriate than before?

ACE = Addenbrooke's Cognitive Examination; DCQ = Dépistage Cognitif de Québec; FES = Frontier Executive Screen; IFS = Institute of Cognitive Neurology Frontal Screening; MoCA = Montreal Cognitive Assessment; SEA = Social cognition and Emotional Assessment; TASIT = The Awareness of Social Inference Test; ToM = Theory of Mind; VOSP = Visual Object and Space Perception Battery.

neuropsychological assessments should be favoured over single assessments.

Contrary to popular belief, executive dysfunction is not always the most prominent deficit in bvFTD and may not even be present on formal neuropsychological test results in the early stages (Pachana *et al.*, 1996; Kipps *et al.*, 2008; Rascovsky *et al.*, 2011). Clinicians should therefore consider qualitative evidence when examining executive tasks performance and errors (Kipps *et al.*, 2008; Harciarek and Cosentino, 2013). For example, although test results may be within normal range, patients with bvFTD may show aberrant strategies and behaviours during the neuropsychological examination, such as stereotypies of speech, impulsivity, rigidity, obsessionality and clock watching. Furthermore, ~10% of pathologically-confirmed bvFTD subjects show marked episodic memory deficits at initial presentation, contrary to current diagnostic criteria (Hodges *et al.*, 2004; Hornberger and Piguet, 2012; Bertoux *et al.*, 2018). That said, in one study the bvFTD group showed significantly better performance on verbal memory tests compared to schizophrenia, bipolar and major depressive disorder patients (Vijverberg *et al.*, 2017*c*).

Interestingly, action naming seems to be more affected in bvFTD, whereas object naming is more disturbed in Alzheimer's disease (Harciarek and Jodzio, 2005). Although not specific to action naming, in a study comparing the neuropsychological profile of 33 patients with bvFTD with 55 patients with miscellaneous psychiatric disorders, language tests, in particular picture naming, were more discriminative than executive tests (Overbeek *et al.*, 2020). One exception is reiterative speech disorders (e.g. logoclonia, palilalia, echolalia, festinant speech, verbal stereotypy, and prominent automatic speech), which may help differentiate bvFTD from other neurodegenerative diseases, but not from schizophrenia (Harciarek and Jodzio, 2005; Ziauddeen *et al.*, 2011). For a summary, see Box 4.

Social cognition

In a broad sense, social cognition encompasses those abilities necessary to participate and communicate effectively in

social situations. It is an umbrella term that includes several subdomains including emotion recognition, (cognitive and affective) theory of mind (Amodio and Frith, 2006), empathy, and moral reasoning. Deficits on all these socio-cognitive functions have been reported in bvFTD (Kumfor *et al.*, 2017*a*).

Emotion recognition has primarily been evaluated via static facial expression stimuli. Emotion recognition impairments have been reported in a multitude of tests including when the patient is asked to label the emotion expressed [e.g. Ekman 60 Faces Test (Lavenu *et al.*, 1999; Diehl-Schmid *et al.*, 2007*a*; Kumfor *et al.*, 2013); and Social Cognition and Emotional Assessment (SEA) (Funkiewiez *et al.*, 2012; Karch *et al.*, 2018)]. In addition to impaired facial expression recognition, bvFTD also showed reduced ability to recognize emotions depicted on (faceless) whole bodies, e.g. the Bodily Expressive Action Stimulus Test (BEAST) (Van den Stock *et al.*, 2015). Studies focusing on performance on these tests comparing bvFTD and PPD are limited. Recent evidence suggests a reduced perception of the intensity for negative emotions in bvFTD, but an increased perception for these emotions in patients with major depressive disorder (Chiu *et al.*, 2018). Accordingly, several studies have found that emotion recognition may discriminate bvFTD from late-life depression (Bertoux *et al.*, 2012; Chiu *et al.*, 2018).

Both cognitive and affective components of the Theory of Mind (ToM) are affected in bvFTD (Kipps *et al.*, 2009*b*; Eslinger *et al.*, 2011). Deficits have also been reported when using dynamic stimuli (i.e. video vignettes, such as The Awareness of Social Inference Test, TASIT), particularly for those using sarcasm (Downey *et al.*, 2015). When compared with PPD, patients with bvFTD scored worse on a ToM task (reading the mind in the eyes, RMET) than patients with bipolar disorder (Baez *et al.*, 2019). Interestingly, while both schizophrenia patients and patients with bvFTD are able to interpret sincere statements on the TASIT, schizophrenia patients show impaired sarcasm and lie detection irrespective of the contextual information provided, whereas patients with bvFTD are impaired at detecting sarcasm and lies, but this is alleviated with additional contextual information (Kosmidis *et al.*, 2008). This aligns with recent evidence that patients with bvFTD may be over-reliant on contextual cues, leading to abnormal behaviour in social contexts (Kumfor *et al.*, 2018). The Cognitive-Affective Judgement of Preference test has been developed to separate cognitive and affective components of ToM (van der Hulst *et al.*, 2015). While it has been tested in ALS and may have utility, direct comparisons between bvFTD and PPD are still lacking.

The empathic deficit in bvFTD has been mostly evaluated using the Interpersonal Reactivity Inventory (IRI), with both cognitive and affective components of empathy typically affected in bvFTD (Rankin *et al.*, 2005; Eslinger *et al.*, 2011), but direct comparisons to PPD is lacking. Changes in processing of moral dimensions in bvFTD have been documented using verbal or pictorial scenarios describing moral situations followed by a moral judgement query (Mendez *et al.*, 2005; Baez *et al.*, 2014).

While scant systematic direct comparisons have been conducted between bvFTD and the most relevant PPD, it is known that social cognitive disturbances are present in autism, schizophrenia, bipolar disorder, and depression (APA, 2013; Ladegaard *et al.*, 2014; Bora *et al.*, 2016; Bonfils *et al.*, 2017). The Ekman 60 Faces Test appeared to be discriminative between bvFTD and a range of psychiatric disorders (Gossink *et al.*, 2018). Further, a recent meta-analysis indicates that the social cognition impairment in bvFTD is more severe than that seen in major psychiatric disorders, as well as developmental disorders such as autism and attention deficit hyperactivity disorder (Cotter *et al.*, 2018).

Questionnaires such as the socioemotional functioning questionnaire may be useful as a brief screening tool or to elicit information from caregivers (Hutchings *et al.*, 2015). Unfortunately, several social cognitive instruments that have been developed for research purposes are yet to have normative data available (see TASIT-S, which has been validated in bvFTD and Alzheimer's disease) (Kumfor *et al.*, 2017*b*; McDonald *et al.*, 2018). Another critical issue is the lack of transcultural adaptation of most of social cognition tests (Engelmann and Pogosyan, 2013). For a summary, see Box 4.

Structural neuroimaging

Structural imaging is an integral part of the diagnostic investigation of bvFTD in patients with adult onset behavioural changes. The presence of pathological atrophy in frontal or anterior temporal areas increases the bvFTD diagnostic certainty from 'possible' to 'probable' in current diagnostic criteria (Rascovsky *et al.*, 2011), which increases the specificity from 82% to 95% (Harris *et al.*, 2013). Major consensus dementia investigation guidelines all recommend structural brain imaging as part of the investigation of bvFTD (Knopman *et al.*, 2001; Filippi *et al.*, 2012; Soucy *et al.*, 2013). Structural imaging should precede other forms of imaging, such as FDG-PET or molecular tracer-imaging tracers (Soucy *et al.*, 2013). Brain MRI is generally recommended over CT scan unless there are availability restrictions or contraindications (Filippi *et al.*, 2012; Soucy *et al.*, 2013).

Assessment of cortical atrophy by standard visual neuroradiological review is often insufficient in the initial stages of bvFTD to differentiate it with normal age-related volume loss (Gregory *et al.*, 1999; Chow *et al.*, 2008; Vijverberg *et al.*, 2016*a*), which can lead to erroneous diagnoses. In the LOF study, brain MRI was found to be useful for the diagnosis of bvFTD versus PPD (Krudop *et al.*, 2016), but lacking sensitivity (70%), particularly in genetic cases (Vijverberg *et al.*, 2016*a*). Of note, there are various reports of statistically significant volume loss in major psychiatric disorders (e.g. ventricular enlargement in schizophrenia, hippocampal atrophy in major depression), but these are

based on group statistic and the magnitude of change is not sufficient to be detected reliably at the individual levels (Selvaraj *et al.*, 2012).

The development of volumetric analytic techniques (e.g. voxel-based morphometry, cortical thickness) have gathered significant interest as a potential tool to improve diagnostic accuracy of bvFTD (Meeter *et al.*, 2017) and to track disease progression (Gordon *et al.*, 2010). In particular, these methods may help capture subtle atrophy that starts several years prior to the onset of symptoms (Rohrer *et al.*, 2015*b*; Whitwell *et al.*, 2015), and could prove useful for the differential with PPD. Most studies have focused on the differential diagnosis between FTD, Alzheimer's disease and controls, often yielding diagnostic accuracy in the 80–90% range (McCarthy *et al.*, 2018). Unfortunately, this literature greatly suffers from a lack of replication across samples and prospective validation at the individual subject level, particularly in populations with ambiguous behavioural changes. It is also unclear at present if those methods are superior to the systematic use of standard visual rating scales of atrophy [e.g. global cortical atrophy, medial temporal atrophy (Scheltens *et al.*, 1995), Kipps (Kipps *et al.*, 2007)] (Davies *et al.*, 2009; Chow *et al.*, 2011*a*; Harper *et al.*, 2016). Atrophy patterns can further give cues towards genetic aetiology, such as the involvement of the parietal cortex, asymmetric hemispheric atrophy and white matter hyperintensities with GRN mutations (Cash *et al.*, 2018).

Machine-learning algorithms using MRI volumetry to develop diagnostic classifiers fare well against controls but achieve maximal performance of 82% in separating well-characterized cases of bvFTD from Alzheimer's disease (Moller *et al.*, 2016; Canu *et al.*, 2017; McCarthy *et al.*, 2018). Less is known about the performance against PPD, but a recent study has shown potential usefulness (Zhutovsky *et al.*, 2019). Overall despite promises, prospective application of machine learning in real-life clinical setting remains challenging (Klöppel *et al.*, 2015). While currently not clinically indicated, diffusion-weighted sequences and arterial spin labelling (as an alternative for FDG-PET) hold promises for improved diagnostic accuracy (Bron *et al.*, 2017). Resting state functional MRI has provided insight on the network disruptions due to bvFTD but has no clinical application at this point. For a summary, see Box 5.

Nuclear imaging

Although single photon emission tomography (SPECT) is still used, studies have shown clear superiority of FDG-PET and consequently, SPECT is becoming less utilized in expert centres (Döbert *et al.*, 2005; Mosconi *et al.*, 2008). PET provides a higher imaging sensitivity by identifying half of the bvFTD cases that remain undetected by MRI techniques (Kerklaan *et al.*, 2014). This is particularly useful in the context of diagnostic uncertainty in atypical cases of early-onset dementia (Foster *et al.*, 2007; Panegyres *et al.*, 2009). Unfortunately, the presence of hypometabolism seems to be of limited specificity when used in a neuropsychiatric cohort with adult-onset behavioural changes with up to 40% of PPD subjects having some abnormal findings (Vijverberg *et al.*, 2016*a*). In ambiguous cases, a normal FDG-PET scan tends to support the exclusion of neurodegenerative aetiologies (Kipps *et al.*, 2009*a*; Cerami *et al.*, 2015; Vijverberg *et al.*, 2016*a*), but it does not completely exclude FTD (such as definite genetic cases that do not show the expected hypometabolism) (Kipps *et al.*, 2009*a;* Levy *et al.*, 2019). In specialized memory clinics, a second FDG-PET performed at least 1 year later in patients with persisting diagnostic incertitude reduced the number of unclear diagnoses from 80% to 34%, and led to diagnostic change in 24% of cases (Bergeron *et al.*, 2016). Standardized computer-assisted approaches with quantitative analysis could reduce the impact of inter-rater and inter-centre variability and potentially increase diagnostic accuracy (Mosconi *et al.*, 2008; Cerami *et al.*, 2014), but has to be interpreted by a specialist in FDG-PET. For a summary, see Box 5.

Regarding amyloid imaging, because of its high negative predictive value, absence of amyloid binding reliably points towards a non-Alzheimer's disease cause of dementia, such as bvFTD (Rabinovici *et al.*, 2014). While searching for amyloid biomarkers can be helpful in the context of ambiguous dementia phenotypes that include Alzheimer's disease on the differential, a negative result will not assist to differentiate FTD from PPD. More recently, tau-specific PET ligands have promised to track the spatial and temporal distribution of tau pathology in Alzheimer's disease, but there are major limitations currently in FTLD tauopathies (Saint-Aubert *et al.*, 2017).

In a clinical setting, the benefits of molecular PET tracers need to be carefully weighed against availability, cost and adverse effects, considering methodological and ethical considerations. Currently, we recommend functional neuroimaging techniques be reserved for cases of diagnostic uncertainty despite extensive clinical evaluation and for atypical presentations of early-onset dementia.

CSF and blood biomarkers

CSF biomarkers achieved through lumbar puncture have great promise to one day accurately diagnose FTD or one of its underlying pathological subtypes (FTLD-tau, FTLD-TDP, etc.) at a low complication rate (Duits *et al.*, 2016). These biomarkers could play a major role in the distinction with PPD; however, in the current clinical diagnostic criteria for bvFTD, the place of CSF analysis is to exclude Alzheimer's disease pathology based on the routine biomarkers CSF tau, phosphorylated tau (p-tau), and amyloid-β_{42} (Rascovsky *et al.*, 2011). Isolated increase of CSF-tau without CSF amyloid-β_{42} reduction is in favour of a bvFTD diagnosis, as CSF amyloid-β_{42} in definite bvFTD has been found to be normal, whereas CSF tau levels are

Box 5 Assessment recommendations for structural and nuclear neuroimaging

Structural neuroimaging		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Brain MRI with T_1 and FLAIR sequences including coronal cuts. • Brain CT with coronal views only if MRI not available or contraindicated. • FDG-PET in ambiguous diagnostic cases without clear CT/MRI frontotemporal atrophy. • SPECT scan only if PET unavailable. • In cases when non-specific FDG-PET hypometabolism is the only abnormal neuroimaging examination, reconsider psychiatric origin.	Minimal requirements + • MRI 3D T_1 sequence (e.g. MPRAGE) • Standard review protocol with a specialized neuroradiologist including standardized rating scales (global cortical atrophy, medial temporal atrophy, Fazekas) and visual qualification of regional cortical atrophy in frontal lobes and anterior temporal poles; or consider automated volumetry if available. Minimal requirements + • FDG-PET reviewed by nuclear medicine physician with expertise in dementia, consider using registration and normalized statistical analyses. • Amyloid biomarker (amyloid PET or CSF) in early-onset atypical cases with Alzheimer's disease on the differential diagnosis.	• MRI 3D T_1 sequence with systematic volumetry and machine learning classifiers. • Diffusion-weighted imaging. • Resting state functional MRI. • Arterial spin labelling. • Molecular tracers able to identify FTLD subtypes, including tau-PET.

Box 6 Assessment recommendations for cerebrospinal fluid and blood biomarkers

CSF and blood biomarkers		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• None	• CSF analysis of amyloid-β_{42}, tau, and p-tau to rule out Alzheimer's disease. • Consider serum or CSF NfL to differentiate bvFTD from PPD if reference values available.	• Analysis of combinations of CSF biomarkers, such as NfL, p-tau/tau ratio, sAPP, and YKL-40 in bvFTD versus PPD. • Validation of candidate biomarkers identified by high-throughput techniques such as proteomics in bvFTD versus PPD.

sAPP = soluble amyloid precursor protein.

normal to increased (Grossman *et al.*, 2005; Bian *et al.*, 2008).

Neurofilaments are components of the axonal skeleton, and their presence in CSF is a marker for neurodegeneration. There is accumulating evidence that both CSF and serum neurofilament light chain (NfL) are discriminative biomarkers between bvFTD and PPD. Studies in definite bvFTD showed a very good performance of CSF NfL to discriminate FTD gene mutation carriers from controls [area under the curve (AUC) 0.99] (Meeter *et al.*, 2018). CSF NfL appeared to be a good discriminator between neurodegenerative disorders and PPD (Eratne *et al.*, 2020). In a study including 22 bvFTD and 25 PPD patients, CSF NfL had a high diagnostic accuracy (AUC 0.93) (Vijverberg *et al.*, 2017*a*). As plasma and CSF NfL levels are highly correlated, blood sampling could take the place of CSF sampling regarding this biomarker (Mielke *et al.*, 2019). Plasma NfL has recently been shown to be elevated in bvFTD compared to schizophrenia, depression, and bipolar disorder (Al Shweiki *et al.*, 2019) and was discriminative from these disorders with AUCs ranging between 0.89 and 0.94. This was confirmed in a larger study including 66 bvFTD and 34 PPD patients with an AUC of 0.83. (Katisko *et al.*, 2020). For a summary, see Box 6.

Genetic testing

Around 30–50% of patients with bvFTD have a positive family history (Chow *et al.*, 1999; Goldman *et al.*, 2005; Seelaar *et al.*, 2008) and an autosomal dominant mode of inheritance is found in 10–27% of all FTD cases (Goldman *et al.*, 2005; Seelaar *et al.*, 2008). There has been some debate as to what constitutes a 'positive family history' of FTD and the Goldman score has emerged as a robust measure of the 'strength' of family history that takes into account the degrees of relativity within families (Goldman *et al.*, 2011; Wood *et al.*, 2013). Mutations in *GRN* and *MAPT* occur almost exclusively in patients with a strong family history, whereas the *C9orf72* expansion can also commonly occur in apparent sporadic disease. Indeed,

genetic causes are found in 1–10% of sporadic bvFTD cases (Rademakers *et al.*, 2012). While *C9orf72*, *MAPT* and *GRN* are the most common mutations, many other rare genetic causes exist, including mutations in *CHMP2B*, *VCP*, *TBK1*, *TIA1*, *OPTN*, *TARDBP*, *CCNF* and *CHCHD10* (Pottier *et al.*, 2016).

The diagnostic dilemma between genetic FTD and PPD is best illustrated by *C9orf72* mutations (Ducharme *et al.*, 2017), which is the most common genetic cause of FTD (Rademakers *et al.*, 2012). The number of repeats in FTD and ALS patients vary from >30 to several thousands, while healthy controls carry between 2 and 20 copies (Pottier *et al.*, 2016). The exact pathogenic threshold is not yet definitely established, but $\geqslant 30$ repeats is considered pathogenic. *C9orf72* repeat expansions have almost complete penetrance, but some carriers have not shown symptoms >80 years of age (Boeve *et al.*, 2012; Majounie *et al.*, 2012). The most common clinical presentations include bvFTD, ALS or the combination of both, but also prodromal psychiatric syndromes (Rohrer *et al.*, 2015*a*; Ducharme *et al.*, 2017). A long disease duration of up to 22 years in a proportion of patients is possible, and *C9orf72* has been identified as a cause of very slowly progressive FTD (Khan *et al.*, 2012). Neuroimaging usually shows symmetric atrophy of frontal, temporal, and parietal lobes, as well as cerebellum and thalamus (Whitwell *et al.*, 2012). However, MRI and even FDG-PET can be normal during initial assessment (Solje *et al.*, 2015).

In *C9orf72* repeat expansions carriers, reports have emerged of bipolar disorder, obsessive compulsive disorder and schizophrenia occurring in patients in the years preceding FTD (Galimberti *et al.*, 2013; Ducharme *et al.*, 2017; Saridin *et al.*, 2019). In these individuals, delusions and hallucinations, mostly auditory, were reported in 21–56% (Dobson-Stone *et al.*, 2012; Devenney *et al.*, 2014, 2017, 2018*b*; Ducharme *et al.*, 2017). Delusion subtypes reported include: persecutory, jealousy, grandiosity, religiosity and somatic and these may precede the classical presentation of bvFTD symptoms by up to a decade (Block *et al.*, 2016). Further, increased rates of PPD including schizophrenia and autism spectrum disorder have also been reported in kindreds of *C9orf72* mutation carriers (Devenney *et al.*, 2018*b*), possibly related to incomplete expansion (Galimberti *et al.*, 2013). On the other hand, *C9orf72* repeat expansions do not occur more often in schizophrenia, schizoaffective and bipolar disorder patient cohorts ($<0.1\%$) than in controls (Huey *et al.*, 2013; Fahey *et al.*, 2014; Floris *et al.*, 2014; Galimberti *et al.*, 2014*b*, *c*; Yoshino *et al.*, 2015; Solje *et al.*, 2016; Watson *et al.*, 2016). Within these cohorts, the small number of patients that were found to carry the *C9orf72* expansion were often those with a family history of either neurodegeneration or neuropsychiatric disease. While psychotic symptoms are present in up to 26% of sporadic FTD cases, they are much less severe than those observed in cases with the *C9orf72* expansion and are likely overshadowed by other behavioural abnormalities, suggesting that severe psychotic symptoms are a potential marker of an associated genetic abnormality (Devenney *et al.*, 2017).

In *GRN* mutations, visual hallucinations and delusions occur in up to 25% of patients during the course of the disease, and can also be the presenting symptom (Boeve *et al.*, 2006; Snowden *et al.*, 2006; Le Ber *et al.*, 2008; Watson *et al.*, 2016). There seems to be an association between late-onset bipolar disorder type 1 and *GRN* mutations, as mutations have been described in patients with bipolar disorder that evolved into bvFTD (Cerami *et al.*, 2011; Galimberti *et al.*, 2014*a*). Occurrence of paranoid delusions and hallucinations has been described in a few cases with *MAPT* mutation (Saito *et al.*, 2002; Spina *et al.*, 2007), but are absent in other cohorts.

Box 7 Assessment recommendations for genetic testing

Genetic testing		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Access to clinical care provider and laboratory that can perform FTD genetic testing.	• Genetic testing (all FTD mutations) in probable bvFTD with at least one first-degree relative with bvFTD, late-onset PPD, ALS or other early onset neurodegenerative disease. • *C9orf72* screening in all cases with possible or probable bvFTD, regardless of family history. • *C9orf72* screening in late-onset PPD with at least one first-degree relative with FTD or ALS. • Strongly consider *C9orf72* screening in all cases of suspected bvFTD not meeting full diagnostic criteria if there is prominent psychiatric symptoms or family history of late-onset PPD.	• Whole exome or genome sequencing in multiple (>2) family members with unknown genetic deficit.

Genetic testing for the three common genetic abnormalities of bvFTD (*GRN*, *MAPT* and *C9orf72*) is currently indicated if at least one first-degree relative is affected. A positive family history should be considered to extend beyond FTD and young-onset dementia to include Parkinson's disease or related disorders, ALS and unexplained late-onset psychiatric disorders. Given the strong overlap with psychiatric phenotypes and the significant proportion of mutations in apparent sporadic cases, testing for the *C9orf72* expansion is increasingly justified in every patient with a late-onset behavioural presentation (whether they meet full clinical bvFTD criteria or not), and even in the absence of neuroimaging abnormalities in some patients. In this case, genetic testing serves as a diagnostic tool, rather than to identify the underlying aetiology in patients with clear bvFTD diagnoses. Prior to testing, patients and their families should receive counselling on the implications of genetic testing; however, there was too much variation across countries in terms of access to a specialized genetic counsellor to include this as a formal recommendation. For a summary, see Box 7.

Discussion

At present the diagnosis of bvFTD is still a challenge because of overlapping characteristics with PPD combined with the lack of highly accurate biomarkers. This review elicited a number of gaps in the clinical approach to the distinction between bvFTD and PPD that are familiar to all clinicians involved with those populations. In particular, diagnostic methods that can be useful to distinguish bvFTD from other dementias such as clinical scales and cognitive tests do not fare as well against PPD, and therefore have limited clinical utility in this context. Our consortium has established clinical practice recommendations with the hope of improving the diagnostic process by systematizing approaches across sites and setting the stage for research validation of new tools. These recommendations are summarized in a step-by-step diagnostic approach algorithm (Fig. 1). The summary of minimal requirements and clinical recommendations per theme is also available in Supplementary Table 1.

While many of these recommendations are already in place in most clinics, some conclusions of the consortium will likely require some changes to current practices. Among those is the recommendation to include at least one social cognition test [e.g. Ekman 60 Faces Test, Social Cognition and Emotional Assessment (SEA) or Mini-SEA] in the standard neuropsychological battery for bvFTD. We emphasize the importance of high-resolution 3D-T_1 brain MRI with a standardized review protocol with validated visual atrophy rating scales, and to consider volumetric analyses if available. We also clarify the role of

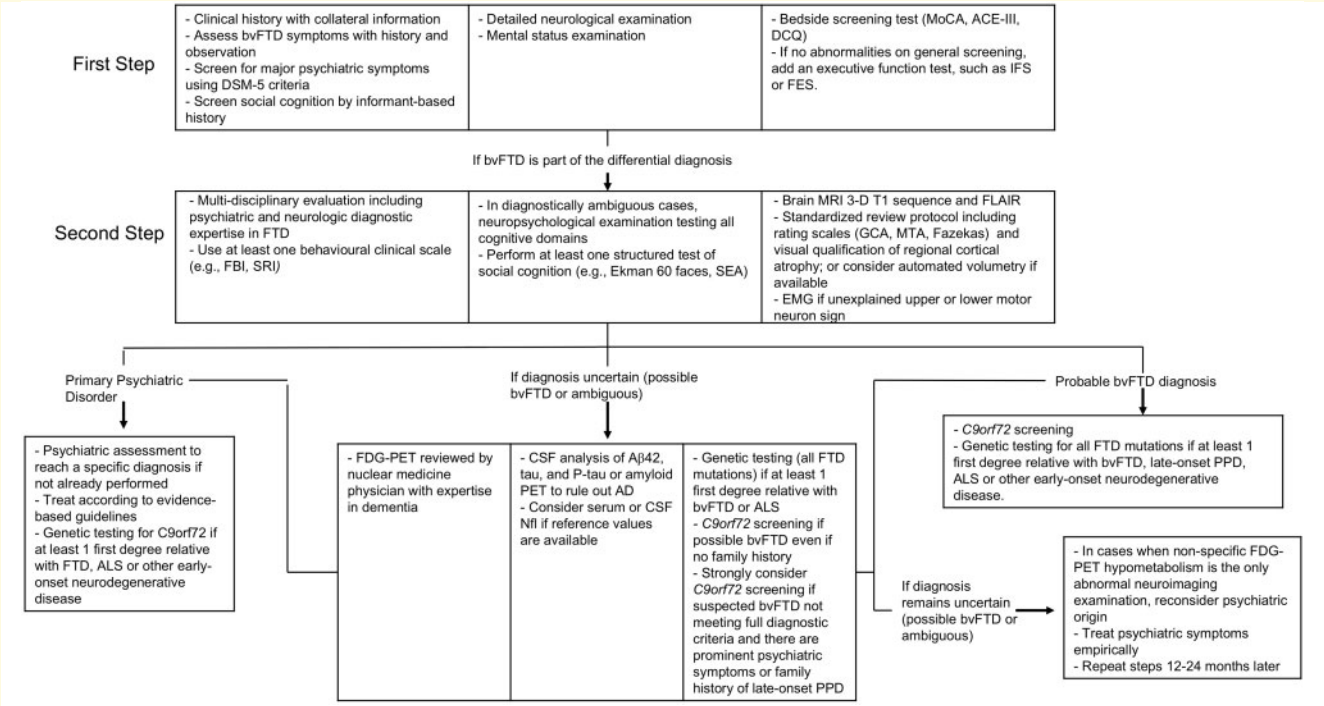

Figure 1 Diagnostic algorithm for the approach to the patient with late-onset behavioural changes. ACE-III = Addenbrooke's Cognitive Examination 3rd edition; AD = Alzheimer's disease; DCQ = Dépistage Cognitif de Québec; DSM-5 = Diagnostic and Statistical Manual Of Mental Disorders - 5th edition; FBI = Frontal Behavioral Inventory; FES = Frontier Executive Screen; GCA = Global Cortical Atrophy; IFS = Institute of Cognitive Neurology Frontal Screening; MTA = Medial Temporal lobe Atrophy; MoCA = Montreal Cognitive Assessment.

FDG-PET, which is useful to exclude bvFTD when within normal limits, whereas abnormal non-specific regional hypometabolism should not be over-interpreted in the case of a psychiatric differential diagnosis. The recent literature evidencing that CSF or serum NfL is a good biomarker for the distinction between bvFTD and PPD will gradually pave the way for its application in a clinical setting, and therefore this test can be considered in clinical sites where age and sex-specific reference laboratory values are available (Bridel *et al.*, 2019). Finally, based on the increasing literature and clinical experience, the consortium determined that screening for *C9orf72* mutation should be strongly considered in all possible/probable bvFTD cases and suspected cases with strong psychiatric features that do not meet full bvFTD criteria. This practice is already in place in several centres.

Despite the application of optimal clinical investigations, some patients remain with ambiguous diagnoses. In those cases, longitudinal follow-up often becomes the diagnostic arbiter until pathology is available. Cases of non-progressive bvFTD phenotypes ('phenocopies') with a predominance of male subjects with modest cognitive deficits are particularly challenging (Hornberger *et al.*, 2009). Small sample studies have shown that a few per cent (6.25%) are caused by *C9orf72* mutation (Devenney *et al.*, 2018*a*) and that on average they have mild right temporal volume loss (Steketee *et al.*, 2016). However, there tends to be no progression over long periods and a significant fraction (50% based on four cases) have no FTLD pathological changes (Devenney *et al.*, 2018*a*; Valente *et al.*, 2019). We advocate for specialized psychiatric assessment to identify treatable psychiatric conditions and careful characterization of features such as relational problems and cluster C personality traits that are common in this patient population (Gossink *et al.*, 2016*a*). Our algorithm (Fig. 1) will hopefully assist clinicians to correctly diagnose a subset of those cases with unexpected mutation or misrecognized PPD, but some patients will likely remain with a distinct phenocopy entity (Devenney *et al.*, 2018*a*).

There is a need for better prognostic tools, and several potential approaches requiring further development were identified as part of this review. This includes clinical scales focusing specifically on the differential diagnosis between bvFTD and PPD, and several MRI techniques such as machine learning classifiers. In particular, several CSF biomarkers hold promise for the future but need to be studied in larger number of patients, ideally in pathologically and/or genetically confirmed cohorts of bvFTD. Major ongoing studies of genetically at-risk populations such as the Genetic Frontotemporal Dementia Initiative will be of great value to identify and validate those types of early stage biomarkers (Rohrer *et al.*, 2015*b*); however, it remains uncertain if the progression of clinical features and biomarkers is identical for genetic and sporadic bvFTD. Given that FTD is a relatively rare disease, the development and validation of a new diagnostic technique will require an international collaboration for data collection. The NIC-FTD aims to establish a common research database to systematically collect and share biomarkers of patients presenting with late-onset behavioural changes. We hope that the dissemination of these recommendations will make the assessment of late-onset behavioural changes more systematic to improve detection of bvFTD and minimize false diagnoses. This is of key importance to ensure that patients suffering with PPD are offered evidence-based psychiatric treatments for their conditions. Furthermore, given the insufficient number of clinicians with expertise in behavioural neurology and neuropsychiatry, we believe that these recommendations could help with the training of students and general neurologists/psychiatrists to better assess these patients. Our long-term aim is to create a solid diagnostic algorithm for the diagnosis of bvFTD versus PPD.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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