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master in de biomedische wetenschappen

Masterthesis

Psychiatric Symptomatology in Frontotemporal Dementia: Hallucinations and Delusions in C9orf72 versus Non-C9orf72 Patients

Pauline Van Dyck

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

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Psychiatric Symptomatology in Frontotemporal Dementia: Hallucinations and Delusions in *C9orf72* versus Non-*C9orf72* Patients*

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**Psychiatric disorders in FTD: C9orf72 vs Non-C9*

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Keywords: Frontotemporal dementia, *C9orf72* mutation, psychiatric symptoms, hallucinations, delusions, Mini-international neuropsychiatric interview

GLOSSARY

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant FTD; *C9orf72,* chromosome 9 open reading frame 72; CBS, corticobasal syndrome; FTD, frontotemporal dementia; FUS, fused-in-sarcoma; *GRN*, progranulin; *MAPT,* microtubule associated protein TAU; nfvPPA, nonfluent variant primary progressive aphasia; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; TAU, tubulin associated unit; TDP-43, TAR DNA binding protein 43

ABSTRACT

Frontotemporal dementia (FTD) encompasses a spectrum of neurodegenerative disorders, characterized by clinical, pathological, and genetic heterogeneity. A GGGGCC hexanucleotide repeat expansion in the *C9orf72* gene constitutes the most prevalent genetic cause of FTD and is associated with atypical psychiatric manifestations. Accurate clinical evaluation of these psychiatric symptoms is crucial to differentiate between primary psychiatric disorders and neuropsychiatric phenotypes related to FTD. Although previous studies have suggested an increased frequency of these psychiatric symptoms, a detailed characterization remains limited. This study aims to evaluate the frequency and characteristics of hallucinations and delusions in *C9orf72* FTD versus non-*C9orf72* FTD. We used the Mini-International Neuropsychiatric Interview (MINI) and the scale for the assessment of positive symptoms (SAPS) to evaluate in detail hallucinations and delusions in 13 *C9orf72* and 26 non-*C9orf72* FTD patients. The study revealed a higher frequency of hallucinations in *C9orf72* FTD compared to non-*C9orf72* FTD, with an equal distribution between auditory and visual hallucinations within each group. In addition, delusions were more frequent in *C9orf72* patients when considering the prodromal and clinical phases of FTD, with a high presence of persecutory delusions, followed by jealousy delusions. This study provides a detailed clinical description of hallucinations and delusions in *C9orf72* and non-*C9orf72* FTD. These findings underscore the importance of considering this mutation in middle-aged individuals presenting with hallucinations and/or delusions, as accurate characterization is essential to enhance the diagnostic process. Future research is needed to determine whether psychiatric symptoms in FTD differ from those seen in psychiatric and neurodegenerative diseases.

INTRODUCTION

Frontotemporal dementia (FTD) or frontotemporal lobar degeneration (FTLD) encompasses a clinically, genetically, and pathologically heterogeneous group of neurodegenerative disorders hallmarked by the atrophy of frontal and/or anterior temporal lobes. FTD syndromes are characterized by progressive behavioral disorders, as well as language and cognitive deficits, while memory remains unaffected in the earlier disease stage. In some cases, these core clinical features are accompanied by prominent psychiatric manifestations, which will be the focus of this paper (1-5). FTD represents approximately 10% of all degenerative dementias, making it the third most common form of dementia, following Alzheimer's disease (AD) and Lewy body dementia (LBD) (6, 7). Globally, it is estimated that FTD affects between 1.2 and 1.8 individuals, with approximately 3,900 patients identified in Belgium (6, 8). This second most common early-onset neurodegenerative dementia (onset <65 years) is typically diagnosed in the sixth decade of life, with a mean age of onset of 58 years (9, 10). FTD is an incurable disease with an average survival of 8-10 years after the first clinical symptoms (11-14). To date, there is no available curative treatment or drug that slows down or stops the pathological progression (15).

FTD is classified into distinct phenotypes based on their predominant clinical presentations at onset (Figure 1). Behavioral-variant frontotemporal dementia (bvFTD) is the most prevalent form of FTD, accounting for approximately two-thirds of FTD cases (6). BvFTD is characterized by early changes in behavior, personality, and cognitive disorders concomitant with predominant frontal cortical degeneration. Typical behavioral changes include 1) apathy, 2) disinhibition, 3) repetitive and compulsive behaviors, 4) alterations in eating habits, 5) diminished empathy, and 6) cognitive deficits such as executive dysfunction and social cognition deficits (16, 17). These cognitive deficits and pronounced behavioral symptoms may lead to misdiagnosis with psychiatric disorders (in particular with depression) or other degenerative dementias such as AD. Due to the lack of definitive biomarkers for FTD, differential diagnosis can remain challenging (4, 18-20). To reduce the level of misdiagnosis, Rascovsky *et al*. (2011) have elaborated diagnostic criteria of bvFTD based on behavioral changes, cognitive deficits, neuroimaging, genetics, and post-mortem examination, with three levels of certainty: possible, probable, or definite. A diagnosis of "possible" bvFTD requires the presence of at least three of the six clinically discriminative features described above. "Probable" includes supportive neuroimaging findings consistent with bvFTD, i.e., frontal or anterior temporal atrophy on magnetic resonance imaging (MRI) or hypometabolism on positron emission tomography (PET) imaging. "Definite" bvFTD relies on histopathologic evidence of FTD hallmarks, based on post-mortem confirmation of the diagnosis or the presence of a known causal pathogenic mutation (4).

Conversely to bvFTD, language-dominant syndromes of FTD called primary progressive aphasia (PPA) are characterized by an insidious decline in language skills as the primary feature (5, 17). As described by Gorno-Tempini et al. (2012), PPA's diagnosis criteria are divided into different clinical variants based on the pattern of language breakdown (17, 21-23). The nonfluent/agrammatic variant PPA (nfvPPA) is characterized by agrammatism in language production, evident in the use of short, simple phrases and missing grammatical words. People with nfvPPA also have effortful, slow, and labored speech production. These symptoms constitute the core diagnostic criteria, of which at least one must be present. A hallmark feature, sometimes observed as an initial symptom, is an articulation planning deficit, i.e., apraxia of speech, in the setting of left-sided cortical atrophy. The semantic variant of PPA (svPPA) is probably the most consistently defined clinical syndrome within the PPA classification. According to current diagnostic guidelines, the core features are difficulty finding words (anomia) and single-word comprehension deficits, associated with anterior temporal atrophy, both essential for definitive diagnosis (5, 17). A third linguistic variant, logopenic PPA, is not detailed here, as most cases can be considered an atypical presentation of underlying AD pathology (24).

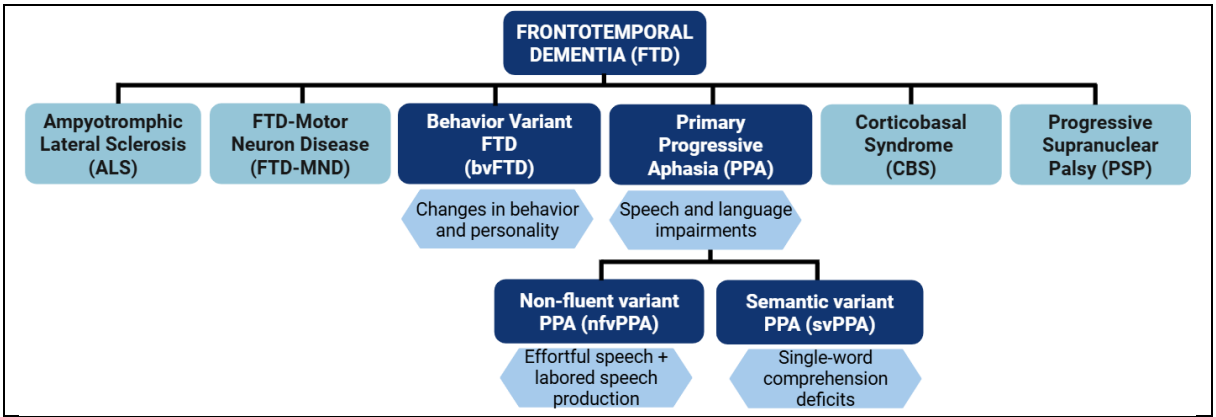

Fig. 1 – Clinical variants of frontotemporal dementia (FTD). FTD can be classified into distinct clinical phenotypes based on their predominant clinical presentations at onset.

For some patients, FTD also encompasses two atypical parkinsonian syndromes associated with frontal cognitive dysfunction and overlapping with FTD phenotypes, i.e., corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) (22). CBS condition may manifest as a combination of parkinsonian symptoms such as rigidity and akinesia, along with frontal cognitive impairments (dysexecutive syndrome), difficulties with movement planning and execution (apraxia), and motor abnormalities such as dystonia (abnormal postures) or myoclonus (involuntary muscle jerks) (25, 26). PSP is hallmarked by supranuclear ophthalmoplegia, postural instability, and frontal cognitive dysfunction (27, 28).

Like many other neurodegenerative diseases, FTDs are characterized by abnormal protein aggregation, forming toxic inclusions in neuronal and glial cells, which sensitize cells to damage and ultimately lead to cell death (29-34). This heterogeneous neurodegenerative process is hypothesized to originate in specific brain regions and to spread from cell to cell within neural networks in a prion-like manner (35). The underlying neuropathologies of FTD are heterogeneous too, with the pathological classification divided into three major subgroups based on the predominant protein abnormality, relating to either TAR DNA-binding protein 43 (TDP-43), tubulin-associated unit (TAU), or fused in sarcoma (FUS) proteins, respectively called FTLD-TDP, FTLD-TAU, and FTLD-FUS (36).

TDP-43 proteinopathies are the most common causes of FTD, accounting for about 50-60% of cases, followed by TAU (about 30-40%) and FUS (10%) pathologies (Figure 2). Briefly, TDP-43 and FUS proteins are involved in RNA metabolism (RNA splicing, transport, microRNA biogenesis, *etc.*), whereas TAU plays a significant role in microtubule assembly and stabilization. More broadly, the biological mechanisms implicated in FTD include lysosomal dysfunction, alteration in autophagolysosomal trafficking, endoplasmic reticulum-mitochondrial signaling, and axonal transport. Currently, only a limited number of specific fluid- or imaging-based biomarkers are available to support the diagnosis of FTD, while reliable biomarkers for distinguishing its pathological forms are still lacking (10, 36-38).

FTD represents a highly heritable group of disorders characterized by extensive genetic heterogeneity (Figure 2) (39). In general, FTD occurs sporadically and genetically, with 30-50% of cases being familial (40). Advances in understanding the genetics and molecular aspects of FTD have significantly progressed in recent years, primarily driven by the development of next-generation sequencing technologies (39, 41). The genetic forms of FTD typically follow an autosomal dominant inheritance pattern (42).

A GGGGCC hexanucleotide repeat expansion on chromosome 9 (*C9orf72*) is the most common genetic cause of FTD worldwide, surpassing mutations in progranulin (*GRN*) and microtubule-associated TAU protein (*MAPT*) genes, as well as 20 other primary genetic factors that are much less frequent (43, 44). *GRN* and *C9orf72* collectively represent 70-75% of familial FTD (1, 45). Notably, 5-10% of cases without a reported family history harbor *C9orf72* or *GRN* mutations. Possible explanations include the occurrence of de novo mutation or incomplete penetrance, despite its high penetrance in both genetic forms by the age of 80 (46).

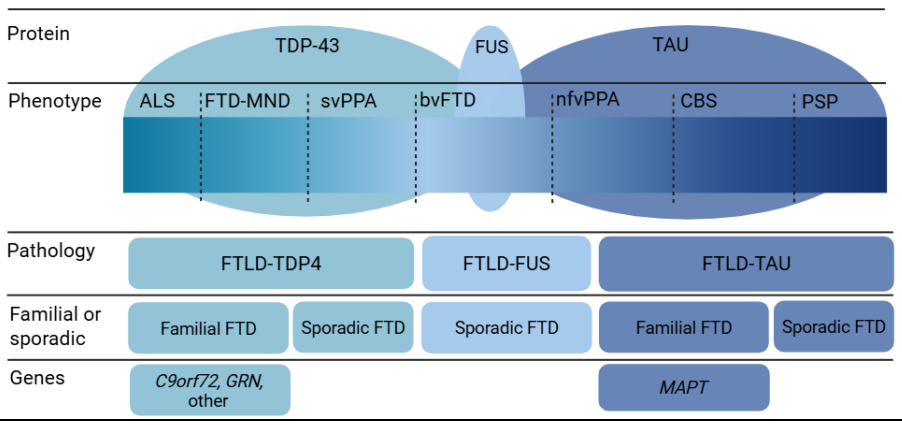

Fig. 2 – Clinical, pathological, and genetic spectrum of FTD. The clinical spectrum of FTD encompasses a range of underlying pathologies and genetic variations. *C9orf72* repeat expansions and *GRN* mutations primarily lead to TDP-43 proteinopathy, whereas *MAPT* mutations lead to TAU pathology. ALS and FTD-MND phenotypes are infrequently caused by FTLD-FUS pathology, but this detail is omitted from the figure for simplicity.
ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72; CBS, corticobasal syndrome; FTD-MND, frontotemporal dementia with motor neuron disease; FTD, frontotemporal dementia; FUS, fused-in-sarcoma; GRN, progranulin; MAPT, microtubule-associated protein TAU; nfvPPA, nonfluent variant primary progressive aphasia; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; TDP-43, TAR DNA binding protein 43. Modified from Meeter, L. et al. Imaging and fluid biomarkers in frontotemporal dementia. Nature Reviews Neurology. 2017;13(7):406-19.

The clinical presentations associated with disease-causing mutations are variable. *GRN* mutations are mostly associated with bvFTD (70%) and less frequently with PPA (20%), mostly agrammatic/non-fluent or a clinical phenotype mimicking CBS or other dementias (5-10%) (47, 48). The major clinical presentations associated with *C9orf72* expansions are a bvFTD, an amyotrophic lateral sclerosis (ALS), or a combined FTD-ALS phenotype (49, 50). BvFTD is associated with ALS in approximately 15% of the patients (51). ALS is a progressive disease linked to the progressive degeneration of the upper and lower motor neurons, resulting in limb weakness, amyotrophy, and bulbar motor symptoms and rapidly progressing to complete paralysis and ultimately to death within 3 to 5 years after symptom onset (37, 51, 52).

In rarer cases, *C9orf72* disease presents with atypical psychiatric symptoms, as reported for the first time by Snowden *et al*. (2012) (50, 53). Psychiatric disturbances present in *C9orf72* patients are still poorly characterized. However, previous studies showed that *C9orf72* patients can present with a wide range of psychiatric symptoms. Notably, psychotic features have been reported in approximately 21%-56% of individuals with *C9orf72* expansions, most frequently presenting as hallucinations and delusions. Additional psychiatric phenotypes include late-onset mania, obsessive-compulsive disorder, depression, typical schizophrenia, or bipolar disorder (50, 54-56). Compared to other dementia syndromes, patients with bvFTD have the highest risk of being misdiagnosed with a primary psychiatric disorder (57). In particular, psychiatric symptoms are more present across the spectrum of *C9orf72*-related diseases than in non-*C9orf72* bvFTD (58).

Previous studies have shown that psychiatric symptoms may represent the earliest clinical manifestations of *C9orf72* bvFTD, occurring several years prior to definitive clinical diagnosis. In other cases, they may appear during the course of FTD/ALS. These observations underscore the importance of detailed psychiatric assessment in patients with *C9orf72* mutations to differentiate primary psychiatric disorders (not related to any genetic or metabolic cause) and phenotypes associated with *C9orf72* disease (50).

However, studies examining the full spectrum of psychiatric symptoms in genetic FTD remain limited so far (59). Given the increased prevalence and broad spectrum of psychiatric symptoms in patients carrying a *C9orf72* mutation, detailed characterization is essential to improve diagnostic accuracy, guide patient management, and enhance our understanding of the underlying pathophysiological mechanisms (4).

This study aims to evaluate the frequency, severity, and phenotypic presentation of psychiatric symptoms in bvFTD, with a specific focus on comparing *C9orf72* bvFTD with non-*C9orf72* bvFTD. Our primary objective was to evaluate the frequency, type, and characteristics of hallucinations, whatever their modality (visual, auditory, olfactory, cenesthetic), and delusions (of persecution, jealousy, identity, dysmorphophobia, ruin/guilt, grandiosity, religion, reference, influence, ego disorders, or somatic delusions – defined as fixed false beliefs concerning the presence of a physical illness or bodily dysfunction, despite contradictory medical evidence (60).

EXPERIMENTAL PROCEDURES

Recruitment of patients – This monocentric study was conducted at the Memory Institute, a national reference center for FTD, at the Pitié-Salpêtrière hospital, Paris, France.

The clinical diagnosis of bvFTD was confirmed by an expert neurologist according to the diagnostic criteria of bvFTD as defined by Rascovsky *et al*. (2011) (4). All participants underwent genetic analysis, including analysis of the *C9orf72* gene, prior to their inclusion in the study. This expert center systematically proposes the analysis in a diagnostic setting to all patients with bvFTD.

All participants or their legal representative signed informed consent for clinical research prior to their inclusion in the study. The study and procedure were approved by the Salpêtrière Hospital ethics committee and carried out according to the Declaration of Helsinki guidelines. Inclusion and exclusion criteria in the study were applied to ensure homogeneity and appropriate representation of the study population. Inclusion criteria required participants to be at least 18 years of age and to meet the international clinical criteria of bvFTD. Exclusion criteria included taking toxic drugs, pro-hallucinatory treatments (pro-dopaminergic, etc.), refusal to undergo genetic analysis, and other neurological diseases unrelated to the FTD spectrum.

In total, 42 patients with bvFTD, aged between 33 and 80, were recruited. Three participants were excluded from the analysis because of inconsistent data between patient and informant questionnaires. The final population of 39 patients included 13 patients carrying the *C9orf72* mutation (*C9orf72* bvFTD) and 26 patients with bvFTD not linked to a *C9orf72* mutation (non-*C9orf72* bvFTD).

Demographics – Demographic and clinical characteristics (in particular gender, educational level, laterality, consumption of drugs, age at onset, age at inclusion, and disease duration at inclusion) were collected for each participant in a standardized form at the time of the evaluation.

Psychiatric evaluation – To ensure the most accurate characterization of these symptoms, evaluations were performed collaboratively by expert psychiatrists and neurologists.

An interview was conducted to complete the standardized questionnaires assessing psychiatric evaluation. Psychiatric disorders and symptoms were evaluated using both a patient-reported (whenever possible) and an informant-reported version. Concordance between patient and informant reports was systematically examined. In cases where patients were unable to participate in the interview due to mutism, only the informant-reported version was used (n=13).

In this study, several psychiatric domains were studied: hallucinations, delusions, bizarre behavior, obsessive behavior, compulsive behavior, and negative psychiatric symptoms. More specific interest was given to hallucinations and delusions, as the other domains overlap between bvFTD and psychiatric disorders and were therefore assessed with less specificity and reliability in this context.

Data collection of psychiatric disorders was based on the patient's personal medical history, considering three distinct temporal phases relative to FTD onset: (1) the preclinical phase, defined as more than 10 years before the manifestation of FTD symptoms, with return to normal between psychiatric and neurological symptoms, (2) the prodromal phase, encompassing the 10 years preceding the onset of neurological symptoms, with the presence of subtle cognitive and/or behavioral changes, and (3) the clinical phase, corresponding to onset of psychiatric symptoms occurring concomitantly or after the clinical onset of FTD (61).

Psychiatric assessments - The MINI (Mini-International Neuropsychiatric Interview), SAPS (scale for the assessment of positive symptoms), SANS (scale for the assessment of negative symptoms), and Y-BOCS (Yale-Brown obsessive compulsive scale) were used to evaluate the presence and severity of the following psychiatric disorders: 1) hallucinations, defined as

perceptions without external stimuli experienced as real; 2) delusions, fixed false beliefs arising from a distorted interpretation of reality, persisting despite clear evidence to the contrary; 3) stereotyped behavior; 4) bizarre behavior; 5) positive formal thought disorder, a syndrome characterized by disorganized forms of thinking and language; 6) affective flattening or blunting; 7) poverty of speech/content; 8) avolition/apathy; 9) anhedonia/asociality; 10) attention; 11) obsessions; 12) compulsions (62-64).

MINI - The MINI is a validated qualitative hetero-questionnaire specifically focused on capturing the presence and severity of delusions, hallucinations, and stereotypic behaviors. The MINI scoring system is structured per diagnostic module, each representing a specific psychiatric category. In this study, a questionnaire was adapted from the MINI to evaluate the most relevant items to assess and quantify psychiatric symptoms in the particular context of FTD patients. The assessment has a patient and informant version of, respectively, 98 and 99 "yes or no" questions (65).

SAPS – The SAPS utilizes a 5-point Likert scale from 0 (absent) to 5 (severe) to evaluate 34 items of positive symptoms. Each category comprises a distinct number of questions, along with a supplementary question designed to assess the severity of the category, denoted here as "+1", as shown in the supplementary assessments: hallucinations (6+1), delusions (12+1), bizarre behavior (4+1) and non-deficit formal thought disorder (8+1). Higher scores indicate more severe symptoms (66).

SANS – The SANS assesses 25 items of negative psychiatric symptoms: affective withdrawal/poverty (7+1), poverty of speech/content (4+1), avolition/apathy (3+1), anhedonia/social withdrawal (4+1), attention (2+1)). The scoring modalities are similar to the scoring of the SAPS (67).

Y-BOCS – The Y-BOCS assesses the severity of obsessive-compulsive disorder (OCD). The scale is a clinician-rated instrument comprising 10 items, each item rated on a 5-point Likert scale ranging from 0 (no symptoms) to 4 (extreme symptoms) (68).

The SANS and Y-BOCS scores were assessed but excluded from analysis, as all identified symptoms were attributed to the underlying bvFTD symptomatology rather than primary psychiatric pathology. The MINI and SANS scales are presented in the supplemental material for additional information.

Cognitive evaluation – FTD disease severity was evaluated at the time of the interview or in an interval of +/- 6 months from the interview using the scores of the mini-mental state examination (MMSE) evaluating global cognitive efficiency and the frontal assessment battery (FAB), a screening test designed to assess executive dysfunction (69, 70). Both are commonly used to evaluate dementia syndromes.

Statistical analysis – Statistical analyses were performed using R 4.4.2 software. Demographic and clinical characteristics were compared between *C9orf72* patients and non-*C9orf72* bvFTD patients using the Mann-Whitney U test for continuous data and Fisher's exact test for categorical measures, after normality was checked using the Shapiro-Wilk test. Data were presented as medians and quartiles [Q1 and Q3] with a significance level of 5%. With n1=13 and n2=26, the minimal detectable effect size (Cohen's h) at 90% is 1.10, which corresponds to a very large effect (71). This means that, given our sample sizes, only very large differences in proportions between the groups can be statistically detected. Given the small sample size and the exploratory nature of this study, no correction for multiple comparisons was applied. The results should therefore be interpreted with caution.

RESULTS

Study population characteristics – Table 1 presents the demographic and clinical characteristics of the population and the subgroups of *C9orf72* and non-*C9orf72* bvFTD patients. No significant differences were observed between the two groups regarding demographic and clinical characteristics. A family history of neurological disorders was significantly more frequent in the *C9orf72* group compared to the non-*C9orf72* group (p=0.033).

Table 1 - Demographic and clinical characteristics of *C9orf72* bvFTD patients (n=13) and non-*C9orf72* bvFTD patients (n=26).

	C9orf72 bvFTD	Non-*C9orf72* bvFTD	p-Value	Total population
N, number of participants	13	26		39
Median age-at-onset (years)	59.0 [55.0-61.0]	59.5 [54.3-66.8]	0.474	59.0 [54.5-64.0]
Median age at inclusion (years)	63.4 [62.4-65.4]	64.7 [57.7-71.3]	0.541	64.3 [59.0-68.5]
Median disease duration at inclusion (years)	5.0 [4.0-6.0]	4.0 [3.0-5.8]	0.203	4.0 [3.0-6.0]
Clinical characteristics				
bvFTD + ALS (%)	0.0%	15.4%	0.281	10.3%
bvFTD + Parkinson (%)	15.4%	3.8%	0.253	7.7%
Gender female/male (n)	9/4	13/13	0.318	22/17
Laterality right/left (n)	12/1	23/3	1.000	35/4
Family history of neurological disorder (%)	84.6%	43.5%	0.033*	58.3%
Family history of psychiatric disorder (%)	61.5%	39.1%	0.299	47.2%
Neuropsychological tests				
MMSE Total score (/30)	23.0 [11.0-26.0]	23.0 [20.0-25.0]	0.823	23.0 [19.0-26.0]
FAB Total score (/18)	12.5 [4.8-14.0]	12.0 [9.0-14.0]	0.566	12.0 [9.0-14.0]

Results are presented as number/percentage or median [Q1 and Q3] for demographic and clinical characteristics of *C9orf72* bvFTD and non-*C9orf72* bvFTD. Group comparisons were performed using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data with *p<0.05 as significant.

ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination.

Psychiatric symptomatology – In total, 53.9% of *C9orf72* patients experienced hallucinations and delusions, compared to 46.2% of non-*C9orf72* patients (Table 2).

In the *C9orf72* group, no psychiatric symptoms were reported during early life. Psychiatric symptoms predominantly emerged during the prodromal phase, affecting 30.8% of *C9orf72* patients, while 23.1% experienced psychiatric symptom onset during the clinical phase of bvFTD.

Non-*C9orf72* bvFTD patients demonstrated a different pattern of psychiatric symptom onset compared to the *C9orf72* group, although this difference was not statistically significant. Notably, 11.5% of non-*C9orf72* patients presented with psychiatric symptoms during the preclinical phase, a prevalence absent in the *C9orf72* group. Conversely, during the prodromal phase, symptom frequency was lower in non-*C9orf72* patients (7.7%) compared to *C9orf72* bvFTD (30.8%). In the clinical phase, the frequency was comparable, with psychiatric symptoms observed in 26.9% of cases.

Additionally, both groups were characterized according to the type of psychiatric symptoms. In *C9orf72* patients, hallucinations were the most prevalent symptom (46.2%), followed by delusions (38.5%). Hallucinations were equally distributed between the prodromal and clinical phases (23.1% each). Remarkably, during the clinical phase, delusions were only present in one patient (7.7%), whereas the majority of affected individuals (30.8%) experienced delusions during the prodromal phase.

In the non-*C9orf72* group, hallucinations were observed in 15.4% of patients, with auditory hallucinations restricted to the prodromal phase and visual hallucinations limited to the clinical phase (7.7% each). Delusions were more prevalent, reported in 46.2% of non-*C9orf72* patients, occurring in 11.5% during the preclinical phase and 26.9% during the clinical phase. Notably, the prevalence of delusions during the prodromal phase was lower in the non-*C9orf72* group (7.7%) compared to the *C9orf72* group (30.8%).

Table 2 – Clinical psychiatric characteristics of *C9orf72* bvFTD patients (n=13) and non-*C9orf72* bvFTD patients (n=26).

	C9orf72 bvFTD	Non-*C9orf72* bvFTD	p-Value	Total population
N, number of participants	13	26		39
Frequency of patients with hallucinations/delusions	53.8%	46.2%	0.741	48.7%
Auditory hallucinations	23.1%	7.7%	0.310	12.8%
Visual hallucinations	23.1%	7.7%	0.310	12.8%
Delusions	38.5%	46.2%	0.740	43.6%
Temporal distribution of psychiatric symptom onset				
Preclinical (Phase 1)	0.0%	11.5%	0.538	7.7%
Auditory hallucinations	0.0%	0.0%	1.000	0.0%
Visual hallucinations	0.0%	0.0%	1.000	0.0%
Delusions	0.0%	11.5%	0.538	7.7%
Prodromal (Phase 2)	30.8%	7.7%	0.153	15.4%
Auditory hallucinations	15.4%	7.7%	0.589	10.3%
Visual hallucinations	7.7%	0	0.333	2.6%
Delusions	30.8%	7.7%	0.153	15.4%
Clinical (Phase 3)	23.1%	26.9%	1.000	25.6%
Auditory hallucinations	7.7%	0	0.333	2.6%
Visual hallucinations	15.4%	7.7%	0.589	10.3%
Delusions	7.7%	26.9%	0.229	20.5%

Results are presented as the percentage of patients with hallucinations and/or delusions among *C9orf72* bvFTD and non-*C9orf72* bvFTD, including their temporal distribution across clinical phases (preclinical, prodromal, and clinical). Comparisons made between groups were done with a Fisher's exact test for categorical data, with *p<0.05 as significant.
bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72.

Frequency of Hallucinations – The frequency of hallucinations was higher among *C9orf72* bvFTD patients (46.2%) compared to non-*C9orf72* bvFTD patients (15.4%) (Figure 3). Although this difference did not reach statistical significance, it demonstrated a trend toward significance (p=0.056). Auditory and visual hallucinations were the only types reported and occurred with equal frequency within each group. None of the patients experienced other types of hallucinations or a combination of auditory and visual hallucinations.

Auditory hallucinations were present in 12.8% of the overall population, accounting for 23.1% of *C9orf72* patients and only 7.7% of non-*C9orf72* patients (p=0.310).

An identical distribution was observed for visual hallucinations, which were also present in 23.1% of *C9orf72* patients, and in 7.7% of non-*C9orf72* patients (p=0.310).

Characteristics of auditory hallucinations in C9orf72 bvFTD – Auditory hallucinations accounted for 50.0% of the hallucinations present in *C9orf72* patients. In all cases, the hallucinations consisted of the perception of voices, words, or phrases from outside the body. These voices were constant in identity and personally directed toward the patient. In 66.7% of cases, patients perceived the voices as familiar and reported interactive experiences, such as dialogical interaction or active attempts to locate the source of the voice. In addition, one patient reported auditory hallucinations comprising not only voices, words, or phrases but also music and sounds.

Characteristics of Auditory hallucinations in non-C9orf72 bvFTD – Auditory hallucinations represent 50.0% of the hallucinations present in non-*C9orf72* patients. Their characteristics were similar to those reported in the *C9orf72*. Patients perceived voices, words, or phrases originating from outside the body. The voices were constant in identity and personally directed towards the patient. In all cases, interaction with the voice was possible through dialogue. In contrast to the *C9orf72* group, neither described the voices as familiar, and no auditory hallucinations involving music or sounds were reported.

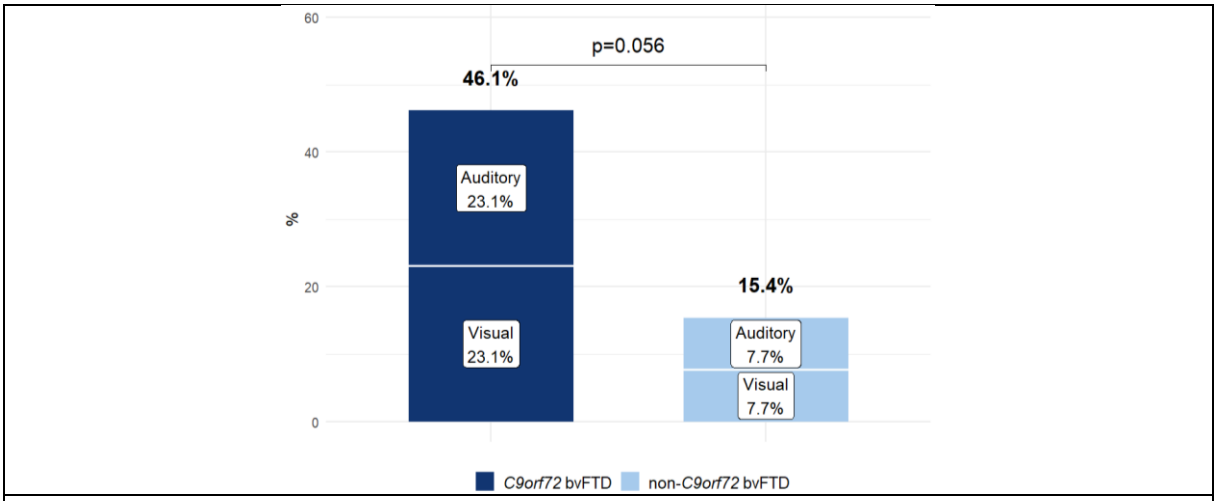

Fig. 3 – The presence of hallucinations and their characteristics in *C9orf72* versus non-*C9orf72* bvFTD patients, assessed with MINI and SAPS. In the *C9orf72* group, 46.2% reported hallucinations, equally divided between auditory and visual hallucinations (23.1% each). In the non-*C9orf72* group, 15.4% reported hallucinations, also divided between auditory and visual hallucinations (7.7% each). The trend toward a higher prevalence of hallucinations in the *C9orf72* group compared to the non-*C9orf72* group approached statistical significance (p=0.056), as assessed by Fisher's exact test.
bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72, MINI, Mini-International Neuropsychiatric Interview; SAPS, scale for the assessment of positive symptoms.

Visual hallucinations in C9orf72 bvFTD – Visual hallucinations accounted for 50.0% of the hallucinations present in *C9orf72 patients*. All patients experienced hallucinations involving individuals (100.0%), while one patient also reported visual hallucinations of objects (33.3%). These were predominantly experienced as static (66.7%) or animated film-like scenes (33.3%). A detailed description is provided in the supplemental material (Supplemental Table 1).

Visual hallucinations in non-C9orf72 bvFTD – Visual hallucinations accounted for 50.0% of the hallucinations present in non-*C9orf72* patients. In all cases, visual hallucinations consisted of objects, faces, figures (50.0%), or animals (50.0%). In contrast to the *C9orf72* group, none of the non-*C9orf72* patients described the hallucinations as film-like scenes. A more detailed description is given in the supplemental material (Supplemental Table 2).

Frequency of delusions – The global frequency of delusions was lower in *C9orf72* patients (38.5%) compared to non-*C9orf72* bvFTD patients (46.2%), although not statistically significant (p=0.740). It should be emphasized that, on the other hand, delusions are more common in *C9orf72* if we consider the prodromal phase of bvFTD (30.8%), although it is not significantly different from the non-*C9orf72* group (7.7%) (p=0.153). In the total population, persecution was the most frequent theme of delusions (88.2% of all delusions), followed by jealousy (35.3% of all delusions) (Figure 4).

No significant differences were found regarding the frequency of delusions or subtypes of delusions between *C9orf72* and non-*C9orf72* bvFTD patients (p=0.740).

Characteristics of delusions in C9orf72 bvFTD – 100.0% of the delusions present in *C9orf72* patients were of persecution. A subset of 40.0% also exhibited delusions of jealousy (40.0%) and delusions of influence (20.0%). No delusions pertaining to identity, reference, ego disorders, somatic themes, grandiosity, or ruin/guilt were reported in *C9orf72* patients.

Characteristics of delusions in non-C9orf72 bvFTD – Delusions of persecution (83.3%) were predominant before delusions of jealousy (33.3%) and of identity (25.0%, all believing people seen on TV or in pictures are real). In addition, a subset of patients reported other types of delusions: delusions of reference (16.7%), ego disorders (16.7%), somatic delusions (16.7%), grandiose delusions (8.3%), or delusions of ruin/guilt (8.3%).

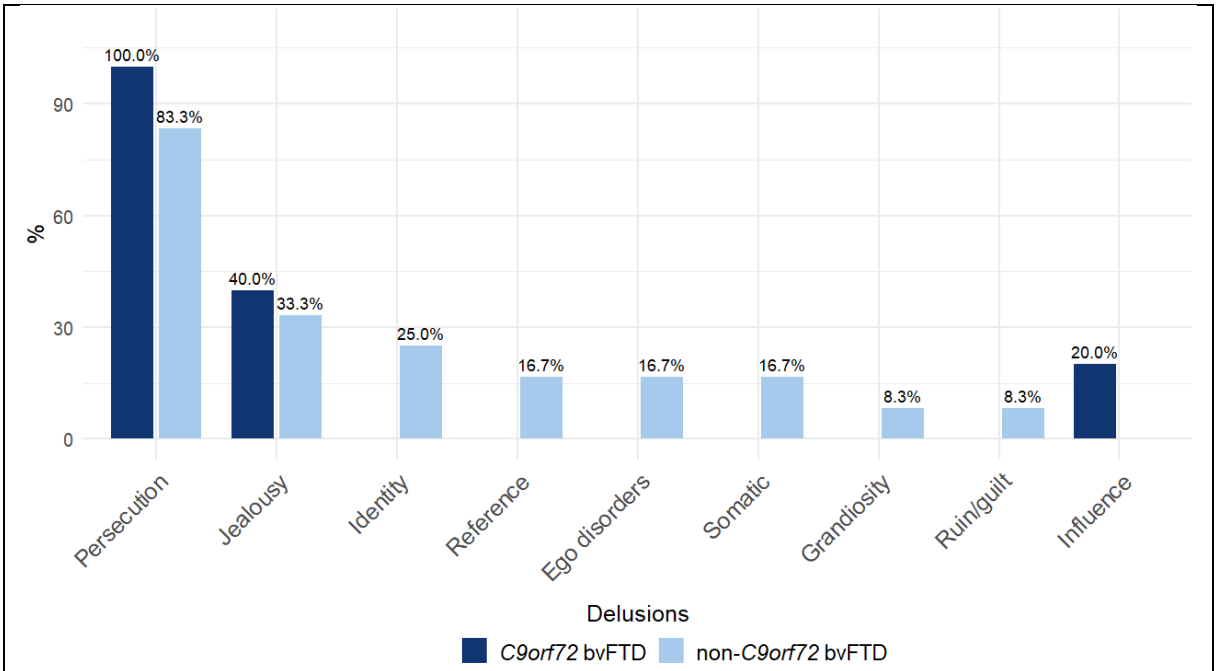

Fig. 4 – The presence of different types of delusions in *C9orf72* versus non-*C9orf72* bvFTD patients, assessed with MINI and SAPS. Delusions of persecution are most common in both groups, with a higher prevalence in *C9orf72* bvFTD (100.0%) than in non-*C9orf72* bvFTD (83.3%). Other types, such as delusions of jealousy, identity, reference, somatic, and grandiose delusions, are less frequent. The frequencies of delusion subtype were compared between *C9orf72* bvFTD and non-*C9orf72* bvFTD using Fisher's exact test, and no significant differences were observed.
bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72; MINI, Mini-International Neuropsychiatric Interview; SAPS, scale for the assessment of positive symptoms.

Hallucinations and delusions – A comprehensive overview of the clinical characteristics associated with hallucinations and delusions among the study population is provided in Supplemental Table 2. In the *C9orf72* group, 4 out of 6 patients (66.7%) exhibited a combination of delusions and hallucinations, with an equal distribution between auditory and visual types. In comparison, all 4 (100.0%) non-*C9orf72* bvFTD patients experienced hallucinations as well as delusions (Supplemental Fig. S1).

All the personal experiences regarding hallucinations and delusions are summarized in Supplemental Table 3.

DISCUSSION

Previous research has proven the prevalence of psychiatric symptoms in patients with bvFTD. Interestingly, neuropsychiatric symptom analysis revealed a higher frequency of delusions in individuals with the *C9orf72* mutation compared to non-*C9orf72* bvFTD, but a precise characterization is necessary (53, 72). Previous studies have additionally demonstrated that the accurate identification of *C9orf72* mutations in patients with late-onset psychiatric symptoms is challenging, as psychiatric symptoms may precede the emergence of typical FTD symptoms by up to 4-5 years, and the progression of symptoms can remain slow and subtle over many years (73, 74). It is important, therefore, to investigate the frequency and characteristics of these symptoms in a cohort of *C9orf72* patients in comparison with non-*C9orf72* bvFTD.

The present study investigated the presence of psychiatric symptoms in people with bvFTD, specifically the *C9orf72* patients. Our objective was to examine the frequency and characteristics of psychiatric symptoms, focusing on hallucinations and delusions, and the difference between *C9orf72* and non-*C9orf72* bvFTD patients.

The frequency of patients with psychiatric symptoms is 48.7% in our study, with a frequency of 53.8% in *C9orf72* patients compared to 46.2% in non-*C9orf72* bvFTD patients. Consistent with our findings, previous research has demonstrated that psychiatric symptoms are frequently observed in *C9orf72* bvFTD. Their overall frequency ranges from 24%

to 87.5% in other studies (53, 75-77). More specifically, Ducharme *et al.* (2017) demonstrated that between 21% and 56% of these patients exhibit psychosis, including delusions and/or multimodal hallucinations. The variability in the reported frequency across these studies may be attributed to the inclusion of different clinical variants, differences in frequency of the total population, differences in observation periods, and the use of diverse instruments/scales to assess psychiatric symptoms.

Interestingly, the psychiatric symptoms were the most common during the prodromal phase for the *C9orf72* group, whereas in the non-*C9orf72* group, psychiatric symptoms were least common during the prodromal phase and most prevalent during the clinical phase. This suggests that the occurrence of hallucinations or delusions of persecution or jealousy prior to the onset of bvFTD is a strong indicator warranting investigation for a *C9orf72* expansion. These results are in line with previous research, showing that psychotic symptoms, such as visual and auditory hallucinations and delusions, often precede the symptomatic FTD phase by 1 to 5 years in *C9orf72* patients. Detailed patient histories further support an increased incidence of psychosis in individuals with *C9orf72*-related bvFTD compared to non-*C9orf72* bvFTD (50, 53, 57, 76, 78).

We studied the hallucinations in both groups in more detail. Their frequency was different, as 46.2% of *C9orf72* patients experienced hallucinations, while only 15.4% of non-*C9orf72* bvFTD patients did, although no statistical difference could be found. In both groups, hallucinations were limited to either the auditory or visual modality, with an equal distribution. These findings align with previous studies reporting visual and auditory hallucinations more frequently than tactile and olfactory hallucinations in bvFTD (79, 80).

Auditory hallucinations were similar in both groups regarding structure (single, personally directed voices), interaction (dialogue), and source (outside of the body). However, *C9orf72* patients were more likely to perceive familiar voices, which was absent in non-*C9orf72* bvFTD, although this difference was not statistically proven. Although limited research has been done regarding characteristics, our results are in line with a study that observed that the auditory hallucinations were all in the second person (75).

In contrast, visual hallucinations were more diverse among both groups. Overall, these visual hallucinations seem hard to distinguish from reality in both groups, as their characteristics closely resemble daily life perceptions and visual experiences. The *C9orf72* presented with fixed or animated film-like scenes of personages. The non-*C9orf72* bvFTD group exhibited more heterogeneous forms of visual hallucinations, characterized by a diverse range of perceptual experiences, including objects, faces, figures, and animals. Remarkably, in contrast to the *C9orf72* group, the non-*C9orf72* patients did not experience these visual hallucinations as a film-like scene, but no statistical differences were observed.

Accordingly, the presence of personages experienced in a film-like scene in comparison to objects and animals without experience in a film-like scene may serve as distinguishing factors between the 2 groups. Although limited research has been done regarding detailed characteristics, our results align with a study that observed visual hallucinations in the form of people, both alive or dead, or animals in a group with both *C9orf72* and non-*C9orf72* FTD patients, with no cases exhibiting GRN or MAPT mutations (75).

Although the rate of delusions was found to be higher in non-*C9orf72* bvFTD (46.2%) compared to *C9orf72* patients (38.5%), this result should be interpreted with caution. When considering both the prodromal and clinical phases of bvFTD, delusions appear to be more prevalent in the context of the disease among *C9orf72* patients, suggesting a broader temporal expression of psychotic features in this genetic subgroup. Persecutory delusions were by far the most common in both groups, followed by jealousy delusions, whose frequencies were comparable in both groups.

Our findings align with previous studies reporting a higher frequency, up to 50.0%, of specific delusions in these carriers, a much larger frequency than in other FTD subtypes. Paranoid delusions were the most frequently reported subtype, consistent with our results (81). In addition, the variety can be confirmed by previous research, which reported subtypes including persecution, jealousy, grandiosity, and religion (50, 82).

To contextualize our findings and outline future research directions, it is important to consider neuroimaging studies that have investigated the neural correlates of psychiatric symptoms in *C9orf72* carriers. Through

neuroanatomical investigations, Sellami *et al.* (2018) demonstrated that the psychiatric symptoms are associated with region-specific patterns of brain atrophy, with alterations in the frontal cortex being particularly prominent in *C9orf72* cases. Left frontal cortical atrophy was mainly associated with the presence of delusions in *C9orf72* individuals. Cerebellar atrophy was found to be correlated with anxiety in these carriers. These brain areas are part of large-scale networks that are also involved in primary psychiatric disorders such as schizophrenia and depression. Consequently, and as previously mentioned, patients with *C9orf72* mutations are sometimes misdiagnosed with psychiatric disorders (84).

The limitations and strengths of this study need to be considered. The small sample size, with only 13 *C9orf72* bvFTD patients, may limit the generalizability of results and reduce the statistical power to detect significant effects. Furthermore, the reported hallucinations and delusions were based on retrospective accounts, which may affect the accuracy and reliability of the data. Comparing these findings with other genetic mutations, such as *GRN* or *MAPT*, would be interesting, as clinical overlap is observed between these variants (83). Additionally, the lack of comparison with healthy controls, psychiatric patients, or other neurodegenerative diseases limits the broader interpretability of the results. However, the primary aim of the study was to examine neuropsychiatric symptoms specifically between *C9orf72* and non-*C9orf72* bvFTD.

Despite these limitations, the study exhibited numerous strengths. A key strength of this study lies in the use of a tailored version of the MINI psychiatric diagnostic tool, which selectively incorporates the most relevant items to capture and quantify hallucinations and delusions in FTD patients. Compared to widely used instruments like the Neuropsychiatric Inventory (NPI), the MINI provides a more detailed assessment, allowing for differentiation in the modality and phenomenology of psychiatric symptoms. In contrast, the NPI primarily evaluates the general presence of psychiatric symptoms based on caregiver reports, without exploring their qualitative characteristics (85). In addition, conducting the MINI with both patients and their informants allowed for a more accurate and nuanced evaluation of this clinical population.

Although psychiatric disorders in bvFTD patients are a prominent focus of current research, no study to date has provided a detailed characterization of these manifestations in *C9orf72* patients. This study fills a critical gap in research by providing valuable insights into the detailed characterization of psychiatric symptomatology in patients with bvFTD.

CONCLUSION

These results are valuable to indicate the presence of hallucinations and delusions in FTD patients, specifically in *C9orf72* patients. In line with this, our study highlighted a higher frequency of hallucinations in *C9orf72* compared to non-*C9orf72 bv*FTD patients, with an equal distribution between auditory and visual hallucinations. In addition, delusions were more frequent in the prodromal and clinical phases of *C9orf72* bvFTD patients, with an overall high presence of persecutory and jealousy delusions.

Our findings underscore the importance for recognizing the heterogeneous nature of clinical presentations, which are often challenging to identify due to their overlap with primary psychiatric disorders and the delayed onset of hallmark FTD features. With these findings, we hope to better guide the differential diagnostic process for psychiatrists and neurologists and reduce diagnostic wanderings in the future. In individuals presenting with hallucinations and/or delusions during midlife, clinicians need to be aware of the possibility of the presence of this C9orf72 mutation and obtain a comprehensive family history of neurological and psychiatric disorders to assess for hereditary neurodegenerative risk.

Future large-scale studies are required to determine whether and how psychiatric symptomatology may differ in patients with bvFTD compared to psychiatric populations and other neurodegenerative diseases. Furthermore, to advance our understanding of the neuroanatomical bases of psychiatric symptoms in *C9orf72* patients, future studies incorporating advanced neuroimaging techniques will be essential.

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SUPPLEMENTAL

Supplemental Table 1 – Detailed characteristics of visual hallucinations in *C9orf72* bvFTD (n=3).

C9orf72 bvFTD patients	Visual hallucinations
Patient 1	Mobile
Patient 2	Mobile, realistic, in relief, and colored
Patient 3	Immobile, realistic, in relief, and colored

bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72.

Supplemental Table 2 – Detailed characteristics of visual hallucinations in non-*C9orf72* bvFTD (n=2).

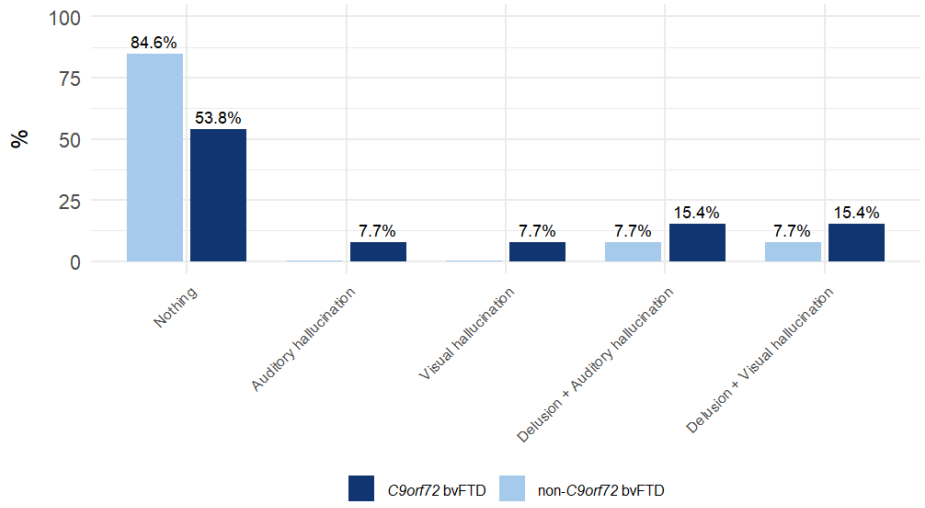
Non-*C9orf72* bvFTD patients	Visual hallucinations
Patient 1	No characteristics
Patient 2	Mobile, realistic, in relief, and colored

bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72.

Supplemental Table 3 – Personal experiences of hallucinations and delusions among *C9orf72* bvFTD patients (n=13) and non-*C9orf72* bvFTD patients (n=26).

	Hallucinations				Delusions			
	C9orf72	Non-*C9orf72*	p-Value	Total population	*C9orf72*	Non-*C9orf72*	p-Value	Total population
N, number of participants	6	4		10	5	12		17
General aspect (n)								
Neutral	83.3%	50.0%	0.489	70.0%	0	8.3%	1.000	5.9%
Unpleasant	16.7%	50.0%		30.0%	100.0%	91.7%		94.1%
Pleasant	0	0		0	0	0		0
Emotional reaction patient (n)								
Indifferent	80.0%	50.0%	0.518	60.0%	0	18.2%	0.299	12.5%
Anxious/fearful	20.0%	50.0%		30.0%	40.0%	63.6%		56.3%
Angry	0	0		0	60.0%	18.2%		31.3%

bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72.



Supplemental Fig. S1 – Crossover between auditory or visual hallucinations and delusions in *C9orf72* versus non-*C9orf72* bvFTD patients, assessed with the MINI and SAPS. In *C9orf72* bvFTD, isolated hallucinations were observed in 1 out of 3 patients, while all 4 non-*C9orf72* bvFTD patients exhibited hallucinations accompanied by delusions.
bvFTD, behavioral variant frontotemporal dementia; C9orf72, chromosome 9 open reading frame 72; MINI, Mini-International Neuropsychiatric Interview; SAPS, scale for the assessment of positive symptoms.

Mini-International Neuropsychiatric Interview (MINI)

HALLUCINATIONS

Auditory hallucinations:

1. Have you ever heard your own thoughts out loud?
2. Have you ever heard voices (words or phrases) that others couldn't hear?
   VOICES PERCEIVED AS COMING:
   FROM OUTSIDE THE BODY/BRAIN
   FROM INSIDE THE BODY/BRAIN
3. Question to informant: 'Has your relative ever behaved as if he was hearing something?'
4. Were the voices directed at you?
5. Did the voices insult or threaten you?
6. Did the voices give you orders?
   NEGATIVE ORDERS / NEUTRAL ORDERS / POSITIVE ORDERS
7. Did the voices talk to each other
   CONTENT: NEGATIF / NEUTRAL / POSITIVE

Did the voices describe/communicate your actions/thoughts?

8. Were they always the same voices?
   SPECIFY:
9. Did you recognize the voices?
   SPECIFY:
10. Did you interact with the voices?
    BY ENGAGING IN A DIALOGUE WITH THEM
    BY TRYING TO LOCATE THE SOURCE OF THE VOICES
    OTHER:

11. Have you ever heard other noises, sounds, or music that others could not hear?
    PERCEIVED AS COMING FROM:
    OUTSIDE THE BODY/BRAIN
    INSIDE THE BODY/BRAIN
12. Were the noises, sounds, or music always the same?
13. What were the characteristics of these noises, sounds, or music?
    NOISES/SOUNDS: CLEAR / DEEP / SHRILL / RESONANT / OTHER
    MUSIC: SAD / CHEERFUL / SIMPLE / COMPLEX / OTHER

14. Have you ever frequently talked to yourself? / Was a soliloquy present during the interview?

Visual hallucinations:

15. Have you ever had a strong sensation of the presence of a being near you, while no one or nothing was there (and without any sensory cues)?
16. Did you know who or what was present?
    IF YES: HUMAN / ANIMAL / SPECTRAL / LIVING INDIVIDUAL / DIED INDIVIDUAL
17. Did this sensation of presence always occur in the same location?
    IF YES: BESIDE / BEHIND
18. Have you ever seen things that others could not see?
19. Did these impressions always appear at the same time?
    MORNING / EVENING / NIGHTTIME / WHILE FALLING ASLEEP / UPON WAKING / VARIABLE
20. Were these visions well-defined?
    OBJECTS / FIGURES / ANIMALS / CHARACTERS
21. Did you experience them as a scene from a movie?
    STILL SCENES / ANIMATED SCENES
22. Did the visions always have certain characteristics?
    | MOBILE - IMMOBILE | | TINY – REALISTIC - GIGANTIC | | IN RELIEF - FLAT | | COLORED - COLORLESS |

Olfactory/gustatory:

23. Have you ever sensed a taste or smell that others did not notice?
24. Did the tastes or smells always have the same characteristics?
    | PLEASANT – NEUTRAL – UNPLEASANT |
    TASTE/SMELL: SWEET / AROMATIC / SAVORY / PUTRID / METALLIC / GASOLINE-LIKE / OTHER:
25. Did these sensations originate from your body?
26. Did these sensations come from an external source?

Cenesthetic:

27. Have you ever felt unusual sensations on your skin?
28. Did these sensations always have the same characteristics?
    PRICKLING / BURNING / TOUCHING / CRAWLING SENSATIONS / OTHER:

29. Have you ever felt unusual sensations inside your body?
30. Did you perceive them as a weight or discomfort in your body?
31. Have you ever had the impression that your body was transforming or changing?
32. Have you ever had the impression that your body was emptying or filling up?
33. Have you ever felt that a part of your body or your organs was no longer functioning or existing as before in a strange way?

General questions about hallucinations:
General perception by the patient: Pleasant / Neutral / Unpleasant
Patient's reaction: Amused / Indifferent / Anxious or frightened / Angry
Interaction with hallucinations: No / yes
Endangering Oneself or Others as a Reaction to Hallucinations: No / yes
Frequency of episodes: Occasional (<1 day) / Episodic (1–6 months) / Chronic (>6 months)
Hallucinations Present Throughout the Day, for Several Days During an Episode: No / yes
Duration of a Single Episode: Seconds / Minutes / Hours
Criticism on hallucinations: Completely / Partially / Not at all
Ability to Control Hallucinations: Possible / Partially possible / Impossible
Response to Treatment: Complete / Partial / None / No treatment
Estimated Impact on the Patient's Life: None / Moderate / Severe
Question to informant: 'Estimated Impact on the Relative's Life: None / Moderate / Severe'
Onset date:
Date of the last episode:

Comments & clarifications:

DELUSIONS

Persecution/prejudice:

34. Have you ever felt that people wanted to harm you or that you were the target of a conspiracy? PERSECUTED / SPIED ON / MONITORED / POISONED
35. Have you ever been convinced that others were hiding or stealing your belongings?
36. Have you ever been convinced that your spouse or loved ones wanted to abandon or institutionalize you?

Jealousy:

37. Have you ever been convinced that your spouse was having a romantic relationship with someone else?

Identity:

38. Have you ever been convinced that your spouse or loved ones might be impostors?
39. Have you ever believed that people seen on television or in photographs were real?
40. Have you ever thought that you were someone else when looking in the mirror?
41. Have you ever thought that there were other people in your house/apartment when you were alone?
42. Have you ever been convinced that the place where you live was not your real home?

Dysmorphophobia:

43. Have you ever been convinced that your body has changed in appearance?

Cotard's syndrome:

44. Have you ever been convinced that you no longer exist or are already dead?
45. Have you ever been convinced that your body is ill, malfunctioning, or no longer exists? HEART / INTESTINES / CIRCULATION / URINARY SYSTEM / DEFECATION / GENITAL ORGANS

Ruination/Guilt (Depressive Tone):

46. Have you ever been convinced that you do not have enough food to feed yourself?
47. Have you ever been convinced that you do not have enough money to survive?
48. Have you ever thought that you have committed a terrible sin or done something unforgivable for which you should be punished?

Grandiosity:

49. Have you ever thought that you have special powers or extraordinary abilities?

Religious delusions:

50. Have you ever been preoccupied with false beliefs of a religious nature?

Reference delusions:

51. Have you ever felt that remarks or daily events (e.g., broadcasts on television or radio) were about you or held a special meaning for you?

Delusions of influence:

52. Have you ever felt that your thoughts or actions were controlled by an external force?

Ego disorders:

53. Have you ever thought that others could read or know your thoughts?
54. Have you ever felt that your thoughts were being broadcast so that others could hear them out loud?
55. Have you ever felt that thoughts that were not your own had been inserted into your mind?
56. Have you ever felt that your thoughts were stolen?

General questions about delusions:
General perception by the patient: Pleasant / Neutral / Unpleasant
Patient's reaction: Amused / Indifferent / Anxious or frightened / Angry
Endangering Oneself or Others as a Reaction to delusions: No / yes
Frequency of episodes: Occasional (<1 day) / Episodic (1–6 months) / Chronic (>6 months)
Duration of a Single Episode: Seconds / Minutes / Hours
Criticism on delusions: Completely / Partially / Not at all
Disruption of the Patient's Life: None / Moderate / Severe
Question to informant: 'Disruption of the Relative's Life: None / Moderate / Severe'
Bizarre or Fantastic Quality of the Delusion: Non-existent / Present
Different Delusional Ideas Connected to Each Other: No / Yes
Response to Treatment: Complete / Partial / None / No treatment
Onset date:
Date of the last episode:

Comments & clarifications:

REPETITIVE THOUGHTS AND ACTIONS

57. Have you ever felt compelled to repeatedly perform the same act?

58. Were these acts related to a strong urge to go to the toilet?
    SIMPLE ACTS (EG., REPEATEDLY STATING THE NEED TO GO TO THE TOILET)
    COMPLEX ACTS (EG., CHECKING IF THERE IS ENOUGH TOILET PAPER AND BUYING MORE IF NOT)
59. Were these acts triggered by fears or thoughts?
    RELATED TO: CONTAMINATION / DIRT / DYSFUNCTION OF THE URINARY OR DIGESTIVE SYSTEM

60. Were there any other acts of washing or cleaning?
    RITUALIZED OR EXCESSIVE: HANDWASHING / OTHER PERSONAL HYGIENE PRACTICES / CLEANING OBJECTS
    OTHER ACTIONS TO AVOID OR ELIMINATE CONTACT WITH CONTAMINANTS
    SPECIFY:
61. Were these acts triggered by fears or thoughts?
    RELATED TO: CONTAMINATION / DIRT / CONCERN ABOUT ANIMALS / THE IDEA OF TRANSMITTING ILLNESS TO OTHERS
62. Have you always been particularly concerned about cleanliness?

63. Were these acts of verification?
    CHECKING DOORS/LOCKS/STOVE/…
    CHECKING FOR THE ABSENCE OF A CATASTROPHIC EVENT
    CHECKING THAT NOTHING COULD HARM OTHERS
    CHECKING FOR THE ABSENCE OF ERRORS
    CHECKING THAT NOTHING COULD HARM THEMSELVES
    OTHERS:
64. Were these acts triggered by fears or thoughts?
    SPECIFY:
65. Was such behavior always present in you in a more discreet manner?
66. Were these acts related to order/organization/symmetry?
    ARRANGING OBJECTS IN A CERTAIN WAY / A SPECIFIC PLACE
    NEEDING THINGS TO BE SYMMETRICAL OR PARTICULARLY STRAIGHT
67. Were these acts triggered by fears or thoughts?
    ACCOMPANIED BY MAGICAL THINKING: YES / NO
    SPECIFY:

68. Have you always had a personality particularly concerned with order/organization/symmetry?

69. Were these acts related to religion/esotericism?
    INCREASED FREQUENCY OF ATTENDING CHURCH
    INCREASED INTENSITY OF PARTICIPATION IN LITURGY/CEREMONIES
    INCREASED INTENSITY/FREQUENCY OF ESOTERIC RITUALS
70. Were these acts triggered by fears or thoughts?
    ACCOMPANIED BY THE IDEA OF HAVING SINNED: NO / YES
    SPECIFY:
71. Have you always had a religious/esoteric personality?

72. Was it the repetitive counting of something?
73. Were these acts triggered by fears or thoughts?
    SPECIFY:
74. Have you always been particularly drawn to numbers?

75. Was it the repetitive rereading or rewriting of something?
76. Were these acts triggered by fears or thoughts?
    SPECIFY:
77. Have you always been particularly drawn to letters/literature?

78. Were these acts related to music in a broad sense?
    SINGING THE SAME SONG
    WHISTLING/HYMMING THE SAME MELODY
    CLAPPING THE SAME RHYTHM
    OTHERS:
79. Were these acts triggered by fears or thoughts?
    SPECIFY:
80. Have you always been particularly musical?

81. Were these acts repetitive verbal/oral expressions?
    REPEATING THE SAME PHRASES/WORDS/SYLLABLES/SOUNDS
    RECITING THE SAME RHYME
    REPEATING THE SAME TOPICS DURING CONVERSATIONS
    ECHOLALIA / GRUNTING / BUZZING / MUMBLING
82. Were these acts triggered by fears or thoughts?

83. Are daily life activities always repeated in the same way, in a very rigid manner?
    MEAL SCHEDULES / SLEEP SCHEDULES / HYGIENE/TOILETRY ROUTINES /
    TABLE RITUALS / INSISTING ON ALWAYS TAKING THE SAME ROUTE/PATH / TASKS PERFORMED IN THE SAME ORDER/IN THE SAME WAY
84. Were these acts triggered by fears or thoughts?
    SPECIFY:
85. Have you always had a personality particularly attached to habits?

86. Was it the repetition of certain movements without purpose?
    SIMPLE MOVEMENTS: FULL BODY / HEAD / HAND/FINGERS / LIP/MOUTH / EYES
    COMPLEX MOVEMENTS/ LOCOMOTION (TURNING IN CIRCLES, JUMPING, WANDERING AIMLESSLY)

87. Were these potentially self-harming acts?
    HAIR PULLING / SKIN PICKING / HITTING ONESELF / BITING ONESELF / NAILBITING
    OTHERS:

88. Was it interacting with certain objects in a repetitive manner?
    TOUCHING/HITTING/RUBBING OBJECTS / STARING AT OBJECTS / PUTTING OBJECTS IN THE MOUTH / FASCINATION WITH MOVING OBJECTS / CLOCKWATCHING

89. Have you ever spent a lot of money on gambling or betting?
    SPECIFY:

90. Have you ever spent a lot of money on special promotions or winning offers?
    SPECIFY:

91. Have you ever collected/gathered/accumulated things?
    SPECIFY:

92. Was it collecting all objects without a purpose?
93. Did these objects have emotional value for you?
94. Did these objects have practical value for you?
95. Was it because you were unable to throw them away?
96. Is your apartment/house overwhelmed with objects?
97. Would it be unpleasant for you if someone else threw the objects away?
    REACTION: FEAR / ANGER / SADNESS / STRESS/AGITATION
98. Have you always been a collector?

General questions about repetitive actions:
General aspect for/according to patient: Pleasant / neutral / unpleasant
Duration per day:
Perturbation of patient's life: None / Moderate / Severe
Question to informant: 'Pertubation of relative's life: None / Moderate / Severe'
Perceived as involuntary, excessive, or unreasonable: Yes / partially / no
Recognition of impossibility by own intention: No / Yes
Felt to be inconsistent with the patient's personality and values: No / yes
Attempt to ignore or repress impulses to act: With success / without success / no attempt
Acts intended to neutralize/prevent (unpleasant) thoughts: No / Yes
Behavior intended to neutralize or prevent an undesirable event: no / yes
Motivation for actions: None / pleasure/gratification / boredom / generalized tension / anxiety
Reaction if patient is prevented from performing acts: Neutral / Tension / Anxiety / Anger
Sensitivity to treatment: Complete / Partial / Not at all / No treatment
Date of first appearance:
Date of last appearance:

Comments & precisions:

Scale for the assessment of positive symptoms (SAPS)

SAPS scoring system
0 = None/Not at All
1 = Questionable
2 = Mild
3 = Moderate
4 = Marked
5 = Severe

HALLUCINATIONS

1. Auditory Hallucinations
   The patient reports voices, noises, or other sounds that no one else hears.
2. Voices Commenting
   The patient reports a voice which makes a running commentary on his behavior or thoughts.
3. Voices Conversing
   The patient reports hearing two or more voices conversing.
4. Somatic or Tactile Hallucinations
   The patient reports experiencing peculiar physical sensations in the body.
5. Olfactory Hallucinations
   The patient reports experiencing unusual smells that no one else notices.
6. Visual Hallucinations
   The patient sees shapes or people that are not actually present.
7. Global Rating of Hallucinations
   This rating should be based on the duration and severity of the hallucinations and their effects on the patient's life.

DELUSIONS

8. Persecutory Delusions
   The patient believes he is being conspired against or persecuted in some way.
9. Delusions of Jealousy
   The patient believes his spouse is having an affair with someone.
10. Delusions of Guilt or Sin
    The patient believes that he has committed some terrible sin or done something unforgivable.
11. Grandiose Delusions
    The patient believes he has special powers or abilities.
12. Religious Delusions
    The patient is preoccupied with false beliefs of a religious nature.
13. Somatic Delusions
    The patient believes that somehow his body is diseased, abnormal, or changed.
14. Delusions of Reference
    The patient believes that insignificant remarks or events refer to him or have special meaning.
15. Delusions of Being Controlled
    The patient feels that his feelings or actions are controlled by some outside force.
16. Delusions of Mind Reading
    The patient feels that people can read his mind or know his thoughts.
17. Thought Broadcasting
    The patient believes that his thoughts are broadcast so that he himself or others can hear them.
18. Thought Insertion
    The patient believes that thoughts that are not his own have been inserted into his mind.
19. Thought Withdrawal
    The patient believes that thoughts have been taken away from his mind.
20. Global Rating of Delusions
    This rating should be based on the duration and persistence of the delusions and their effect on the patient's life.

BIZARRE BEHAVIOR

21. Clothing and Appearance
    The patient dresses in an unusual manner or does other strange things to alter his appearance.
22. Social and Sexual Behavior
    The patient may do things considered inappropriate according to usual social norms (e.g., masturbating in public).
23. Aggressive and Agitated Behavior
    The patient may behave in an aggressive, agitated manner, often unpredictably.
24. Repetitive or Stereotyped Behavior
    The patient develops a set of repetitive actions or rituals that he must perform over and over.
25. Global Rating of Bizarre Behavior
    This rating should reflect the type of behavior and the extent to which it deviates from social norms.

POSITIVE FORMAL THOUGHT DISORDER

26. Derailment
    A pattern of speech in which ideas slip off track onto ideas obliquely related or unrelated.
27. Tangentiality
    The patient replies to a question in an oblique or irrelevant manner.
28. Incoherence
    A pattern of speech that is essentially incomprehensible at times.
29. Illogicality
    A pattern of speech in which conclusions are reached that do not follow logically.
30. Circumstantiality
    A pattern of speech that is very indirect and delayed in reaching its goal idea.
31. Pressure of Speech
    The patient's speech is rapid and difficult to interrupt; the amount of speech produced is greater than that considered normal.
32. Distractible Speech
    The patient is distracted by nearby stimuli which interrupt his flow of speech.
33. Clanging
    A pattern of speech in which sounds rather than meaningful relationships govern word choice.
34. Global Rating of Positive Formal Thought Disorder
    The frequency of this rating should reflect the frequency of abnormality and the degree to which it affects the patient's ability to communicate.