Review

Progress and Challenges in Frontotemporal Dementia Research: A 20-Year Review

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Abstract. The landscape of frontotemporal dementia (FTD) has evolved remarkably in recent years and is barely recognizable from two decades ago. Knowledge of the clinical phenomenology, cognition, neuroimaging, genetics, pathology of the different subtypes of FTD, and their relations to other neurodegenerative conditions, has increased rapidly, due in part, to the growing interests into these neurodegenerative brain conditions. This article reviews the major advances in the field of FTD over the past 20 years, focusing primarily on the work of Frontier, the frontotemporal dementia clinical research group, based in Sydney, Australia. Topics covered include clinical presentations (cognition, behavior, neuroimaging), pathology, genetics, and disease progression, as well as interventions and carer directed research. This review demonstrates the improvement in diagnostic accuracy and capacity to provide advice on genetic risks, prognosis, and outcome. The next major challenge will be to capitalize on these research findings to develop effective disease modifying drugs, which are currently lacking.

Keywords: Behavioral variant frontotemporal dementia, diagnosis, genetics, interventions, pathology, prognosis, progressive nonfluent aphasia, semantic dementia

INTRODUCTION

Trying to recall what we knew about frontotemporal dementia (FTD) 20 years ago is like trying to remember what your children looked like two decades ago. It is an almost impossible task: you have to dig out old family photos, even then the images are not quite real. Looking at some of the papers on FTD from the 1990s produces the same effect. The term Pick's disease was still in use as a clinical label and FTD referred purely to what we now term behavioral variant FTD (bvFTD). Semantic dementia (SD) was just getting recognized but the distinction from the non-fluent forms of progressive aphasia was being worked out and these were not generally considered under the rubric of FTD. Very little was known about the pathology of FTD: some cases were found to have tau inclusions and others with ubiquitin positive inclusions which was known to be non-specific. The discovery of TDP-43 did not occur until the mid 2000s. Similarly, in the area of genetics, the high rate of familial transmission was evident but only one of the gene mutations responsible for the disease, *MAPT*, had been identified. The overall prevalence of FTD was unknown, information on prognosis was limited, and we did not have clear implementable diagnostic criteria. It was recognized that occasionally patients with FTD develop motor neuron disease (MND) and vice versa, but the extent of the clinical overlap was not realized, nor was the pathology and genetics overlaps between FTD and MND. Most studies at that time involved small numbers of cases and it was difficult to draw firm conclusions. While we have learned a lot over the

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past 20 years, sadly effective therapies still elude us. The best we can do is counsel, support, and help the families of patients with this devastating collection of diseases. Since 2000, over 6,000 papers have been published on FTD, which is twenty times the number in the previous decade. It is impossible to cover the whole topic and this review unashamedly focuses on our own work.

BEHAVIORAL VARIANT FTD

We turn first to the most common clinical form of FTD, which is now referred to as bvFTD. A renaissance of interest in the focal dementias began in the 1970s [1] and accelerated in the1980s. Workers from Lund, Sweden [2] reported on a large series of patients with dementia and found that a high proportion had evidence of frontal lobe degeneration. Since only a small proportion had Pick bodies—the remainder had very similar findings but without specific inclusions—the Lund group preferred to adopt the term "frontal degeneration of non-Alzheimer type". At approximately the same time, the Manchester group [3] began a series of important clinico-pathological studies of patients with pre-senile dementia. They, likewise, found a high proportion of cases with a progressive frontal lobe syndrome who had neither the changes (plaques and tangles) typical of Alzheimer's disease (AD) nor specific inclusion pathology. They introduced the term "dementia of frontal type". Over the next few years, other groups described similar cases under the labels "frontal lobe degeneration" [4] and "dementia lacking distinct histological features" [5]. Gradually, the label of FTD [6] was applied to such cases, but later, after the realization that patients with progressive aphasia share clinical and pathological features, the term bvFTD was adopted [7, 8]. Epidemiological studies have established that collectively FTD is the second most common cause of dementia under age 65 with a prevalence that approximates that of AD [9, 10].

Much of our early research focused on the cognitive features of bvFTD in an attempt to understand the clinical manifestations with the view to improve diagnosis. It became apparent that conventional so-called 'frontal lobe' tests, based largely on executive abilities (planning, set-shifting, problem solving), are not sensitive to the early changes of bvFTD. A range of research over the past 15 years has therefore focused on ways to measure other clinical features, in particular the alterations in social cognition which are core to the syndrome. Social cognition is an umbrella term that refers to a set of complex abilities necessary for successfully engaging in social interactions. These include the ability to recognize emotion in others, mentalizing about other people's states of mind (theory of mind, ToM), empathy, knowledge of social norms, moral reasoning, as well as reward sensitivity, evaluating the personal relevance of incoming social and emotional information, and using this information flexibly to behave appropriately within social contexts [11]. Numerous tests have been developed in recent years that attempt to unpack these different aspects of social cognition; some of which include the Empathy for Pain task [12], or the Awareness of Social Inference Test which uses video vignettes [13, 14].

Inspired by the work in autism spectrum disorder, which in many ways resembles bvFTD, we published the first study showing that patients with bvFTD have an acquired deficit in "theory of mind" [15], meaning that they have difficulty appreciating the mental state and perspective of others. This is a key deficit that almost certainly contributes to their impaired empathy, a source of considerable carer distress [16]. One way of assessing ToM is via the use of cartoons which may or may not have a ToM element. A recent study using cartoons showed an associated between ToM abilities and the right anterior temporal lobe in bvFTD as well as in patients with SD involving right sided structures [17]. Using a task which requires the interpretation of intent of interacting abstract shapes the Frith-Happé shape task [18] revealed an association between performance and a wide network comprising frontoinsuslar, frontal, and lateral temporal regions [19]. In keeping with this, an exploration of cognitive and affective aspects of empathy highlighted the role of the frontoinsular cortex in empathy [20].

At around the same time as the ToM study, we explored the hypothesis that bvFTD patients may also have deficit in emotion recognition. This hypothesis was confirmed by us [21] and others [22] and led the way to a series of studies charting the extent of the emotion processing deficits and their relation to pathology of the orbito-frontal, anterior insular cortices, and amygdala [23] regions that have been shown to be affected early in the course of bvFTD and that contain a unique population of von Economo cells [24, 25]. For example, patients may be presented with a facial emotional expression and asked to match the expression with the emotional label,

to decide whether two faces portray the same emotion, or be asked to point to a face from an array, which matches a specific expression [26]. It is now clear that bvFTD patients demonstrate generalized deficits in facial emotion recognition [26, 27], in part mediated by face recognition deficits [28, 29]. This pattern is observed regardless of the specific task demands and has been interpreted as evidence of a primary emotion processing impairment a hypothesis that is supported by the finding that bvFTD patients are also poor at recognizing emotions from non-face stimuli such as laughter, retching, and crying [21]. Furthermore, we have shown that even recognition of emotion portrayed in music is impaired [30, 31]. At the behavioral level, it seems that in bvFTD, recognition of all negative emotions is impaired, with no clear evidence of disproportionate impairment of any one emotion over another. Interestingly, however, we have demonstrated using voxel-based morphometry neuroimaging techniques that recognition of specific basic emotions does indeed appear to be linked with the degree of atrophy to specific brain regions [23].

One recent proposal that explains this breakdown in social cognition has been to see these deficits as reflecting a failure to correctly process and incorporate contextual information that will help determine the relevant social cues for an appropriate response [32]. This process is supported in part by the anterior insula, a brain region which acts as a hub where information from various sources (perceptual, cognitive, interoceptive) is integrated toward an adaptive response. Importantly, the insula is one of the regions most vulnerable to the pathological processes in bvFTD. Patients with bvFTD demonstrate a reduced capacity to integrate these various sources of information in a meaningful and relevant ways, with marked deficits in apportioning the appropriate weight to these bits of information toward a decision. For example, bvFTD patients have been found to be particularly sensitive to peripheral/contextual information rather than central (facial) features when making decision regarding someone's emotional state [33]. Alteration in sensitivity to social rewards also appears to pay a role the social cognitive deficits in bvFTD and is an active area of current research likely to generate important information in coming years [34, 35]. Although tests of social cognition have told us a great deal about the underlying cognitive deficits in bvFTD, a challenge for the next few years will be to develop tests that are clinically applicable.

Our work also examined other behavioral changes in bvFTD. For example, work that began by

quantifying the disturbance in eating behavior observed in bvFTD has since blossomed to reveal a range of metabolic changes [36]. Increased food consumption with a craving for sweet food is one the characteristic and discriminating features of bvFTD [37]. We have shown that this reflects early involvement of the hypothalamus [38] as well as alterations in a complex network (cingulate and orbitofrontal cortices and cerebellum) that controls food intake [39]. These behavioral changes are accompanied by alterations in cholesterol, insulin, neuroendocrine levels, and metabolic rate which appear to have significant effect on survival [40]. This work indicates a re-think on how FTD should be regarded: as not simply a disease of the brain but one that has a global impact on body functions. It also opens the way for potential interventions and patient management by targeting these behaviors.

It was long believed that impaired episodic memory was the early hallmark of AD whereas memory was preserved in bvFTD, with relative sparing of episodic memory in the context of impaired executive function being one of the diagnostic criteria for the disease. A series of landmark studies by our group showed this simplistic dichotomy to be false. On formal tests of episodic memory, patients with bvFTD score in the same range as those with AD [41, 42]. Prior findings most likely reflected the admixture of true bvFTD patients and phenocopy cases in clinical cohorts. The neural basis of the memory impairment in bvFTD has been explored with evidence of both frontal and hippocampal contributions to the deficit [43, 44]. Additional work also uncovered deficits in other aspects of memory, such as personal autobiographical memory, future thinking, and imagination [20, 45], some of which again being as severe as those found in AD. Our recent work has focused on spatial memory and topographical orientation, processes that depends upon the integrity of the posterior cingulate/precuneus/retrosplenial cortices, regions known to be affected very early in AD but spared in bvFTD. Early work suggests that tests of spatial memory are helpful in helping discriminate between these two syndromes [46]. This is an area ripe for further exploration.

SEMANTIC DEMENTIA AND PROGRESSIVE NONFLUENT APHASIA

Progressive aphasia in association with focal left temporal lobe atrophy was recognized by Arnold

Pick over a 100 years ago, but the paper in 1982 by Marsel Mesulam [47] really put this disorder on the medical map. Following Mesulam's seminal paper it became gradually clear that, although the term primary progressive aphasia (PPA) was being applied to a range of very different cases, two identifiable and distinct aphasic syndromes emerged within this spectrum: SD and progressive nonfluent aphasia (PNFA). The features of SD were clarified in our seminal paper of 1992 [48]. Moreover, the importance of this syndrome became clear in that it reflects the only "pure" disorder in which semantic memory disintegrates with preservation of other aspects of memory and elements of cognition. Semantic memory is the term applied to the component of long-term memory that represents our knowledge about things in the world and their inter-relationships, facts, and concepts as well as words and their meaning [48, 49]. The syndrome of SD has been particularly important from a theoretical perspective because, in contrast to AD, patients have relatively good day-to-day (episodic) memory and recent autobiographical memory [45, 50], intact immediate or working memory (at least as assessed by digit span), and good visually based problem solving and visuo-perceptual abilities [48, 51]. This relative selectivity of the semantic memory impairment in SD makes these patients ideal subjects for the study of the effects of semantic dissolution uncontaminated by other cognitive deficits. Over the past decade, it has become clear that as well as a unique cognitive syndrome, SD is associated with a highly characteristic pattern of asymmetric brain atrophy involving the perirhinal cortex and anterior temporal pole, a region that acts as a hub in the semantic network linking information held in other cortical regions and with a typically asymmetric distribution with greater left than right temporal lobe involvement [52–55]. This typical L > R pattern raises the issue of the cognitive and/or behavioral signatures of the less common pattern of R > L, temporal atrophy. The first clearly documented patient (VH) with this reverse pattern of R > L atrophy presented with gradually progressive prosopagnosia [56]: VH was unable to identify from face or name even very famous people (e.g., Margaret Thatcher) yet had relatively intact general semantic and autobiographical memory. In parallel with this literature, the group led by Bruce Miller in San Francisco drew attention to the bizarre behaviors (including irritability, impulsiveness, alterations in dress, limited and fixed ideas, and decreased facial expression) exhibited by patients with predominantly right temporal lobe atrophy [57, 58].

A study in 2003, drawing on our experience of 80 cases of whom a quarter had right-predominant atrophy, pulled together these observations by demonstrating that the right > left group tended to present with changes in person recognition *and* alterations in personality, while the more common left > right group had the typical deterioration of semantic memory for words and objects [59]. We have shown that deficits in face emotion processing and face detection are also seen in such patients similar to those seen in bvFTD [28, 60]. A recent study using modern longitudinal structural brain imaging methods has showed that the patterns of progression in these two variants of SD also differ in ways that the atrophy spreads through the brain over time [61] suggesting that the two variants are not simple mirror images of each other.

The uniqueness of SD has been underlined in the modern genetic FTD era. In contrast to bvFTD where a strong family history is found in up to 40% of affected individuals [62], genetic mutations are rarely found (<5%) in SD patients [51]. Moreover, the pathology is distinct. Although sharing with other syndromes a deposition of the protein TDP-43, the histopathological appearance of the deposition is unique and termed FTLD TDP-43 type C [63–65].

In contrast to SD, PNFA is a much more heterogeneous disorder in that patients share the characteristic of halting speech with pauses and distortion but this may or may not be accompanied by distortion of speech, phonological errors, or syntactic deficits. The early literature identified a range of underlying pathology including FTD (with tau and with TDP-43) and AD [66].

Based upon landmark clinical and imaging work from the UCSF group, clarity emerged with a splitting of the nonfluent cases into two groups [67]. The first true nonfluent cases have apraxia of speech and/or agrammatism. The atrophy in such cases focuses on Broca's region and the insular cortex. The other progressive nonfluent aphasic syndrome, referred to as logopenic progressive aphasia (LPA), is characterized by anomia and phonological errors accompanied by marked reduction in verbal span [68–70]. The atrophy in such cases centers on the angular gyrus and superior temporal lobe [67, 71]. The tripartite classification of the progressive aphasia has been enshrined in International consensus criteria [72] which proposed clear criteria for the diagnosis of each variant. We were among the first to substantiate this classification using amyloid-based Pittsburgh compound B imaging to show that LPA was invariably

associated with AD pathology, which was present in a minority of those with the other two forms of progressive aphasia. We also proposed a simplified classification system based features of which could be derived from our clinical language assessment [73]. To aid further with the diagnosis of the progressive aphasias, we have developed a multimodal language test, the SYDBAT, which is gaining wide usage [74]. Despite this work, the nonfluent progressive aphasic syndromes remain problematic as differentiation depends on expert assessment and subjective opinion on the nature of the language features and patients often present at an advanced stage when clinical features become blurred.

Importantly, it is now evident that changes in social cognition are not limited to bvFTD and are also found in the language presentations of FTD. Indeed, early on, changes in emotion recognition and emotion processing, as well as ToM were reported in the early stages of SD. Recent investigations have demonstrated that patients presenting with nonfluent progressive aphasia also exhibit subtle social cognition deficits. Importantly, this work indicates that deficits in facial emotion recognition can be remediated to some degree in these patients, when making the relevant information more salient, indicating that part of this deficits is caused by an attentional deficit, rather than a primary emotion processing deficit perse [75].

The addition of social cognition investigations may be relevant in improving diagnosis accuracy in these language presentations. Indeed, despite clearly defined clinical features and criteria, overlap between PNFA and the other nonfluent presentation of primary progressive aphasia (LPA), is common, despite their marked difference in the pathological process involved (FTLD in PNFA but AD in LPA) and the location of brain atrophy (inferior frontal and insula in PNFA, but posterior superior temporal and temporo-parietal junction in LPA). This lack of clinical diagnostic specificity has important repercussions, given that patients with underlying AD pathology may potentially benefit from acetylcholinesterase inhibitors whereas those with underlying FTLD will not. In a recent study [76], we showed that the combination of reduced episodic memory with preserved social cognition was indicative of AD pathology whereas the reverse pattern was suggestive of FTLD pathology. Clinically, integrity or otherwise of the motor system may provide further useful cues and help differentiate between the two nonfluent progressive aphasia syndromes, where extrapyramidal

features tend to be more common in PNFA than in LPA [77, 78].

FRONTOTEMPORAL DEMENTIA WITH MOTOR NEURON DISEASE

Although MND has traditionally been regarded as a disorder which spares higher cognitive abilities, it has become increasing clear since the 1990s that the rate of dementia in MND is significantly greater than expected, and conversely a significant minority of patients with FTD develop features of MND (for review, see [79]).

While only 10 to 15% of patients with MND develop behavioral changes of sufficient severity to reach criteria for FTD, up to 50% have more subtle behavioral and/or cognitive changes which typically precede the onset of motor symptoms [80, 81]. Such features have a significant impact on caregiver burden and present considerable management problems [82]. Conversely, while approximately 10% of patients with FTD will develop MND, a much higher proportion show subclinical motor changes [83]. A concurrent onset of bvFTD and PPA may predict later development of MND [84]. The past decade has seen a fundamental change the concept of MND as a pure motor disorder and led to the introduction of various behavioral/cognitive screening instruments in MND clinics [85, 86].

Patients with the MND-dementia/aphasia complex may have characteristics that set them apart from other FTD cases. A mixed behavioral and language syndrome is typical with disproportionate impairment of verb, compared with noun, knowledge [87, 88], and marked impairment of grammatical processing [89].

PATHOLOGY OF FTD

The neuropathology of FTD is far more complex than that of AD. Patients with clinically diagnosed AD, whether young or old, familial or sporadic, tend to have very similar pathological changes (intraneuronal tangles and extracellular amyloid plaques). In contrast, the pathological changes found in FTD are heterogeneous. Twenty years ago, cases were classified as those with and without tau positive inclusions. We now know that a range of inclusion pathologies are found in FTD [90]. Three major patterns are currently recognized.

The first group includes cases with tau-positive inclusion pathology. This group, in turn, encompasses a number of subforms: cases with classic intraneuronal tau-positive Pick bodies; corticobasal degeneration (CBD) characterized by tau-positive pathology with ballooned achromatic neurons and astrocytic plaques; globular glia tau inclusions and finally argyrophilic grain disease in which the tau staining is punctate and "grain"-like particularly involving the medial temporal lobe [91]. The second group includes cases with Tar DNA binding protein 43 (TDP-43) positive inclusion pathology. This group has been further subdivided in 5 subforms (A to E) each with distinctive morphological appearance depending on the cellular distribution of TDP-43 and the appearance of the inclusion pathology [92, 93]. The third group includes cases with fused in sarcoma protein (FUS) protein pathology. Such patients are rare, typically sporadic and associated with young onset and a high rate of neuropsychiatric symptoms.

Given the wide range of pathologies found in FTD, a holy grail of research in the field is to find biomarkers that can determine the exact pathology *in vivo*. There are some predictable associations: the vast majority of those with SD show TDP-43 type C pathology [51, 94] those with clinical FTD-MND almost invariably have TDP-43 positive inclusion pathology while in PNFA, the commonest pathology is tau inclusion positive [95]. Unfortunately, the pathological substrate of the commonest form, bvFTD, remains the least predictable with approximately equal numbers with tau-positive and tau-negative pathology [7, 63]. Many studies are underway to unearth better biomarkers. It is hoped that tau ligand-based PET might provide the answer although the availability of this technology is likely to remain relatively limited.

GENETICS OF FTD

The discovery of a range of genetic mutations which now account for the majority of cases of familial FTD has undoubtedly been one of the major advances in the field. As non-geneticists, our review of this topic is brief. The first mutation involving the tau coding for the microtubule stabilizing protein tau on chromosome 17 was found almost 20 years ago [96–99]; this lead to an explosion of interest in the molecular pathology of tau and eventually the creation of transgenic mice with FTD tau pathology [100]. But it became evident that such mutations

accounted for only a small proportion of familial cases. The next significant breakthrough was the finding of mutations in the gene encoding progranulin, also on chromosome 17 [101, 102], associated with TDP-43, rather than tau deposition. A number of different mutations were reported but again this turned out not to be a common cause of familial FTD. Then in 2011 two groups discovered a novel hexanucleotide expansion in the C9orf72 gene, located on chromosome 9. This genetic abnormality is far more common than the other mutations and can manifest as either FTD or MND but frequently results in a FTD-MND overlap syndrome [103–105]. Work on the clinical, pathological, and biological aspects of the C9orf72 expansion has been fast moving: a quick look on PubMed revealed almost 1,000 papers and much of this work has focused on molecular mechanisms of pathology. From a clinical perspective, it has become clear that the presentation and prognosis is highly variable. The majority of cases present with bvFTD and the rate of psychotic features is unusually high. Many patients may have a very long psychiatric prodrome to their dementia whereas others deteriorate rapidly [106–108]. Moreover, within families some patients present with FTD while other have MND or a mixed FTD-MND syndrome. The modifying factors that underlie this variability are unknown. The discovery of this common genetic abnormality has resulted in the uncovering of many at risk pre-symptomatic individuals harboring the expansion who are the focus of major projects [109] aimed at finding the earliest manifestations of the disease and hopefully intervening to prevent disease onset.

UNDERSTANDING DISEASE PROGRESSION IN FTD

Together with diagnosis, one of the most common questions patients with dementia and their families ask is regarding prognosis. Disease duration in frontotemporal dementia is approximately 7–9 years on average from onset of clinical symptoms. It is, however, highly variable, and ranging between 18 months and >20 years [51, 110, 111]. Disease duration also varies across FTD subtypes. It tends to be longer in the language than the behavioral syndromes [10, 51, 110, 111].

In bvFTD, the disease progression is also variable. Importantly, the current diagnostic criteria for a diagnosis of 'probable' bvFTD offer high clinical certainty. Indeed, the overwhelming majority of indi-

viduals meeting the 'probable' criteria at baseline will continue to do so over time, or will move to the 'certain' diagnostic category (either because of postmortem confirmation or because of results from genetic investigations) [112]. In other words, while the exact underlying pathology in these individuals may still be unclear, the likelihood of being FTLD is high. The provision of the 'possible' and 'probable' disease certainty classification in the revision of the consensus criteria [37], has enabled the identification and investigation of 'possible' cases. In these individuals, the initial clinical presentation is unclear, often because of a lack of supporting neuroimaging evidence, or because of a limited constellation of clinical symptoms. Progression of these 'possible' bvFTD cases over time is becoming better understood, whereby half of these individuals will end up meeting the more stringent criteria for 'probable' or even 'definite' bvFTD over time. In these, individuals, the presence of memory deficits on cognitive testing at baseline, together with a positive family history of dementia appear to be the best predictors of a future 'probable' diagnosis [112].

Follow up studies of patients with bvFTD revealed two separate categories of patients. First a group with a predictable downhill course typically resulting in nursing home care and death approximately 10 years from symptom onset. By contrast, a group of men, clinically indistinguishable from the former group, fail to progress after many years and who do not develop a frank debilitating dementia [113]. Such patients were termed slow or non-progressors and more recently the label phenocopy syndrome has been preferred. A series of studies have revealed prognosis markers of this syndrome, notably a lack of atrophy on MRI, normal FDG-PET imaging, normal performance of some cognitive tasks and general preservation of activities of daily living [114, 115]. Pathological information in the phenocopy syndrome is sparse but one long-term follow-up study of two patients with incidental deaths showed no evidence of FTD at autopsy [108]. It seems likely that such patients have lifelong personality disorders or cryptic neuropsychiatric disorders rather than a true dementia. The discovery of this mimic of bvFTD had an influence on the formulation of the 2011 International Consensus criteria for bvFTD which have differentiated three levels of certainty: possible, probable, and definite bvFTD [37]. The definite category denotes the presence of a pathogenic gene mutation or established FTD pathology. The probable level has been shown to be highly predictive of underlying FTD

pathology whereas cases in the possible category are equally likely to have the phenocopy syndrome or will eventually progress to the probable or definite categories over time [112]. Our research has also identified clinical features that can help predict change over time in the more common sporadic, non-familial cases diagnosed with probable bvFTD. In this syndrome, language difficulties at initial presentation is associated with a poorer prognosis [111]. In particular, presence of nonfluent language deficits carries an increased risk of developing amyotrophic lateral sclerosis over the following 2 years [84], although this risk appears to decline after this time period.

A number of studies have also examined the trajectories of brain changes with disease progression as observed on neuroimaging. Whilst the early structural changes are relatively focal encompassing the insula, the anterior cingulate, and the orbitofrontal cortices [116, 117], progressive deterioration of the grey and white matter become apparent in the posterior brain regions [118, 119]. Similar patterns of progressively widespread and bilateral neuroimaging changes are also evidenced in the language subtypes of FTD, despite their initial unilateral presentations (e.g., [120, 121]). Importantly, these studies highlight the dynamic nature of these disorders over long periods of time but also demonstrate that changes in the white matter are more widespread than originally thought. Indeed, such changes are not restricted to the regions directly underlying grey matter changes but are also found in more distal regions, suggesting a de-coupling, or somewhat independent unfolding, of these processes.

As with the prediction of clinical changes over time, determination of the disease trajectory in any given individual based on neuroimaging changes remains fraught with difficulty. This is due in part to large inter-individual differences but also to technical difficulties inherent to this type of investigations, such as increased risk of movement artefacts with disease progression, hardware and software limitations in detecting small changes particularly in regions susceptible to signal artefacts (e.g., orbitofrontal cortices, medial temporal lobes), and the difficulty in modelling nonlinear changes over time in small study samples. Further effort in this area is needed to identify reliable neuroimaging markers of changes in FTD. Such markers will be necessary to evaluate the efficacy of novel pharmacological compounds used in drug trials. Such markers may also be useful to establish the effect of non-pharmacological interven-

tions on disease progression. Ideally, research will identify brain regions in which pathological changes occur at different times and with different timescale. As such, a combination of regions experiencing early changes together with brain regions which become susceptible to 'late' pathological changes, as well as regions experience rapid versus slow changes will be needed.

In recent years, attention has focused on the genetic forms of FTD to with the aim to identify early clinical and neuroimaging markers of disease in the years preceding the onset of frank clinical changes (i.e., prodromal period). The identification of the main genes (*C9orf72, MAPT, GRN*) responsible for an autosomal transmission of FTD in families affected across multiple generations has made this possible. Investigating 220 individuals from 76 families (with about half (118) carrying a pathogenic mutation on the *C9orf72, MAPT,* or *GRN* genes), the GENFI study (Genetic Frontotemporal Dementia Initiative) has demonstrated that atrophy in the anterior insula is present on structural brain imaging some 15 years prior to clinical disease onset in individuals carrying a genetic mutation, compared to individuals without the mutation [109].

INTERVENTIONS AND CARER RESEARCH IN FTD

One disappointment over the past 20 years is the lack of progress in developing effective pharmacological treatments for FTD. Disease-modifying treatments specific to this disease remain years away as demonstrated by the recent negative findings of a recently completed double-blind, placebo-controlled trial of LMTM, a drug targeting tau protein aggregation, which was trialed in patients with bvFTD [122]. Drugs used in AD, such as acetylcholinesterase inhibitors, or NMDA receptor inhibitors, provide no benefits in FTD and may even have a negative impact on cognition. Similarly, symptomatic treatments of challenging behaviors (e.g., disinhibition, agitation, aggression) with selective serotonin reuptake inhibitors or antipsychotics have yielded mixed results.

On a more positive note, over the same time period, effort has been dedicated to the development of non-pharmacological interventions, particularly in the areas of management of difficult, or inappropriate, behavior and of language deficits. As has been well described previously, repetitive behaviors,

such as lining up objects or engaging in repetitive activities such as jigsaw puzzles, become increasingly common in a subset of bvFTD and SD patients as the disease progresses. Interventions, such as the Tailored Activities Program (TAP), that directly target a specific behavior and redirect it into personalized activities (which are selected in consultation with the carer) have demonstrated positive results, both in reducing the disruption associated with the behavior, increased meaningful activity engagement, and reduction in carer stress [123].

The second area of interventions receiving increased attention in recent years is that of language retraining in SD and PNFA. Unlike in bvFTD where loss of insight is an early feature, individuals presenting with the language variants are generally aware of their changes and difficulties, early on, which make them ideal candidates for retraining interventions. One successful program targeted word re-learning in SD patients. This was a highly personalized approach that targeted words that had been lost from semantic categories that were meaningful to the patient (e.g., garden tools, kitchen utensils). After identifying the relevant words, learning sets were created which varied in requirements. Across different paradigms, these studies demonstrated that the greatest benefit was obtained through a multimodal presentation (look, listen, repeat). An intensive training program over 4 weeks (5 days/week), generally resulted in a 90% successful naming performance by the end of the program in most individuals from 25–30% naming performance prior to the beginning of the program. The addition of a written component to the training protocol did not seem to provide additional benefit. Also, most improvement took place within the first 4 weeks with no significant additional benefit found on longer training programs [124, 125].

In addition to enabling re-learning of words, this approach demonstrated that SD patients were able to maintain their gain post training for a period of at least 6 months (which was the longest time period examined), with the aid of occasional booster sessions. Importantly, the frequency of the booster sessions necessary to maintain performance over time was related to the disease severity. In other words, patients in a more advanced stage needed more frequent booster sessions than patients in the earlier stages, but still less frequently than during the active relearning sessions. Overall, this program demonstrated, patients are not only able to improve cognitive skills that are at the core of their clinical presentation,

but also maintain these gains, even in the presence of an underlying progressive neurodegenerative brain condition [125, 126].

CARER RESEARCH

Care is predominantly provided informally by partners, family members, and friends of the person with dementia. Patients with FTD have marked changes in their activities of daily living even at presentation to the clinic [127] and carers, particularly those caring for patients with bvFTD, show very high levels of burden characterized by increased stress, anxiety, decreased psychological wellbeing and sense of connection with the patient [128–131]. In the clinic, these aspects are easily and rapidly captured by questionnaires such as the Zarit burden interview or the Intimate Bond Measure. Some of the variables that modulate the presence and severity of burden in carers of dementia patients are related to the carer's own psychological make up (e.g., coping mechanisms, personality type), socio economic status, cultural background, as well as their social network.

Recent research has also demonstrated that the type, and stage of dementia also impacts on the burden experienced by carers. Not surprisingly, burden of care tends to increase with disease progression, regardless of the type of dementia, although this is not universal [129]. Nevertheless, for a given level of severity, prevalence of significant burden is much higher in bvFTD compared with the other FTD subtypes or with AD. Similarly, some disease specific variables have also emerged. For example, in bvFTD, the quality of the relationship was related to the empathy capacity of the patient. In other words, a preserved capacity by the patient to understand the carer's point of view was associated to a strong feeling of intimacy of the carer toward the patient. In SD, however, direct burden was associated with the presence of behavior changes, something that was not observed in bvFTD. This possibly reflects the fact that behavior changes, which are prominent from an early day in this group, are generally discussed during the medical visits. This would enable carers and family members to adjust expectations and anticipation of these changes in behavior. In contrast, SD is most commonly apprehended as a predominant language disturbance. Possible occurrence of behavioral changes, which tend to become more common with disease progression, may not be necessarily discussed and therefore not anticipated, resulting in an increased sense of burden when these unfold [16].

CONCLUSIONS

From this review, it is clear that a great deal has been learned about the phenomenology, clinical characteristics, and the biology of FTD, and its pathology in the past two decades. More importantly, the knowledge base is continuing to expand at a rapid pace. The assessment, diagnostic accuracy, and ability to provide advice on prognosis and outcome have all improved markedly, despite the marked interindividual variability. We now can give much clearer genetic advice and are able to identify the genetic mutation in the majority of familial cases. Families are better informed and supported but the outstanding need remains for disease modifying drugs. In the light of the explosion of research on FTD, we are hopeful that the next decade will finally see meaningful advances in the field of therapeutics which build upon the huge knowledge base that has been accumulating on the molecular mechanisms underlying the pathology in FTD.

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