Behavioural Variant Frontotemporal Dementia: Recent Advances in the Diagnosis and Understanding of the Disorder

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Introduction

Over the past 30 years, the understanding of the clinical phenomenology, neuroimaging, genetics and pathology of frontotemporal dementia (FTD) has undergone a metamorphosis. This has, in turn, opened the door to potential treatment trials, which would have been thought to be out of reach not that long ago. Since the original descriptions of FTD, originally known as Pick's disease, our ability to accurately diagnose and differentiate patients presenting with predominantly behavioural changes (so-called behavioural variant FTD) and with forms of primary progressive aphasias has improved considerably. Recently, the concept of frontotemporal lobar degeneration spectrum disorders has evolved to encompass the overlap between FTD and amyotrophic lateral sclerosis (ALS), as well as conditions such as progressive supranuclear palsy and corticobasal degeneration.

FTD primarily refers to a group of neurodegenerative brain disorders characterised by atrophy of the frontal and anterior temporal lobes. Prevalence studies suggest that FTD is the second most common cause of younger onset dementia [1, 2]. Three main clinical syndromes of FTD are generally recognised, based on their clinical presentations: a behavioural variant FTD (bvFTD) in which deterioration in social function and personality is most prominent and two language presentations, classified under primary progressive aphasia (PPA), in which an insidious decline in language skills is the primary feature. These PPAs are divided based on the pattern of language breakdown into semantic dementia (SD, also labelled semantic variant PPA) and progressive nonfluent aphasia (PNFA, also labelled nonfluent variant PPA) [3, 4]. Each of these syndromes has distinct clinical symptoms, imaging and pathological characteristics, although considerable heterogeneity and overlap exist in clinical practice, particularly as the disease progresses.

This chapter specifically focuses on bvFTD and on the recent advances in our understanding of the clinical features of this syndrome, its diag-

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nosis, including its overlap with ALS. Other chapters of this special issue will cover the genetic, pathological and imaging advances.

A major advance in the field of bvFTD was the publication, in 2011, of international consensus diagnostic criteria with increasing levels of diagnostic certainty (Table 1). At the lowest level of diagnostic certainty is possible bvFTD: a pure clinical diagnosis requiring the presence of three of six behavioural changes, namely disinhibition, apathy, loss of empathy, perseverative/compulsive behaviours, hyperorality and a dysexecutive neuropsychological profile. A diagnosis of probable bvFTD is based on the clinical syndrome, plus demonstrable functional decline and structural or functional changes in the frontotemporal regions on neuroimaging. A diagnosis of definite bvFTD is limited to those patients with the clinical syndrome and evidence of a pathogenic mutation or FTLD histopathology [5]. It has been shown that the probable level is robust and consistent when cases are followed over a number of years while only a half of those with possible bvFTD progress to clear-cut FTD over a 3-year follow-up period [6], and a proportion of such cases have the phenocopy syndrome discussed below.

Table 1 Key diagnostic symptoms of bvFTD, forming part of diagnostic criteria [5]

A. Early *behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
A.1. Socially inappropriate behaviour
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions
B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
B.1. Apathy
B.2. Inertia
C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
C.1. Diminished response to other people's needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth
D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech
E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects
F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

* Refers to symptom presentation within first 3 years

While in the early 2000s research understandably focused on cognition, it has become apparent that tests of executive dysfunction have limited specificity in detecting bvFTD. More recent studies have examined other aspects which are not included in the current diagnostic guidelines [5] or have attempted to get at the core changes in social cognition and emotion processing. (Fig. 1). In addition, there has been the realisation that the effects of bvFTD are more widespread and affect physiological functioning.

Physiological Functioning

It is increasingly recognised that the changes in bvFTD are not simply restricted to behaviour, cognition and motor function, but that fundamental alterations in bodily functions including satiety and metabolism, as well as autonomic function occur. These changes have been linked to the disruption of large-scale neural networks linked to the hypothalamus with associated neuroendocrine changes [7].

Central to our understanding of physiological disturbances in bvFTD are changes in hypothalamic volume which have been shown in a number of neurodegenerative conditions including FTD and ALS [8], with abnormalities in eating and metabolism in bvFTD linked to potential connections between the hypothalamus and reward pathways [9]. Two studies have examined hypothalamic volumes in bvFTD. In the first, posterior hypothalamic atrophy was associated

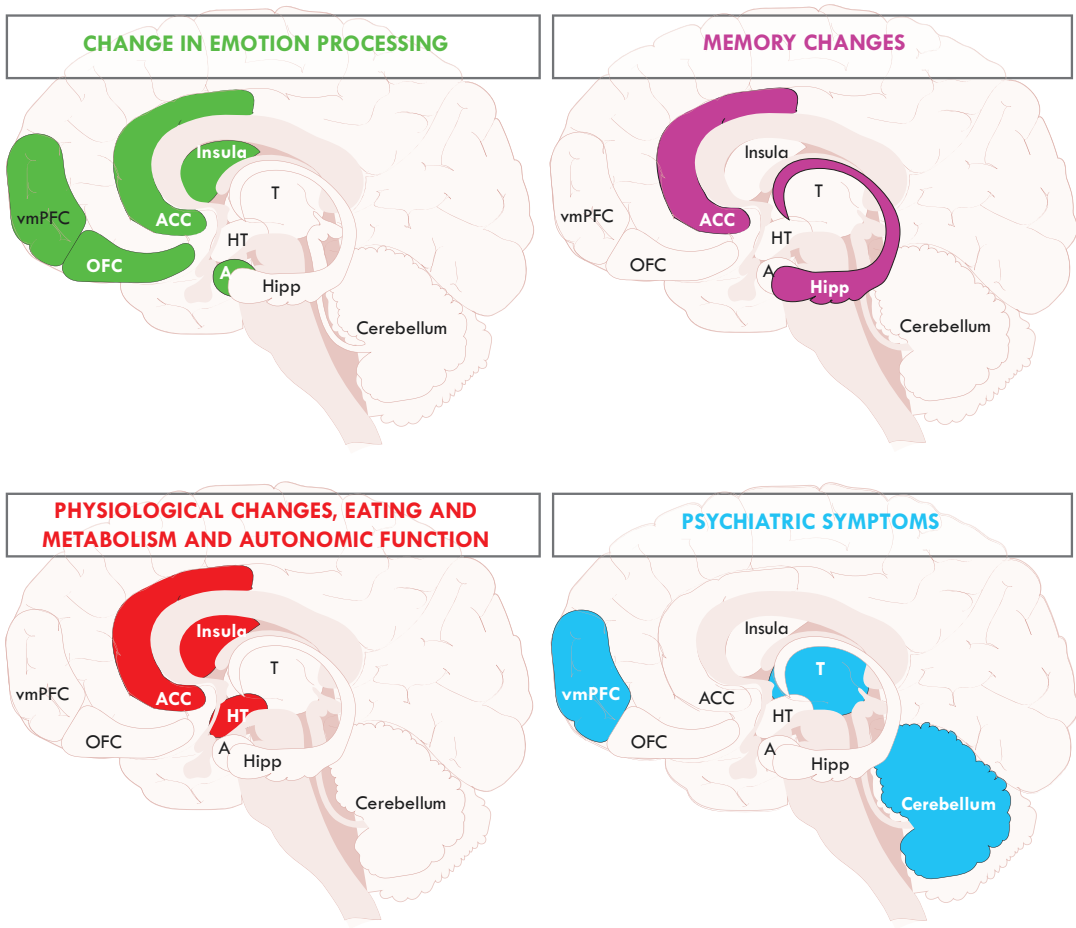

Fig. 1 Key neural structures implicated in each of the emerging symptom groups in bvFTD. (*vmPFC* ventral medial prefrontal cortex; *OFC* orbitofrontal cortex; *ACC* anterior cingulate cortex; *HT* hypothalamus; *T* thalamus; *Hipp* hippocampus; *A* amygdala)

with feeding abnormalities [10]. This relationship was observed within 2 years of disease onset, with continuing atrophy over the course of the disease. Importantly, atrophy was more pronounced in cases with transactive response DNA binding protein 43 kDa (TDP-43) inclusion pathology than in those with tau inclusions, pointing to a potential in vivo biomarker [10]. A second study reported a 17% reduction in hypothalamic volume on neuroimaging in bvFTD compared to controls, again particularly involving the posterior hypothalamus [11].

Eating and Metabolism in Behavioural Variant Frontotemporal Dementia

Hyperorality and dietary changes, which form one of the six core criteria for the diagnosis of bvFTD [5], are reported in over 60% of patients at initial presentation [12]. Such changes discriminate FTD from other dementias, notably Alzheimer's disease [13]. The changes in eating habits vary across the clinical subtypes of FTD. Alterations in bvFTD patients have been characterised by hyperphagia, indiscriminate eating, increased preference for sweet foods and other oral behaviours compared to patients with Alzheimer's disease [14]. In SD, changes are

also present but take a different flavour. In this syndrome, patients show prominent changes in food preference including increased selectivity and rigidity surrounding food consumption [14–16]. It has been suggested that this may be related to changes in knowledge about different foods [17].

Recently, ecologically valid methods, such as test meal approach used in obesity research to measure food intake, have been applied in FTD. When offered a test meal of breakfast after fasting, Ahmed and colleagues (2016) demonstrated a markedly increased total caloric intake in bvFTD patients compared to both AD and control subjects and a preference for sugar. In addition, they also revealed rigid eating behaviour and a strong sugar preference in SD patients [18]. A number of brain regions were found to be associated with abnormal eating behaviour. In bvFTD, consistent regions identified have been a distributed set of frontoinsular and anteromedial temporal brain areas [19, 20], which parallel those involved early in bvFTD [21, 22]. Increased caloric intake in bvFTD has also been related to atrophy of a network involving the bilateral anterior and posterior cingulate gyri, the thalamus, bilateral lateral occipital cortex, lingual gyri and the right cerebellum. These structures are also implicated in the control of cognitive reward, autonomic, neuroendocrine and visual modulation of eating behaviour [18]. Changes in eating behaviour have also been linked to hypothalamic atrophy and changes in key neuroendocrine peptides (Fig. 2) including agouti-related peptide, neuropeptide Y (NPY) and leptin [8, 23]. How hypothalamic changes and changes in neuroendocrine peptides control eating behaviour in bvFTD and interact with cortical networks controlling eating behaviour requires further investigation.

Given the prominent changes in eating behaviour in bvFTD, it is not surprising that patients also exhibit changes in metabolism including changes in body mass index (BMI), insulin and cholesterol levels. Both bvFTD and SD patients have modestly increased BMI and waist circumference compared to normal controls [16], although the degree of change is less than one might predict, given the level of eating abnormalities found in bvFTD, raising the question of whether other alterations in metabolic rate are present, similar to those seen in ALS [24], which may counteract some of the effects of these abnormal eating behaviours on BMI [20]. In keeping with this hypothesis, increased energy expenditure with a raised heart rate and autonomic changes have been shown in bvFTD [25] and have been correlated to atrophy in structures known to mediate autonomic function including the anterior cingulate cortex and insula.

Changes in insulin levels and lipid levels including insulin resistance have been identified in both bvFTD and SD with increased insulin and triglycerides and lower HDL cholesterol (reflecting a state of insulin resistance) [26]. Along the ALS-FTD spectrum, changes in lipid levels including increased cholesterol levels have been found to correlate with improved survival [27] and are mediated by changes in fat intake. Interestingly, these changes may occur decades before disease onset, suggesting a potential marker of disease [28]. The overall impact of these changes on disease progression and survival requires further exploration, including whether these changes are the result of atrophy in specific brain areas or actually modify the neurodegenerative process.

Autonomic Functions in Behavioural Variant Frontotemporal Dementia

In addition to changes in eating and metabolism, autonomic dysfunction has been identified in both bvFTD and SD [29]. Anecdotally, many carers report episodes of dizziness, as well as changes in thermoregulation in patients. Carer-based surveys have reported a high rate of symptoms related to blood pressure control, gastrointestinal function, thermoregulation, sweating and urinary symptoms [29, 30]. Objective measures of autonomic processing show abnormal responsiveness to emotion stimuli in FTD using physiological measures such as skin conductance [31, 32]. Changes in pain perception have been reported with bvFTD potentially associated with blunted pain and temperature responsiveness, while heightened

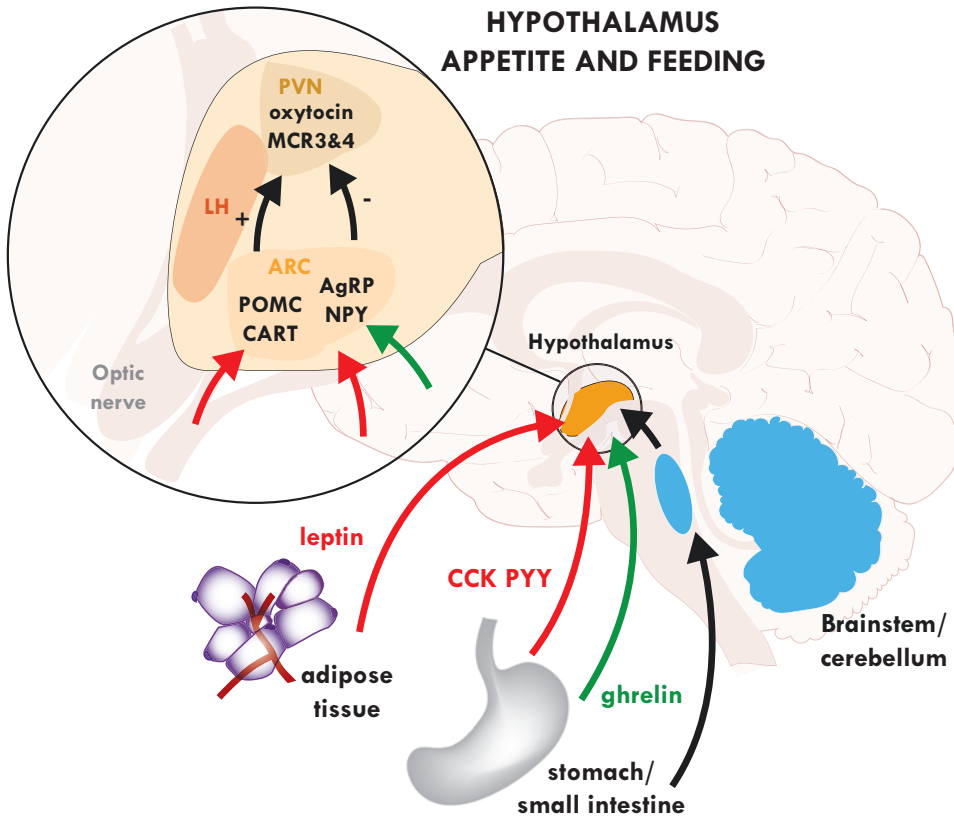

Fig. 2 Eating behaviour and the hypothalamus. Structures implicated in eating behaviour in FTD and pathways controlling eating behaviour in healthy individuals. Structures implicated in FTD include orbito-frontal cortex, right-sided reward structures including putamen, pallidum and striatum and posterior hypothalamus. Normal eating behaviour is controlled by an appetite stimulating pathway (shown in green) which results from ghrelin being released peripherally and targeting neurons of the arcuate nucleus (ARC) of the hypothalamus that contain neuropeptide Y (NPY) and agouti-related peptide (AgRP). An appetite suppressing pathway involves leptin (shown in red) being released from peripheral adipocytes, which then acts on pro-opiomelanocortin (POMC) and the cocaine and amphetamine-related transcript (CART) neurons in the hypothalamus. Peptide tyrosine tyrosine (PYY) and cholecystokinin (CCK), released peripherally, also suppress appetite. AgRp, NPY, POMC and CART neurons in the hypothalamus project to and act on melanocortin receptors (MCR). POMC is cleaved into alpha and beta-melanocyte-stimulating hormones that act on melanocortin receptor subtypes 3 and 4 (MCR 3 and 4) to decrease food intake. AgRP stimulates food intake by antagonism of MCR 3 and 4 receptors. In bvFTD, elevated levels of AgRP have been found. Increased leptin levels have also been found likely secondary to increased adipose stores. Autonomic pathways (black arrow) are also involved in food intake through projections via the brainstem and cerebellum to the hypothalamus. (*PVN* paraventricular nucleus)

responses are observed in SD and PNFA [33]. Recent studies using heart rate monitoring have shown increased heart rate and decreased heart rate variability in bvFTD [34]. Abnormalities in autonomic dilation of pupils in response to auditory stimuli are considered a physiological signature of neurodegeneration in FTD [35].

It is well established that autonomic changes may result from damage to cortical structures including the anterior and mid-cingulate cortices, prefrontal cortex, insula, ventral striatum, amygdala and hypothalamus [36, 37] regions known to undergo marked changes in FTD. Atrophy in the amygdala, ventral striatum, insula and anterior cingulate cortices has been reported in FTD [21,

36]. In bvFTD, pathological changes in these structures have traditionally being linked to disturbance of behaviour and social-emotional functioning [38–41]; however, their role in autonomic function has been recently investigated. Decreased cardiac vagal tone has been linked to left-lateralised structural frontoinsular and anterior cingulate cortex atrophy in FTD [34]. Atrophy in the premotor/anterior cingulate cortex and the putamen/claustrum/insula has been associated with urinary incontinence [42], while changes in the amygdala and insula have been linked to defective emotionally mediated autonomic dysfunction [43]. Pathology in the mesial temporal cortex, insula and amygdala is related to increased resting and sleeping heart rate [25]. The insula is also involved early in the course of bvFTD [21] and atrophy in this region correlates with altered pain and temperature perception [33], with the suggestion that the insula forms a network hub for sensory homeostatic signaling together with the thalamus [44]. Further research is required to examine how atrophy in these key regions regulates changes in autonomic function in FTD, how these changes are reflected in the different clinical phenotypes of FTD and how they could be harnessed as markers of disease progression.

Memory Function in Behavioural Variant Frontotemporal Dementia

Historically, memory functions have been reported to be preserved in bvFTD, with integrity of memory a key feature distinguishing Alzheimer's disease and bvFTD. Indeed, in clinical practice, it is not uncommon to read in clinical letters that a diagnosis of bvFTD is unlikely because the patient is exhibiting impaired memory function on cognitive testing. This position is further reflected in the consensus diagnostic criteria, where the cognitive profile in bvFTD (symptom F) is defined as one of executive/generation deficits, *with relative sparing of memory and visuospatial functions* [5]. Indeed, when present, memory deficit was thought to reflect a disturbance in retrieval efficiency, rather than a true episodic memory deficit, whereby information is encoded appropriately but recall performance is impaired because of an inability to retrieve efficiently and accurately the relevant information. Improvement in performance following the provision of cues (e.g. with recognition or forced-choice recognition formats) provides support for this position.

In the past decade, however, it has become increasingly apparent that various aspects of memory function can be severely affected in bvFTD, to a degree comparable to that seen in patients with Alzheimer's disease. Impaired performance is observed on common tasks of verbal and nonverbal episodic memory, such as short stories, word list learning or design recall, as well as on autobiographical memory and future thinking/prospective memory tasks [45–47], that correlates with the integrity of the hippocampus and other brain regions known to participate in memory functions [40, 48]. Deficits are also observed on tasks that rely on intact episodic and semantic memory systems, such as scene construction [49]. Further, evidence indicates that over time, episodic memory tends to worsen more rapidly in bvFTD than in AD [50]. Performance on topographical memory may, however, differentiate these two groups, where patients in AD tend to experience greater spatial orientation disturbance compared with patients with bvFTD [51].

Arguably, a differential diagnosis is not based solely on the presence/absence of a single clinical feature but is made within the context of multiple indices of clinical phenomenology, background and clinical history and ancillary investigations (e.g. brain MRI). Given the prominence of episodic memory deficit towards a clinical diagnosis of AD, it is important to emphasise that the presence of impaired memory, either on testing or clinical history, should not rule out a diagnosis of bvFTD.

Social Cognition in Behavioural Variant Frontotemporal Dementia

As its name indicates, disturbance in various aspects of social cognition is at the core of the prototypical presentation of bvFTD. In the current diagnostic criteria, these changes are covered by Symptom A (Early behavioural disinhibition) and Symptom C (Early loss of sympathy or empathy), both of which comprise additional subcategories. As is the case with the other symptoms, these symptom lack clear definitions, apart from the fact that they need to be persistent and recurrent, rather than one off or rare events [5]. Nearly 280 peer-reviewed articles have been published investigating social cognition in frontotemporal dementia to date. Of these, over 200 were published in the last decade, denoting the increasing interest in this topic. This should not come as a surprise for at least two reasons. First, social cognition forms a central block of interpersonal relationships. Humans are essentially social beings that have evolved because of their capacity to live in increasingly complex social environments. As such, disturbance in the capacity to engage or respond socially will have an impact not just for the affected individuals but for their broad social structure as well. In addition, evidence from epidemiological studies has shown that social interactions and social networks are protective risk factors against dementia in later life [52].

Second, the increasing availability of novel technologies in recent years, such as functional MRI, eye tracking or virtual reality, has opened the door to a variety of investigations, not possible until then, to understand the phenomenology of social cognition in healthy and clinical populations and their biological substrates (see for example [53] for a review). These investigations in healthy individuals and in clinical – stroke, tumour, neurodevelopmental and neurodegenerative – populations have identified a number of brain regions that play a central role in supporting social cognition. These regions are widespread and include frontal (anterior insula, anterior cingulate, orbitofrontal, medial frontal), temporal (temporal pole, superior temporal sulcus, amygdala) and parietal (temporo-parietal junction) brain regions [53–55].

Investigations in bvFTD have further confirmed the presence of pervasive changes in social cognition, which take many forms including emotion processing (recognition, expression), empathy, theory of mind, moral reasoning, reward sensitivity and understanding of social rules [32, 56–59]. These deficits can occur in isolation or in various combinations. Importantly, these findings suggest that single-test investigations of social cognition integrity are unlikely to be sufficient for ascertaining the presence of positive Symptoms A and C in the clinic.

While remarkable in its phenomenology and variability, the emergence of social cognition deficits in bvFTD is consistent with the pattern of brain atrophy observed in this syndrome. Indeed, the regions most susceptible to neuropathological changes and atrophy are the same that have consistently implicated in social cognition [60]. Importantly, these investigations have also identified that, in addition to brain atrophy, social cognition deficits also arise from global system disturbance, in particular in the autonomic system, leading to inaccurate integration of internal signals with external stimuli, resulting in inadequate or inappropriate responses [32, 61–63].

Importantly, the work of the past couple of decades has also demonstrated that disturbance in social cognition in FTD is not confined to its behavioural variant. Indeed, although beyond the scope of this chapter, it is important to note the emergence of such deficits in the language presentations of FTD, semantic dementia and progressive nonfluent aphasia. The characteristics of these deficits appear to differ from those in bvFTD, in their severity and quality. As such, and similar to what was discussed in the memory section, disturbance of social cognition capacity in the presence of a co-existing language disturbance should not necessarily rule out a diagnosis of language variant of FTD.

Overlap of Behavioural Variant Frontotemporal Dementia and Psychiatric Conditions

The current diagnostic criteria for bvFTD state that behavioural disturbances may not be better explained by a psychiatric condition [5]. The early clinical diagnosis of bvFTD, however, is often made difficult by the overlap with late onset psychiatric conditions. Patients often initially present with apathy and inertia and changes in empathy, which is mistakenly diagnosed as late onset depression. Not uncommonly, patients are placed on anti-psychotic medication, which can lead to changes in eating behaviour and weight gain, often blurring the presence of hyperorality changes. Once patients develop the florid behavioural changes including psychotic features, obsessive compulsive features, they are often misdiagnosed as schizophrenia, schizoaffective disorder or bipolar disorder [64].

Compounding the overlap between bvfTD and psychiatric conditions is the finding of high rates of psychiatric features in bvFTD patients with the chromosome 9 open reading frame 72 (*C9orf72*) gene expansion and the fact that such symptoms may be present for many years before the emergence of more characteristic FTD features. In a recent study of 56 bvFTD cases [65], a third showed psychotic features, with *C9orf72* expansion cases more likely to exhibit psychotic symptoms than non-carriers (64% vs. 26%). Delusions, which comprise of persecutory, somatic, jealous and grandiose types, were more likely to occur in *C9orf72* expansion carriers (57% vs. 19%), as were hallucinations (36% vs. 17%). Increased psychotic symptoms in *C9orf72* expansion carriers correlated with atrophy in a distributed cortical and subcortical network that included discrete regions of the frontal, temporal and occipital cortices, as well as the thalamus, striatum and cerebellum. These structures are similar to structures involved in psychiatric conditions such as schizophrenia [65]. The situation is further confounded by the findings of a large study of 1414 family members of patients with bvFTD that found that relatives of patients with the *C9orf72* gene expansion have an increased incidence of young onset schizophrenia and autism spectrum disorder [66]. Further research is needed to understand the overlap between bvFTD and psychiatric conditions and predisposition to psychiatric conditions as this may aid in earlier detection and treatment targeting.

Behavioural Variant Frontotemporal Dementia Phenocopy Syndrome

Along the bvFTD-psychiatric spectrum are patients that initially present with behavioural and neuropsychiatric features; yet, they do not show frontotemporal atrophy or hypometabolism on imaging and do not progress to develop cognitive decline or functional impairment [67]. It has been proposed that these patients may represent a late onset decompensation of life-long personality disorders or a neuropsychiatric condition, rather than true bvFTD [68]. Two patients with this disorder that went to autopsy showed no evidence of FTD pathology [69]. Caution, however, should be taken when classifying patients with the phenocopy syndrome in the absence of genetic testing for the *C9orf72* gene expansion. Indeed, a recent meta-analysis on the phenocopy syndrome reported 7 cases of slowly progressive FTD that were associated with the *C9orf72* gene expansion, out of a total of 292 reported phenocopy cases [67]. This finding is in keeping with a very long-term follow up of 16 cases from Cambridge, UK, all of whom were tested for the *C9orf72* gene expansion found in 1 case only (6.25%). Reports showing the phenotypic variability in patients with the *C9orf72* gene expansion are also increasing, with reports of patients within the same family having a rapid course in their 40s and death within 3 years and a much more indolent course in their 70s [70]. Further studies are required to ascertain the difference in penetrance and the underlying pathological mechanisms responsible for this. Studies of the effect of repeat size have produced discordant findings, and the contribution of repeat size to penetrance and phenotype remain uncertain and require further investigation [71–73].

Current Areas of Research Development

Amyotrophic Lateral Sclerosis: Frontotemporal Dementia Overlap

Since the mid-2000s, FTD and amyotrophic lateral sclerosis (ALS) have been increasingly conceptualised as representing the opposite ends of a disease spectrum [74, 75], with mounting evidence pointing towards an aetiological overlap between ALS and FTD and a multitude of studies showing behavioural and cognitive changes across the spectrum [27, 76–78]. This has largely been driven by genetics, with the discovery of the *C9orf72* expansion causing both bvFTD and ALS [79, 80]. In contrast to FTD, patients diagnosed with ALS typically exhibit limb or bulbar symptoms at initial presentation [81–83]. Much debate continues over the incidence of cognitive changes in ALS (behavioural, cognitive, language), with most large and community-based surveys reporting some cognitive changes in around 40–50% of cases [84, 85], while up to 15% of patients may satisfy the criteria for a diagnosis of concomitant FTD [86]. Conversely, 10–15% of FTD patients develop ALS, with varying estimates of motor neuron dysfunction in FTD insufficient to reach criteria for ALS, at between 25% and 30% [74, 87]. Further confirmation of the aetiological overlap between FTD and ALS is the finding of TDP-43 pathology in virtually all ALS cases and around half of those with bvFTD, although only 25% of bvFTD patients have similar motor neuron-like neuronal TDP-43 inclusion pathology [88, 89].

Recent research has suggested that bvFTD and ALS with TDP-43 inclusions may potentially result from the regional spreading ('prion like') of TDP-43 in the brain and spinal cord [90–92], with different initiating regions of pathology involved. In ALS, the pathology begins in the motor neocortex, progressing rapidly to the spinal cord and brainstem, prior to the involvement of nearby frontal and parietal regions, and then finally involving the temporal lobes [93]. Such a pattern of spread may potentially explain the late development of cognitive symptoms in ALS. In bvFTD, the disease process is thought to begin in the frontal lobe prior to spreading into the premotor, primary motor, parietal and temporal cortices, and eventually into the spinal cord [94].

In contrast to a suggested spectrum of disease, recent evidence indicates that the overlap between ALS and FTD is far more complex [95], with debate focusing on the cognitive and behavioural differences between ALS-FTD and bvFTD (i.e. are ALS-FTD and bvFTD part of the same disease). Previous studies have shown greater language involvement in ALS-FTD than in bvFTD [96, 97] including reduced sentence comprehension and grammatical difficulties with a language presentation of ALS-FTD with progressive nonfluent aphasia associated with anterior temporal and frontal language area atrophy, while that with prominent semantic problems is associated with temporal lobe and orbitofrontal cortex atrophy [98]. Currently, many studies are focusing on the longitudinal progression of behavioural and cognitive changes in ALS and ALS-FTD. These will help delineate the true nature of the progression and allow us to better clinically phenotype patients, which will aid in clinical trial development.

Predictors of Clinical Progression

One of the most common questions asked in clinical practice is 'how will bvFTD progress' and 'what is a patient's predicted survival'. Longitudinal large-scale follow-up studies of bvFTD patients are limited, but a number of cohort studies including genetic mutation carriers are currently underway around the world. Patients with combined ALS-FTD tend to show more rapid progression to death than those with either pure ALS or bvFTD [99]. It has also been shown that survival in those with both ALS and FTD may be dependent on initial phenotypic presentation, with those with initial motor symptoms having a shorter survival than those with initial cognitive or behavioural symptoms [100]. A recent study examined predictors of progression and survival in a cohort of 75 bvFTD patients. Median survival time from disease onset was

10.8 years and median survival prior to transition to nursing home was 8.9 years. Shorter survival was predicted by shorter disease duration at presentation, greater atrophy in the anterior cingulate cortex, older age and a higher burden of behavioural symptoms. In terms of disease progression, presence of a known pathogenic frontotemporal dementia genetic mutation was the strongest predictor of progression. Deficits in letter fluency and greater atrophy in the motor cortex were also associated with faster progression [101]. Research is now focusing on variables that can aid in early diagnosis including potential markers that develop prior to cognitive change to aid in early diagnosis. These aspects have particularly focused on imaging analyses including examining cerebral blood flow patterns [102], showing abnormalities up to 12 years prior to disease onset and grey matter atrophy patterns between those affected mutation carriers and asymptomatic mutation carriers, with different atrophy patterns visible presymptomatically, between *C9orf72, MAPT* and *GRN* genetic abnormality carriers, but also a common network of atrophy involving the insula, orbitofrontal lobe and anterior cingulate cortex [103]. As discussed above, these regions potentially mediate a number of physiological changes, potentially offering potential physiological markers that could be developed to facilitate earlier diagnosis and monitoring of disease progression.

Treatment and Intervention

Disease-modifying treatments do not currently exist for FTD and recent efforts have yielded disappointing results, for example the double-blind, placebo-controlled trial of LMTM (leuco-methylthioninium bis(hydromethanesulphonate)), a derivative of methylthioninium chloride, a drug targeting tau protein aggregation, in bvFTD [104]. A few clinical trials are, however, in the pipeline, but mostly targeting the familial forms of the disease or symptomatic management (see clinicaltrials.gov). Drugs used in Alzheimer's disease, such as acetylcholinesterase inhibitors, or NMDA receptor antagonists, provide no benefits to bvFTD patients and may even have a negative impact on cognition. Similarly, symptomatic treatments of challenging behaviours (e.g. disinhibition, agitation, aggression) with selective serotonin reuptake inhibitors (SSRIs) or antipsychotics have had mixed results.

A number of non-pharmacological approaches targeting behavioural difficulties, such as apathy or aggression have shown promise. For example, a subset of patients will develop repetitive behaviours over time (e.g. lining up objects, jigsaw puzzles), which can negatively impact on the patient's level of independence and interpersonal relationship. Interventions, such as the Tailored Activities Program (TAP), that directly target a specific behaviour and redirect it into personalised and relevant activities (selected by the carer) have demonstrated positive results, in reducing the disruption associated with the behaviour, increased meaningful activity engagement and reduction in carer stress [105]. Unlike in mild cognitive impairment and in Alzheimer's disease, targeted cognitive retraining has not been widely investigated in bvFTD and its suitability remains to be established. The prominent and early lack of insight, common in this population, complicates direct patient interventions [106], and carer-based interventions may therefore be more suitable.

Supporting families by providing education and coping skills is an avenue with demonstrated success in other clinical populations, such as traumatic brain injury [107]. A pilot study in FTD reported positive findings, but these will need to be replicated on a larger scale to determine their applicability in FTD [108].

Concluding Remarks

It is clear that much has been learnt about bvFTD. In this review, we focus on topics which have been of particular interest to FRONTIER, our frontotemporal dementia clinical research group based in Sydney, Australia. We have shown that the effects of bvFTD extend to fundamental aspects of physiology and metabolism, and that, contrary to clinical opinion, episodic memory is

affected in bvFTD and reflects involvement of the hippocampus. Work on social cognition has emphasised the importance of breakdown in interpreting and expressing emotions, while the overlap between psychiatric disorders and bvFTD has been brought into focus by the finding of high rates of psychotic features in carriers of the *C9orf72* gene expansion and of psychiatric disorders in their family members. We have progressed knowledge on predictors of rapid versus slow decline in bvFTD, yet the holy grail for all researchers in the field – an effective therapy which can modify the clinical course of FTD – still remains beyond our grasp. We will certainly be ready when it comes, and there is some hope given the raft of new drugs under development, at least for use in those with known gene abnormalities who are still symptom free.

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