THE BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA: LINKING NEUROPATHOLOGY TO SOCIAL COGNITION

Authors: Chiara Cerami [a] and Stefano F. Cappa [a]

[a] Neurorehabilitation Unit, Department of Clinical Neurosciences, San Raffaele Scientific Institute and Università Vita-Salute San Raffaele, Milan, Italy

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Corresponding Author: Dr. **Chiara Cerami**

San Raffaele Scientific Institute and Università Vita-Salute San Raffaele

Department of Clinical Neurosciences, Neurorehabilitation Unit

Via Olgettina 60 - 20132 Milano (Italy)

Tel. 0039 02 2643 5760

Fax. 0039 02 2643 5738

E-mail: cerami.chiara@hsr.it – chiara.cerami@libero.it

Abstract

The behavioral variant of Frontotemporal Dementia (bvFTD) is one of the most frequent neurodegenerative disorders with a presenile onset. It is characterized by a long phase of subclinical behavioral changes and social conduct disorders, associated with a progressive modification of personality. Recently, an international consortium of experts developed revised guidelines for its clinical diagnosis, which highlight the supportive role of biomarkers in the diagnostic process. According to new criteria, bvFTD can be classified in "possible" (requiring three of six specific clinical features), "probable" (in the presence of functional disability and typical neuroimaging features) and "with definite frontotemporal lobar degeneration" (requiring the presence of a known causal mutation or a histopathological confirmation). Familial aggregation is frequently reported in bvFTD and frontotemporal lobar degeneration in general, with an autosomal dominant transmission in about 10% cases. The aim of this paper is to review and discuss recent advances in the knowledge of clinical, neuropsychological and imaging features of bvFTD. We also briefly summarize the available genetic information about the frontotemporal lobar degeneration spectrum.

Keywords: Behavioral variant of Frontotemporal Dementia; Frontotemporal Lobar Degeneration; Social Cognition Disorders; Voxel-based Morphometry; [^{18}F]FDG PET imaging.

Introduction

The clinical heterogeneity of the frontotemporal lobar degeneration (FTLD) spectrum is wide [1-2], including many different phenotypes. Within this spectrum, the behavioral variant of frontotemporal dementia (bvFTD) accounts for about half of all clinical cases [1]. It represents the second most common young-onset neurodegenerative dementia subtype after Alzheimer's Disease (AD) [2]. The reported prevalence of FTLD is highly variable among studies. In Italy, it ranges from 17.6 [3] to 35 [4] cases per 100.000 inhabitants, a higher prevalence in comparison to other western countries (i.e. 1.1-15 cases per 100.000 inhabitants) [5-6]. It is presently unknown if this wide variance may be partially related to the specific genetic background of the Italian population, with a possible founder effect. The role of methodological factors needs also to be investigated. For example, a door-to-door study [4] may allow early identification of dementia, and better characterization of the phenotype. The mean age at onset is typically in the 50s, with an equal prevalence in men and women [1]. An earlier onset, between 20s and 40s, has been reported in subjects with underlying fused in sarcoma (FUS) pathology [7]. The latter is an unusual cause of bvFTD. The main neuropathological substrates are FTLD-microtubule protein tau (FTLD-tau) and FTLD-transactive response DNA binding protein (FTLD-TDP43) [8]. These different pathologies share the characteristic of being associated with a selective damage to the frontal and temporal lobes, involving both hemispheres, sometimes asymmetrically [9]. It must be additionally underlined that non-FTLD pathology has been reported in association with a bvFTD syndrome in a clinico-pathological study of focal presentations of AD [10].

Neuropathological heterogeneity well corresponds to the complexity of the bvFTD genetics. In the last few years, multiple genetic autosomal dominant mutations leading to the development of FTLD have been identified, forcing clinicians to constantly reconsider the number of truly sporadic cases. The most frequent mutations involve microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) genes both associated with high phenotypic

variability, as well as the newly identified large hexanucleotide (GGGGCC) repeat expansion in the first intron of *C9ORF72* mutation (see [11] for a review).

New consensus criteria [12] define three levels of certainty for clinical diagnosis of bvFTD: "possible", "probable", or "with definite frontotemporal lobar degeneration". A "possible" diagnosis is based on purely clinical criteria in patients with progressive deterioration of behavior and/or cognition by observation or history. The diagnosis requires the presence of 3 out of 6 clinically discriminating features (i.e. disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality and dysexecutive neuropsychological profile). Imaging changes consistent with bvFTD are fundamental to reach the "probable" level [12]. In addition, evidence of progression with functional disability is also required for a probable bvFTD classification. The certainty of diagnosis needs the presence of "definite frontotemporal lobar degeneration pathology" by means of histopathological confirmation or *in vivo* recognition of a pathogenic gene mutation associated with FTLD.

In this paper, we aim at reviewing and discussing knowledge about bvFTD from a clinical, neuropsychological and imaging point of view, trying to elucidate the distinctive features of this clinical phenotype. We also supply a quick look at the most recent advance in the genetics of frontotemporal dementia.

Behavioral and neurological features

From a clinical point of view, most common manifestations of bvFTD are insidious changes in personality, interpersonal conduct and emotional modulation [1,12-13], in the absence of significant impairment in traditional cognitive tests. Apathy, lack of motivation to pursue previously rewarding activities or hobbies, and social withdraw often coexist with disinhibition, impulsive actions and socially embarrassing behavior. The severity of apathy is correlated with the degree of atrophy in the right dorsolateral prefrontal cortex, while disinhibition reflects

atrophy in the right nucleus accumbens, right superior temporal sulcus, and right mediotemporal limbic structures [14]. Behavioral disinhibition or socially inappropriate behaviors may result from a failure to correctly identify social and emotional signals coming from the environment associated with a potential reward or punishment value. This is a basic ability required to avoid negative social outcomes. Disinhibited behaviors could also result from a deficit in impulsivity regulation resulting in inappropriate responses and behaviors. Patients may inappropriately approach strangers, make offensive jokes or sexual remarks, have rash and impulsive actions, or even commit crimes. They also present perseverative, compulsive and ritualistic behavior, linked to a disruption of the normal mechanisms of reward learning [15], and show hyperorality and dietary changes, probably due to pathological involvement of the posterior hypothalamus [16]. Compared with their premorbid functioning, patients with bvFTD become less warm, extraverted, open to new experiences, and more neurotic. These changes typically lead to a deep modification of personality [17] which progressively impacts on social, professional and familial relations.

In general, in the early stages of disease the pervasive social and emotional modulation disorders (e.g. patient's violation of social conventions, and emotional blunting) dominate the clinical picture, and the patient performance on "frontal lobe" tests assessing executive function may be within normal limits. On the other hand, bvFTD patients perform poorly on laboratory-based tasks including recognition of basic emotions, social decision-making, comprehension and inference of other's mental states and emotions, and maintaining awareness of their own social behavior [18-21]. The lack of insight is also a relevant clinical feature of bvFTD, included in the Neary criteria [13]. Although it is significantly related to the frontal lobe function, and classically considered a peculiar aspect of this dementia subtype, defective insight is very common in many neurodegenerative diseases and neuropsychiatric conditions, and it may not represent a good discriminating factor to differentiate bvFTD from other form of dementia [22].

Emotion recognition has reported to be impaired in bvFTD patients, with a predominant deficit of negative emotion recognition [23]. Impairment facial emotion recognition has been confirmed by recent voxel-based morphometry study [24], in which recognition of angry expressions was positively associated with grey matter density in the bilateral insula cortex. Diminished disgust reactivity measured while watching a disgust eliciting film [25] has been also reported in bvFTD patients. In another study [26], the same authors reported impaired recognition of emotions from music in bvFTD and semantic variant of primary progressive aphasia (svPPA). The disorder was specifically associated with atrophy in fronto-limbic and temporo-parietal areas. This functional network, involving amygdala, insula, anterior cingulate and orbitofrontal cortices, identifying personally salient social signals, appears to be prone to a selective, network-driven neuronal vulnerability in bvFTD [27]. A decreased intrinsic connectivity in this 'salience network' can have an effect on patient's response to social stimuli, affecting their sensitivity to the negative consequences of their own social acts [28].

BvFTD patients may also present social behavioral disorders as a consequence of impairment of knowledge of those concepts describing social behavior, an aspect which seems to be particularly evident in subjects with right lateral anterior temporal damage [29]. In addition, these patients present deficits of high order social information processing, i.e. representation of one's own and others' beliefs, intentions, and emotions (i.e. Theory of Mind or ToM, and empathy abilities) or personal moral reasoning. BvFTD patients show poor performances on ToM tasks (e.g. first-order and second-order false belief, ToM cartoons and stories, faux pas comprehension, and reading social emotions based on photographs of eyes) [30-31]. Using the Interpersonal Reactivity Index scale, an indirect empathy measure obtained by caregivers, Rankin and collaborators described a dysfunction of both cognitive and emotional components of empathy in bvFTD and svPPA [32]. Similarly, compared with AD patients and healthy controls, bvFTD show decreased emotional responsiveness to others and utilitarian decisions in response to personal, emotionally driven moral dilemmas, resulting from ventromedial frontal dysfunction

[33]. Altered judgment of moral dilemmas may also be related to impaired affective ToM [34], suggesting the involvement of a common socio-emotional processing network.

While in the early stages executive functions may be completely or relatively spared, with advancing pathology executive deficits may appear and contribute to social cognition impairment, reducing control and top-down regulation [35-36] and decreasing the monitoring of bottom-up emotional signals, as proved by a neurophysiological study [37]. According to new consensus criteria [12], impaired executive function with a relative sparing of memory and visuospatial abilities is indeed a main neuropsychological feature of bvFTD. Among executive function tests, a recent study [38] indicates prominent disorders in tests of inhibitory control (i.e. Stroop and Hayling tests), as well as in phonemic and semantic fluency, working memory (i.e. Adapted Brown–Peterson, Letter–Number Sequencing), and planning abilities (i.e. Tower of London). Involvement of set shifting and working memory storage capacities have been also reported by a [^{18}F]FDG PET study [39], proving a correlation between bvFTD poor performances on verbal fluency and bilateral or right frontal lobe hypometabolism. Specific executive impairments show precise neuroanatomical localizations. A recent voxel-based morphometry study proved that verbal fluency is associated with left frontal perisylvian cortex, sorting with dorsolateral prefrontal cortex, and a reasoning task (i.e. Twenty Questions), with left anterior frontal cortex, an area preferentially involved in higher-order executive functions [40]. Impaired executive functions help also to detect non-progressing bvFTD cases, or "phenocophies" [41]. At first presentation, performance on executive tests is within normal range for non-progressing bvFTD cases, whereas the progressors present impaired digit span backward, Hayling test, letter fluency, and Trail Making part B performances [42].

Impaired episodic memory is classically considered an exclusion criterion for a clinical diagnosis of bvFTD [12-13], useful to distinguish early bvFTD from AD. Although some group studies proved that bvFTD patients perform better than AD on anterograde memory tasks and do not present accelerated forgetting under delayed free recall conditions, some cases present

predominant memory impairments in the clinical presentation (see [43] for a review). Nevertheless, many studies report episodic memory dysfunction bvFTD similar to the performance of AD patients, even if in presence of differential neural correlates [43-44]. This issue is crucial for the development of memory tests specifically reflecting medial temporal lobe dysfunction [45-46]. Moreover, also lifespan autobiographical episodic recall has been proved to be impaired in patients with FTD, compared to control subjects [47]. This deficit of autobiographical memory may reflect an impaired default-network functioning [48]. Autobiographical memory refers indeed to the shifting of perspective from the present to past personal events, thereby allowing an individual to maintain a sense of self and continuity across subjective time [48].

The degree of damage in grey matter areas and white matter tracts of the Papez memory circuit was recently investigated *in vivo* and at *post-mortem* in bvFTD and AD cohorts using voxel-based morphometry, diffusion tensor imaging and manual volumetric tracing [49]. In this study, the authors proved atrophy on anterior cingulate cortex in bvFTD and posterior cingulate cortex in AD, and a selective damage of subcortical Papez circuit regions (fornix and anterior thalamus) in bvFTD, related with the degree of episodic memory deficits. Moreover, though a similar degree of hippocampal atrophy for bvFTD and AD *in vivo*, bvFTD patients show greater hippocampal atrophy at *post-mortem*. Therefore, hippocampal atrophy does not appear to be an efficient diagnostic marker for underlying bvFTD or AD pathology, although episodic memory deficits associated with marked hippocampal atrophy seem to represent potential markers of FTLD-TDP-43 pathology. Consistently, recent studies on *C9ORF72* mutated cases, which underlie FTLD-TDP43 pathology, reported phenotypic presentation with prevalent memory impairments [50-51].

In addition, it is increasingly evident that a subset of patients with clinical symptoms consistent with bvFTD does not clinical progress over time and remains stable over many years. These non-progressing subjects, or “phenocophies” [41], are basically distinguished from true

bvFTD, because they present with no significant alterations on brain imaging and no progression in time (see [52] for a review). The etiology of phenocopy syndrome is still under debate. Although it has been suggested that a proportion of patients might have a developmental personality disorder in the Asperger's spectrum with late decompensation, recent findings in a cohort of 384 patients with FTD and AD clinical diagnosis identified two subjects with an atypical, slowly progressive phenotype fulfilling criteria for possible bvFTD and carrying *C9ORF72* hexanucleotide expansion [53]. This evidence suggests that some bvFTD slowly progressive cases previously considered "phenocopy" cases [41] may have underlying neurodegenerative pathology, based on a pathological *C9ORF72* mutation.

Neuroimaging Features

Focal lobar atrophy on conventional brain MRI or CT evaluation has a relevant role in the diagnosis of bvFTD, and is extremely useful to evaluate the disease progression, especially combined with clinical and neuropsychological measures. However, in the very early phase of the disease, conventional MRI can often be negative. Although a negative scan in the first stage of disease does not definitely exclude the clinical diagnosis of bvFTD, normal or borderline MRI findings in repeated acquisitions predict significant longer survival [41].

At the beginning, bvFTD patients usually present a focal degeneration of pregenual anterior cingulate cortex (pACC) and frontoinsular cortex [54]. These regions represent basic components of the social and emotional processing network previously mentioned, particularly impaired in bvFTD since the very beginning of the disease. A recent metanalysis on 11 voxel-based studies involving 237 bvFTD patients pointed to prominent regional gray matter loss in the anterior medial frontal cortex (BA 9), extending to other frontal regions (BA 8, 10, 46, 24, 32), and in other brain areas, such as insula and subcortical striatal regions [55]. According with the

progression of atrophy to cortical-subcortical structures and neurons loss seen at MR imaging [56], hippocampus and subcortical structures may also be affected. The prominent atrophy of the amygdala could, in addition, represent an efficient discriminator between bvFTD and other dementias (e.g. AD) [57]. As the disease progress, the degeneration appear more evident, as proved by a serial volumetric MRI study of Chan et al. [58], which shows the higher annual rate of whole-brain atrophy in FTD patients compared to AD patients.

A hierarchical clustering approach described four anatomically definite bvFTD subtypes [59]. The "frontal dominant" subtype is defined by the presence of medial and lateral frontal lobe atrophy, the "frontotemporal" subtype by an extended frontal and temporal lobe atrophy, the "temporal" subtype by a predominant involvement of medial and lateral temporal lobe, and finally the "temporofrontoparietal" subtype by a wide atrophic pattern involving temporal lobes as well as frontal and parietal regions. The anatomical subtype seems a strong predictor of functional decline over time, much more than clinical-neuropsychological measures. In particular, "frontal dominant" and "frontotemporal" subtypes present the most severe prognosis [60].

Genetical cases present different neuroradiological profiles. Specific gene mutations may influence the neuroanatomical pattern of atrophy seen in bvFTD showing prevalent frontal symmetric atrophy in *MAPT* and *C9ORF72* mutated patients and asymmetric in *GRN* mutation carriers [61]. Moreover, *MAPT* mutations are associated with relatively symmetrical temporal lobe atrophy [62]. On the contrary, *GRN* mutated patients mostly show asymmetric cortical atrophy with prevalent parietal involvement [63-64], and *C9ORF72* mutated patients present widespread grey matter loss, with the most striking atrophy in frontal lobes, followed by anterior temporal and parietal lobes, and cerebellum [9]. A voxel-based morphometry study demonstrated also thalamic atrophy in FTD and FTD-MND carriers of the *C9ORF72* hexanucleotide repeat expansion compared to sporadic FTD [65]. Both cerebellum and thalamus atrophy in *C9ORF72* mutated subjects have been also confirmed in a recent longitudinal study [66].

Task-free functional MRI (fMRI) provided also evidence that bvFTD and AD subjects present different network connectivity disruption patterns, anterior "salience" and posterior "default mode" networks respectively, consistent with the clinical-neuropsychological features of the two disorders [28,67]. Microstructural changes in white matter tracts within frontal lobe or connecting frontal and temporal brain regions have been reported in bvFTD, compared with AD [68]. This pattern of white matter damage seems also different from the other main subtypes of frontotemporal dementia. SvPPA present indeed predominant left temporal lobe involvement, with tract abnormalities in the inferior longitudinal and uncinate fasciculi, while non fluent variant of primary progressive aphasia show a damage of left inferior frontal lobe, insula and supplemental motor area, with tract abnormalities in the superior longitudinal fasciculus [69].

Unlike structural imaging, functional neuroimaging may represent a sensitive biomarker for the *in vivo* diagnosis of early, even preclinical, stage of dementia, even at single subject level. Cerebral pattern of glucose hypometabolism in bvFTD selectively involves mesial or dorsolateral frontal cortices, and differs from that observed in AD, in which temporoparietal and posterior cingulate cortices hypometabolism prevails [70].

Genetics of Frontotemporal Lobar Degeneration

Although only 10% of FTLD patients presents a clear autosomal dominant history, up to quite 50% bvFTD has some family history [11]. It suggests a strong familial aggregation within the FTLD spectrum of disorders. To date, to recognize a pathological mutation in one of the above mentioned genes allows to reach the certainty of diagnosis, and thus to classify the bvFTD case with "definite frontotemporal lobar degeneration pathology". Current knowledge about the genetics of FTLD is continuously expanding by the identification of novel genetic defects and chromosomal loci involved in the hereditary forms. Three are the main disease-causing genes currently associated with bvFTD, i.e. *MAPT, GRN,* and *C9ORF72*. Other genes responsible for

FTLD have been, however, recognized: *FUS*, *UBQLN2,* valosin-containing protein (*VCP*)-1, chromatin-modifying protein 2B (*CHMP2B*), and transactive response DNA-binding protein (*TARBDP*).

The first identified gene responsible for bvFTD was *MAPT*, discovered in the 1998 (see [11] for a review). To date, more than 40 pathogenic MAPT mutations have been described (http://www.molgen.vib-ua.be/, last access: December 2012). Though the clinical presentation in *MAPT* mutation carriers is mainly consistent with bvFTD, with a mean onset in the 50s, primary progressive aphasia cases and late age at the onset have been reported. The second gene responsible for the disease that was identified was *GRN* (see [11] for a review), localized in a small region rich of genes, approximately 6.2 Mb in physical distance to *MAPT* locus. More than 70 different mutations have been described from 2006 to date (http://www.molgen.vib-ua.be/, last access: December 2012). *GRN* mutation accounts for about 5–10 % of all FTD cases, markedly varying depending on the population considered. A collaborative study [71] analyzing *GRN* mutations in 434 FTLD patients, clinically ranging from bvFTD to primary progressive aphasias, showed that the most common phenotype was bvFTD (n = 24), while three patients were diagnosed with PNFA, three with AD, and one with corticobasal syndrome. Age at disease onset and clinical features are widely heterogeneous, even in the same family [11], making it really difficult to hypothesize the underlying genotype of a specific phenotype presentation.

The more recently discovered gene associated with FTLD is *C9ORF72* (see [11] for a review). A large hexanucleotide (GGGGCC) repeat expansion in the first intron of *C9ORF72* gene has been recognized as responsible for a high number of familial amyotrophic lateral sclerosis (ALS) or combined FTD-ALS phenotype with TDP-43-based pathology. Many other studies in the last two years proved that *C9ORF72* mutation represent a major cause of both familiar and sporadic ALS cases, and FTD cases, with a percentage almost comparable to that of *GRN* mutations [11], further confirming the genetic continuum between FTD and ALS in a common spectrum of disorders. Though the most common clinical phenotype associated with

C9ORF72 mutation is bvFTD, the phenotype of mutated patients is widely heterogeneous, even within the same family pedigree (i.e. FTD subtypes, ALS or a combination of both) [71]. In particular, mood and psychotic disorders have been described among the clinical presentations of FTD patients with *C9ORF72* mutation [50,72-74].

Conclusion and further directions

Current knowledge of pathological and genetic underlying substrates of bvFTD has enormously increased if compared to what known just a few years ago. Careful familial history, combined clinical-neuropsychological information and instrumental investigations have been proved to increase case identification and to lead to a better classification of the different neurodegenerative conditions. The diagnostic sensitivity will most likely improve with the clinical application of the new proposed criteria [12] in comparison to the earlier one [13], as demonstrated in a multi-site sample of 137 patients with pathologically verified FTLD [12]. Although the revised diagnostic guidelines have a flexible and more sensitive structure compared to previous clinical classification, they still failed to recognize some cases (i.e. 19 of all 137 cases = 13.8%), presenting at an older age and with atypical onset (e.g. prevalent memory impairment suggesting AD) [12]. This finding might be partially related to the presence of a subgroup of *C9ORF72* mutated cases [72], which has been just in the last two years accounted as part of the genetical FTLD spectrum, thus not considered in the study of Rascovsky and co-workers [12]. These subjects seem indeed more prone to present atypical phenotype with memory impairment [50]. Therefore, although the new criteria may increase diagnostic accuracy, they still lack of enough sensitivity to avoid some false negatives, lasting a risk of misdiagnosis.

The revised bvFTD criteria do not include neuropsychological testing of social cognition, which may increase diagnostic sensitivity [19] and be helpful in the differential diagnosis with other dementia conditions or with psychiatric disorders. This is an issue that needs to be considered in

future revisions of the criteria, as it just reflects the restricted clinical application of objective testing tapping specific sub-processes of social cognition. These tools, developed for research purposes, are in the course of clinical validation. Clinical research has been focused at understanding the cognitive and neural basis of the changes in social conduct and, in parallel, developing tests capable of helping in the diagnosis. So, though many developed tasks assessing social cognition disorders remain in the research arena, some well validated tests (e.g. of emotion recognition or empathy) may be soon become part of the screening evaluation of suspected bvFTD. Further refinements of clinical classification are possible as empirical data on neuroimaging and neuropsychological testing (e.g. social cognition measures) continue to evolve. Adapting new criteria by adding social cognition neuropsychological data might thus increase their specificity, reliability and predictive power in the early stage [75]. In conclusion, the combined use in clinical practice of novel, theory-driven neuropsychological assessment, genetic screening and neuroimaging measures will contribute in the near future to the definition of improved operational guidelines.

Finally, the major challenge in the field remains the possibility to predict *in vivo* the underlying neuropathology or genetic substrate. Efforts to identify potential disease biomarkers as well as possible therapeutic target are promising (e.g. plasma progranulin measurement for predicting *GRN* carriers [76], or serum pro-inflammatory cytokine levels [77]); however, further confirmations are required. Therefore, future research efforts have to focus at improving early detection and disease progression prediction and at developing reliable clinical-instrumental markers of the underlying pathological and genetical substrate, in order to better evaluate progression, survival, and disease activity with a view to the putative availability of disease-modifying treatments designed for etiopathogenetic factors.

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