Late Onset Behavioral Changes

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differentiating between bvFTD and psychiatric disorders in clinical practice

Flora Toribia Gossink

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Voor jou,
Mooi wonder
nog niet geboren
al zachtjes bemind…

‘Gracias a la vida que me ha dado tanto
Me dio el corazon que agita su marco
cuando miro el fruto del cerebro humano,
cuando miro al bueno tan lejos del malo,
cuando miro al fondo de la claridad

Gracias a la vida que me ha dado tanto
Me ha dado la risa y me ha dado el llanto
Asi yo distingo dicha de quebranto,
Los dos materiales que forman mi canto,
Y el canto de todos que es el mismo canto’

Mercedes Sosa

‘Thanks to life, which has given me so much
It gave me a heart, that causes my frame to shudder,
when I see the fruit of the human brain,
when I see good so far from bad,
when I see things clearly

Thanks to life, which has given me so much
It gave me laughter and it gave me longing
With them I distinguish happiness and pain
The two materials from which my songs are formed,
And everyone's song, which is a similar song’

Mercedes Sosa

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Preface

Connecting clinical practice to scientific research

Patient A, a 52 year old baker, was referred to a neurologist at a general hospital by his general practitioner because of two inexplicable fainting episodes, behavioral changes and cognitive problems within a short period of time. Upon examination, the neurologist did not find any evidence of acute neurological problems and patient A was referred to a psychiatrist at the same general hospital.

During psychiatric examination, the patient was adamant that his behavior and cognition had not changed in the recent past. However, his wife and adolescent children reported otherwise. They said patient A was showing less initiative, was increasingly irritable, and had even been physically aggressive at home. His wife also reported that the patient's boss had described him as inert and more frequently 'in deep thoughts'. Except for slight affective flattening, the psychiatric examination showed no abnormalities. Further physical examination, neurologic examination and laboratory tests, including tests for HIV, Borrelia, and Magnetic Resonance Imaging (MRI) was without abnormalities. The psychiatrist decided to admit Patient A to the psychiatry department of the hospital for further diagnostics.

During admission to the psychiatric department, memory problems and apraxia were observed. The psychiatrist concluded that there was evidence for progressive behavioral changes and cognitive problems, although he could not provide a detailed description of those problems. A neuropsychological test revealed executive dysfunctions. The hetero-anamnestic information and the neuropsychological deficits supported a diagnosis of behavioral variant frontotemporal dementia although imaging results were not supportive of this diagnosis. Thereupon patient A was referred to an academic memory center for a second opinion.

Two months later in the memory center, the patient's wife —who did most of the talking—emphasized the extensive behavioral problems. In the consulting room the patient did not show emotions or distress. A repeated neuropsychological examination was dominated by executive dysfunctions and a second MRI again showed no abnormalities. A 18-fluordeoxyglucose-(FDG)-PET-CT-scan showed biparietal hypometabolism which allowed for discussion about the clinical relevance. Based upon the clinical picture, informant based history and the neuropsychological deficits, a diagnosis of behavioral variant Frontotemporal

Dementia (bvFTD) was made. Patient A was declared unfit for work. After the diagnosis, his daughter announced in a local magazine that her father had dementia. One year after the diagnosis of bvFTD was made, the patient was seen at the academic memory center again. There was diagnostic doubt when it became apparent that the patient's daily alcohol intake was more than three units. Because of the recurring diagnostic doubt the previously performed FDG-PET-scan was revised. Subtle abnormalities were found in the patient's mesofrontal and temporal lobes and the medical team consisting of neurologists and a nuclear medicine physician could not reach a consensus on whether the presence of these anomalies supported the previous bvFTD diagnosis. The patient's wife reported an increase in behavioral problems, which led the medical team to support the original bvFTD diagnosis.

One year later in the memory center, no further functional decline was apparent in the patient. MRI cerebrum and FDG-PET-scan showed no progression of abnormalities compared to previous results. This gave rise to new diagnostic uncertainty. It was decided to refer the patient for additional diagnostic admission at the department of neuro- and geriatric psychiatry. During this admission the patient again stated that he did not experience behavioral changes during the last years, except for an increase of conflicts in his personal life. Psychiatric examination revealed a low intelligence and prolixity but no other deviations. Mini Mental State Examination (MMSE) was 28 out of 30 and the Frontal Assessment Battery (FAB) –a short clinical test that examines frontal functions globally- was also high with a score of 17 out of 18. It was found that patient knew only a limited number of proverbs but he was able to explain them.

During admission, collateral information was taken. Patients' wife told that she observed an increase of rigidity in thinking, carelessness, aggression, diminution of self-care and sexual disinhibition. According to his daughter, patient suffered from memory problems and he behaved annoyingly protective towards her, but she did not experience other problems. A former colleague told that he did not notice cognitive or behavioral problems in patient. Both the colleague as well as his daughter did not experience apathy, disinhibition, stereotypical behavior or a decrease in empathy in the patient. Patients' biography revealed that patient had shown pervasive submissive and clinging behavior, both at work as well as in his personal life and that he could not make decisions without advice or reassurance from others. This joined in with the way he accepted the diagnosis bvFTD although he did not agree at all. A neuropsychological examination revealed that patients'

level of intelligence was below average and he had difficulties with attention and concentration. During admission, patient frequently asked for recognition of his suffering due to the problems he experienced in his marriage. Disinhibition, stereotypy, apathy, loss of empathy, strange eating behavior or executive deficits were not observed. Therewith, insufficient arguments for the diagnosis bvFTD were found and the diagnosis was rejected. The real cause of the problems was found to be a low intelligence in combination with dependent and avoidant personality traits and relationship problems. After a number of consultations patient and his partner could agree with this conclusion.

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Introduction

The behavioral variant of frontotemporal dementia

The patient presented in the preface was reported by his wife to have frontal neuropsychiatric problems: disinhibition, apathy and aggressive behavior. At the time patient was diagnosed with behavioral variant of frontotemporal dementia (bvFTD), patient met the consensus criteria of bvFTD which were pertinent at that time.[2] To diagnose bvFTD, in 1994 the Lund and Manchester groups were the first who published neuropathological and clinical criteria for frontotemporal dementia.[2] [3] [4] [5] The pathological syndromes were divided in a frontal lobe degeneration type consisting of non-specific neurodegenerative changes, the Pick type including Pick bodies and the motor neuron disease type. [2] The clinical criteria included frontotemporal lobar degeneration (FTLD) as an umbrella term for progressive non-fluent aphasia (PNFA), semantic dementia (SD) and the behavioral variant of frontotemporal lobar degeneration which was called bvFTD.[2] The five core clinical criteria for bvFTD were refined in 1998 and included *insidious onset and gradual progression, an early decline of social interpersonal behavior, an early decline in the regulation of personal behavior, early emotional blunting and an early loss of insight*. Furthermore, a number of supportive features such as pre-senile onset were added. Exclusion features included severe amnesia and spatial disorientation.[4] With the adaptation that the term FTLD must be reserved for the histopathological spectrum and the term FTD for the clinical spectrum, the 1998 criteria have been broadly applied until very recently. The sensitivity of the 1998

diagnostic criteria for bvFTD ranges between 36.5 and 79 % with high specificity (90–100 %)[6 7 8 9]. One of the practical problems with these criteria was the interpretation of rather abstract descriptions. Besides, as all five core criteria needed to be present for a diagnosis of bvFTD, cases with FTLD with less than five criteria would have to be diagnosed alternatively. Other arguments for updating the diagnostic criteria for bvFTD consisted of a need for a more flexible approach to fulfil the criteria and a more structured categorisation of individual items. Moreover, adding a degree of probability to the clinical diagnosis and acknowledging the role of biomarkers and genetics in the diagnosis would be useful in clinical practice.[10 11]

In 2011, the FTDC consensus criteria were launched. [5] The International Behavioural Variant Frontotemporal Dementia Criteria Consortium (FTDC) comprises 46 members with extensive experience in bvFTD. A conceptual set of criteria based on the international literature was discussed and refined during the course of three years. The criteria include *early behavioural disinhibition, early apathy or inertia, early loss of sympathy or empathy, early perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality and dietary changes* and *a neuropsychological profile consisting of executive/ generation deficits with relative sparing of memory* and *visuospatial functio*ns. When patients fulfil a minimum of three main features, they receive a diagnosis of possible bvFTD. A diagnosis of probable bvFTD can subsequently be established when functional decline is observed in the presence of frontotemporal hypometabolism on positron emission tomography (PET), hypoperfusion on single-photon emission computed tomography (SPECT) or atrophy on computed tomography (CT) or magnetic resonance imaging (MRI). A definite diagnosis of bvFTD can be made in the presence of pathological verification through cerebral biopsy or *post-mortem* confirmation or in the presence of a pathogenic mutation. Besides, it is stated that a bvFTD diagnosis cannot be made in the presence of an explanatory psychiatric condition. The sensitivity of the new FTDC criteria has been assessed using an autopsy conformed FTD cohort [5]. The specificity was 95% in a cohort using patients with Alzheimer's Disease (AD) and primary progressive aphasia (PPA) patients as a control group.

Our patient would not have been diagnosed with 'probable' or 'definite' bvFTD according to the new consensus criteria in view of the lack of supportive imaging results, the lack of progression in the second and third hetero-anamneses and the presence of an explanatory psychiatric condition. BvFTD has a set of symptoms

that often overlap with the clinical presentation of psychiatric disorders. Little is known about the specificity and sensitivity in a symptom based cohort. Moreover, little guidance is given on how to exclude an explanatory psychiatric condition.

The late onset frontal lobe syndrome

The late onset frontal lobe syndrome (LOF) refers to a clinical syndrome associated with functional or structural changes in the frontal cortex leading to apathy, disinhibition or stereotypical behavior emerging in middle or late adulthood.[12] Frontal-subcortical circuits have an essential role in regulating behavior: self-awareness, self-regulation, mental flexibility and the capacity for judgment and impulse regulation are under the executive control of the frontal lobes.[13] Many diseases, neurodegenerative as well as psychiatric, may result in structural deterioration or dysfunction of these frontal-subcortical brain networks, leading to this frontal lobe syndrome. [14] [15] AD can present with a clinically apparent frontal lobe syndrome and a specific 'frontal variant' of AD has been described, overlapping the bvFTD clinical phenotype. [16] [15] [17] Likewise, dementia with Lewy Bodies (DLB) and vascular dementia (VaD) can both result in similar symptomatology. [18] [19] In table 1. the main forms of dementia causing a late onset frontal lobe syndrome and their characteristic test results are summarized.

	Neuropsychological examination	MRI abnormalities	CSF
AD	Deficits in -episodic memory -working memory, attention -semantic knowledge	-Atrophy of the medial temporal lobe, posterior cingulate cortex and the temporal neocortex -Symmetrically distributed	-High concentration of t-tau -Low concentration of Aβ42 -High p-tau/Aβ42 ratio
DLB	Impairment of -visuoperceptual function -spatial functions -attention	-Enlargement of the lateral ventricles -Relative focal atrophy of the midbrain, hypothalamus and substantia innominate -Relative preservation of medial temporal lobe	-Lower levels of α-synuclein and p-tau181
VaD	Deficits in -cognitive flexibility -verbal retrieval -verbal recognition memory	-Multiple large vessel infarcts or -A single strategically placed infarct (angular gyrus, thalamus, basal forebrain) -And multiple basal ganglia and white matter lacunes -And/ or extensive periventricular white matter lesions	-Increased total tau and p-tau -Low concentration of Aβ42

Table 1. Differentiation between Alzheimer's dementia (AD), Dementia with Lewy Bodies (DLB) and Vascular Dementia (VaD) based on neuropsychological examination, MRI and CSF results

The distinction between bvFTD and Alzheimer's disease (AD) has become easier by the use of biomarkers that are able to identify underlying AD pathology, such as amyloid-aβ and tau. [20] [21] Differentiating bvFTD from psychiatric disorders, however, is still difficult, particularly since biomarkers for bvFTD are less robust. However, the current clinical criteria require that "if behavioral disturbance is better accounted for by a psychiatric diagnosis, a diagnosis of bvFTD has to be excluded".[5] Previous studies indicate that as a result of symptomatic overlap between bvFTD and psychiatric disorders, bvFTD patients are clinically often mistaken for psychiatric patients and vice versa. One study found that in comparison to other neurodegenerative diseases, bvFTD patients receive a prior psychiatric diagnosis significantly more often (50.7%) than patients with AD (23.1%), semantic dementia (24.4%), or progressive nonfluent aphasia (11.8%).[22]

Psychiatric diagnoses underlying the late onset frontal lobe syndrome

An extensive group of psychiatric disorders can result in a similar frontal lobe syndrome. Emotional blunting, apathy, economy of thought and speech are frequent symptoms of a psychiatric disorder such as major depressive disorder, bipolar disorder and schizophrenia.[23] [24] [25] [26] The negative symptoms in schizophrenia, depression, dysthymic disorder or autism spectrum disorders can be related to involvement of the same frontal subcortical circuits. [27] [12] In manic episodes, bipolar disorder, anxiety disorders, obsessive-compulsive disorder or tic syndromes, the same behavioral disturbances may occur as seen in bvFTD, like stereotypical language, motor or behavior disinhibition.[23] [24] [28] The fact that psychiatric disorders can arise at middle of even older age emphasizes the diagnostic difficulty.[29] Furthermore despite presence of specific symptoms in primary psychiatric disorders, the overlapping symptoms can be prominent (table 2).[30] [31] [32]

	Overlap with bvFTD	**Different from bvFTD**
Major depression	-Apathy -Psychomotor agitation -Inhibition	-Disease awareness -Distress
Mania	-Disinhibition -Inappropriate behavior -Inflated self esteem	-Reduced need for sleep -Fast disease course -Self-destructive behavior
Schizophrenia	-Negative symptoms -Reduced affect -Poverty of speech -Apathy	-More often delusions and hallucinations
Obsessive Compulsive Disorder	-Stereotypical behavior -Clinging to structure -Rituals	-Disease awareness -Distress -Young age of onset -Stereotypical behavior is driven by fear
Autism Spectrum Disorders	-Clinging to structure -Rituals -Solitary minded	-Lifelong pattern -Problematic behavior may be influenced by a well structured environment

Table 2. Overlap and differentiation between bvFTD and primary psychiatric disorders

The correct diagnosis

Compared to other forms of dementia, bvFTD has a higher burden on caregivers: they perceive care-giving as a heavy burden and quite often unfortunately suffer

from depression or stress. [33] [34] [35] Since neurodegenerative diseases are progressive, whereas most psychiatric disorders are treatable, making the distinction is highly essential. As there is still no cure for bvFTD, in case of a psychiatric disorder at least some symptomatic relief can be offered. An accurate diagnosis facilitates caregiver support and better overall management.[36]

The late onset frontal lobe syndrome study

The Late Onset Frontal lobe syndrome study (LOF study) aims to evaluate the spectrum of etiologies underlying LOF and to discern the bvFTD prodrome from the broadest clinically relevant differential diagnosis including psychiatric disorders. An improvement of diagnostics and prompt treatment of psychiatric conditions is to be gained.[37] One of the strengths of the LOF study is that it is symptom-based instead of aetiology-based whereby it resembles clinical practice as much as possible.

Aims of the thesis

The first aim of the thesis was to find clinical markers able to discern a psychiatric origin from behavioral variant frontotemporal dementia and other neurodegenerative diseases in the late onset frontal lobe syndrome. The symptomatic overlap and differentiation of bvFTD, other neurodegenerative diseases and psychiatric disorders were studied longitudinally. The second aim was to define predictors for non-progression in LOF. The third aim was focused at interventions: both effective pharmalogical interventions for bvFTD patients as well as supportive non-pharmalogical interventions for caregivers of dementia patients dealing with frontal behavioral problems were studied.

Design and in and exclusion criteria LOF study

The LOF study is a multicenter observational, cross-sectional, and prospective follow-up study. Patients are recruited through the memory clinic of the Alzheimer Centre of the VU University Medical Centre and the Department of Old Age Psychiatry of the GGZInGeest (inpatients and outpatients), Amsterdam, the Netherlands, between April 2011 and June 2013. LOF has been defined as behavioral changes consisting of apathy, disinhibition, and/or compulsive/stereotypical behavior arising in middle or late adulthood (observed by clinician or reliable informant).

Inclusion criteria were 1. age between 45 and 75 years, with symptom onset between the ages of 40 and 70 and 2. Frontal Behaviour Inventory score of 11 or higher and/or a Stereotypy Rating Inventory score of 10 or higher. Exclusion criteria were as follows: 1. an already established diagnosis of dementia or a psychiatric disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) that could explain behavior problems; 2. Mini-Mental State Exam score less than 18; 3. medical history, including traumatic brain injury, mental retardation, and drugs or alcohol abuse; 4. lack of reliable informant; 5. insufficient communicative skills of either patient or the closest informant (language, serious hearing impairment, or behavioral disturbances, including threatening or physical aggression); 6. acute onset of behavioral problems; 7. clinically apparent aphasia or semantic dementia; and 8. MRI contraindications.[37]

Diagnostic procedure

After the baseline assessment (Figure 1), both the neurologist and the psychiatrist determined the most likely diagnosis and their level of confidence (using a visual analogue scale) separately, blinded to the results of additional investigations (diagnosis 1 in Figure 1). Diagnoses were based on current guidelines.[37]

Then, the neurologist and the psychiatrist reconsidered their previously stated diagnosis, taking the additional neuroimaging and CSF results into account (diagnosis 2 in Figure 1). This was promptly followed by a multidisciplinary meeting, deciding the most likely diagnosis and composing a plan for treatment, psychoeducation, and/or guidance. After 1 year, the assessment summarized in Table 1 was repeated, apart from the Mini-International Neuropsychiatric Interview and the neuropsychological examination. The clinical diagnosis and (therapeutical) management were modified according to possible new clinical insights.

Two years after the baseline assessment, clinical assessment, a neuropsychological examination, and MRI were repeated, providing a prospective longitudinal follow-up. The data collection at baseline and follow-up is summarized in Figure 1.

Besides symptom-based inclusion, one of the strengths of the LOF study is this close collaboration between neurologist and geriatric psychiatrist. Patients suspected of bvFTD who did present with an (atypical) psychiatric condition were detected immediately at baseline whereby the number of patients diagnosed with ‘possible’ bvFTD was relatively low.

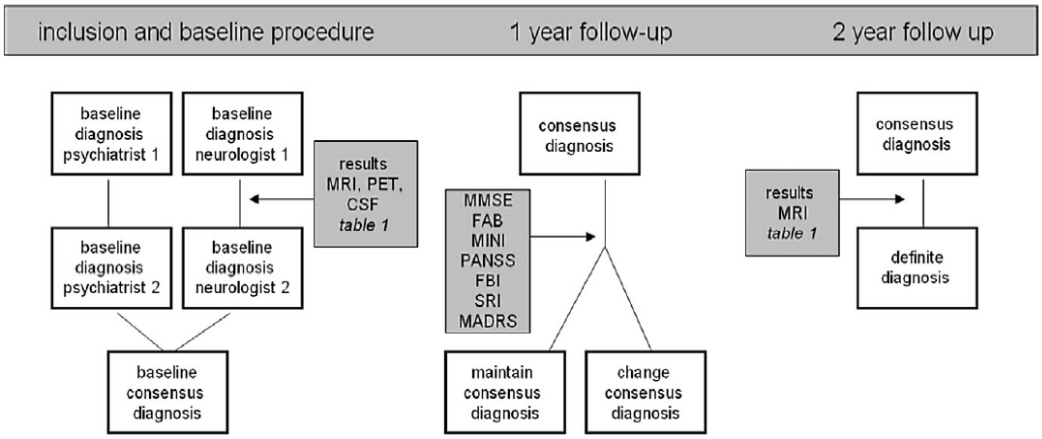

Figure 1. Diagnostic procedure in the late onset frontal lobe syndrome study

	bvFTD (n=55)	**Non-bvFTD (n=82)**	**p-value**
Age in years (SD)	62.7 (6.5)	61.9 (6.9)	0.440
Male sex, N (%)	63 (77)	35 (64)	0.122
Education in years, median (IQR)	10.0 (9.0-14.0)	10.0 (10.0-14.0)	0.448
Years of disease duration, median (IQR)	3.0 (2.0-6.5)	3.0 (2.0-4.0)	0.145

Table 3. Demographics of patients in the LOF study at baseline (n=137)
Difference between groups were tested using $X^{2,}$ and Mann-Whitney U test

Outline of the thesis

The first section focuses on the symptomatic overlap of bvFTD and psychiatric disorders. Chapter 2 of this thesis describes the frequency and character of DSM-IV psychiatric disorders among patients with probable and definite bvFTD compared to possible bvFTD, other neurodegenerative diseases, and psychiatric diagnoses, using MINI-International Neuropsychiatric Interview. We additionally study the frequency and character of past psychiatric disorders in these diagnostic groups. In chapter 3 we systematically and prospectively subtype the wide spectrum of psychotic symptoms in probable and definite bvFTD. We therefore employ a commonly used and validated clinical scale which quantifies the broad spectrum of psychotic symptoms (Positive and Negative Symptom Scale, PANSS) in patients with probable and definite bvFTD (n=22) and patients with a primary psychiatric disorder (n=35) in a late onset frontal lobe cohort.

The second section is aimed at the differentiation of behavioral variant frontotemporal dementia from other neurodegenerative diseases and psychiatric disorders. In chapter 4 we study whether social cognition distinguishes bvFTD from other neurodegenerative diseases and psychiatric disorders in patients presenting with late onset frontal symptoms. Next we study the association of social cognition with the other cognitive domains of executive functioning, memory, visuospatial functioning and attention/concentration/mental speed. Social cognition is determined by the *Ekman 60 Faces test* and *Faux Pas test*. In chapter 5 we examine the role of clinical and demographical variables in predicting psychiatric disorders versus bvFTD. In our late onset frontal lobe cohort odds ratios (OR) are calculated with logistic regression analyses for demographical variables and clinical variables measuring stereotypy and depressive symptoms and we define predictive values for these variables.

The third section describes different aspects of disease course in the late onset frontal lobe syndrome. In chapter 6 we investigate psychological and psychiatric conditions underlying the bvFTD phenocopy syndrome. We include patients with the bvFTD phenocopy syndrome whereby patients with probable bvFTD serve as a control group. Subjects have to have undergone both neurological and psychiatric evaluation. Their charts are reviewed retrospectively with both qualitative and quantitative methods. Psychiatric and psychological conditions associated with the clinical syndrome are determined in both groups and their relative frequencies are

compared. In chapter 7 we investigate predictors that can determine progression and thereby prognosis in patients presenting with late onset behavioral symptoms. Patients are included based on frontal behavior (*Frontal Behavior Inventory* score ≥ 11) or/and stereotypical behavior (*StereotypyRatingInventory* ≥ 10). Progression after 2 years is evaluated by clinical markers as well as repeated neuroimaging.

The fourth section is aimed at pharmacological interventions and care in the late onset frontal lobe syndrome. In chapter 8 we perform a systematic review on pharmacological treatment in patients with bvFTD. While a cure for bvFTD is still lacking, pharmacological treatment in frontotemporal dementia is focused on treating the symptoms, like reducing disinhibition, stereotypy and/or apathy. In this chapter, we present a systematic review on pharmacological interventions in bvFTD. In chapter 9 we describe an explorative pilot study in caregivers of early onset dementia patients with behavioral problems. While caregivers of dementia patients experience high levels of burden, especially caregivers of early onset dementia patients with behavioral problems, we perform a tailored intervention including psychoeducation, social support and behavioral cognitive therapy for caregivers of dementia patients affected by apathy, disinhibition and/or stereotypical behavior. The intervention is given during 6 months and quantitative and qualitative data are collected at baseline and after the intervention.

REFERENCES

1. Gossink FT, Dols A, Kerssens CJ, Scheltens P, Stek ML, Pijnenburg YAL. The behavioural variant of frontotemporal dementia. *Ned Tijdschr Geneeskd*. 2013;157(49).
2. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51(6):1546-1554. doi:10.1212/WNL.51.6.1546.
3. Englund, B. Brun, A. Gustafson, L. Passant, U. Mann, D. Neary, D., Snowden JS. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994;57(4):416-418.
4. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol*. 2001;58(11):1803-1809.
5. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
6. Knopman DS, Boeve BF, Parisi JE, et al. Antemortem diagnosis of frontotemporal lobar degeneration. *Ann Neurol*. 2005;57(4):480-488. doi:10.1002/ana.20425.
7. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007;64(6):830-835. doi:10.1001/archneur.64.6.830.
8. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. *Neurology*. 2009;72(8):732-737. doi:10.1212/01.wnl.0000343004.98599.45.
9. Pijnenburg YAL, Mulder JL, Van Swieten JC, et al. Diagnostic accuracy of consensus diagnostic criteria for frontotemporal dementia in a memory clinic population. *Dement Geriatr Cogn Disord*. 2008;25(2):157-164. doi:10.1159/000112852.
10. Rascovsky K, Hodges JR, Kipps CM, et al. Diagnostic Criteria for the Behavioral Variant of Frontotemporal Dementia (bvFTD): Current Limitations and Future Directions. *Alzheimer Dis Assoc Disord*. 2007;21(4):S14-S18. doi:10.1097/WAD.0b013e31815c3445.
11. Vandenberghe R. Sense and sensitivity of novel criteria for frontotemporal dementia. *Brain*. 2011;134(9):2450-2453. doi:10.1093/brain/awr208.
12. Krudop WA, Pijnenburg YAL. Historical evolution of the frontal lobe syndrome. *Psychopathology*. 2015. doi:10.1159/000381986.
13. Krudop WA, Bosman S, Geurts JJG, et al. Clinico-pathological correlations of the frontal lobe syndrome: Results of a large brain bank study. *Dement Geriatr Cogn Disord*. 2015. doi:10.1159/000430460.
14. Krudop WA, Kerssens CJ, Dols A, et al. Identifying bvFTD within the wide spectrum of late onset frontal lobe syndrome: A clinical approach. *Am J Geriatr Psychiatry*. 2015. doi:10.1016/j.jagp.2015.04.002.

15. Ossenkoppele R, Pijnenburg YAL, Perry DC, et al. The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain*. 2015;138(9):2732-2749. doi:10.1093/brain/awv191.
16. Woodward M, Jacova C, Black SE, et al. Differentiating the frontal variant of Alzheimer's disease. *Int J Geriatr Psychiatry*. 2010;25(7):732-738. doi:10.1002/gps.2415.
17. Blennerhassett R, Lillo P, Halliday GM, Hodges JR, Kril JJ. Distribution of pathology in frontal variant Alzheimer's disease. *J Alzheimer's Dis*. 2014;39(1):63-70. doi:10.3233/JAD-131241.
18. Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? *Neurology*. 1986;36(3):340-345. doi:10.1212/WNL.36.3.340.
19. Johns EK, Phillips N a, Belleville S, et al. Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*. 2009;23(6):765-777. doi:10.1037/a0016792.
20. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128. doi:10.1016/S1474-4422(09)70299-6.
21. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12(2):207-216. doi:10.1016/S1474-4422(12)70291-0.
22. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011. doi:10.4088/JCP.10m06382oli.
23. Kerstein AH, Schroeder RW, Baade LE, Lincoln J, Khan AY. Frontotemporal dementia mimicking bipolar disorder. *J Psychiatr Pract*. 2013;19(6):498-500. doi:10.1097/01.pra.0000438190.04786.16.
24. Cora J. Kerssens, Welmoed A. Krudop, Niels D. Prins, Bart N. M. van Berckel, Annemieke Rozemuller, William W. Seeley, Philip Scheltens MLS& YALP. Schizophrenia as a mimic of behavioral variant frontotemporal dementia. *Neurocase*. 2016. doi:10.1080/13554794.2016.1187178.
25. Roth RM, Flashman LA, Saykin AJ, McAllister TW, Vidaver R. Apathy in Schizophrenia: Reduced Frontal Lobe Volume and Neuropsychological Deficits. *Am J Psychiatry*. 2004;161(1):157-159. doi:10.1176/appi.ajp.161.1.157.
26. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in late-life depression: Common, persistent, and disabling. *Am J Geriatr Psychiatry*. 2015;23(5):488-494. doi:10.1016/j.jagp.2014.06.005.
27. Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE, Hawkins JM. Frontosubcortical neuroanatomy and the continuous performance test in mania. *Am J Psychiatry*. 1999;156(1):139-141. doi:http://dx.doi.org/10.1176/ajp.156.1.139.

28. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *Lancet*. 2009;374(9688):491-499. doi:10.1016/S0140-6736(09)60240-3.
29. Ames D, Chiu E, Lindesay J, Shulman KI. *Guide to the Psychiatry of Old Age*.; 2010. doi:10.1017/CBO9780511776984.
30. Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical Approach to the Differential Diagnosis Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders.
31. Shinagawa S, Catindig J, Block N, Miller B, Rankin K. When a little knowledge can be dangerous: False positive diagnosis of bvFTD among community clinicians. *Am J Neurodegener Dis*. 2014;3:374.
32. Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. doi:10.1136/jnnp-2015-310697.
33. Caceres BA, Frank MO, Jun J, Martelly MT, Sadarangani T, de Sales PC. Family caregivers of patients with frontotemporal dementia: An integrative review. *Int J Nurs Stud*. 2015;55:14. doi:10.1016/j.ijnurstu.2015.10.016.
34. Mourik JC, Rosso SM, Niermeijer MF, Duivenvoorden HJ, Van Swieten JC, Tibben A. Frontotemporal dementia: Behavioral symptoms and caregiver distress. *Dement Geriatr Cogn Disord*. 2004;18(3-4):299-306. doi:10.1159/000080123.
35. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: A review of the literature. *J Am Acad Nurse Pract*. 2008;20(8):423-428. doi:10.1111/j.1745-7599.2008.00342.x.
36. Ibanez A, Manes F. Contextual social cognition and the behavioral variant of frontotemporal dementia. *Neurology*. 2012;78(17):1354-1362. doi:10.1212/WNL.0b013e3182535d0c.
37. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.

Section 1. Behavioral variant frontotemporal dementia and psychiatric disorders

2. Formal psychiatric disorders are not overrepresented in behavioral variant Frontotemporal dementia

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ABSTRACT

Background

While psychiatric misdiagnosis is a well-known phenomenon in bvFTD, a systematic evaluation of standardised criteria for a psychiatric disorder in bvFTD is still missing.

Objective

Our aim was to define frequency and character of DSM-IV psychiatric disorders among patients with probable bvFTD compared to possible bvFTD, other neurodegenerative diseases, and psychiatric diagnoses, using MINI-International Neuropsychiatric Interview. We additionally compared psychiatric prodromes between these disorders.

Methods

Subjects were participants of the ongoing late-onset frontal lobe (LOF) study, a longitudinal multicentre study. In each patient, after baseline diagnostic procedure, a neurologist and geriatric psychiatrist made a joint clinical diagnosis. Independently, a structured diagnostic interview according to DSM-IV and ICD-10 criteria (MINI-Plus) was performed by a trained professional blinded to the clinical diagnosis.

Results

Out of 120 patients, 43 with probable bvFTD, 10 with possible bvFTD, 23 with a non bvFTD neurodegenerative disease and 44 with a clinical psychiatric diagnosis were included. Overall frequency of formal current and past psychiatric disorders in probable bvFTD (23.3% current, 20.9% past) did not differ from other neurodegenerative diseases (17.4% current, 13.0% past) or possible bvFTD (20.0% current, 40.0% past), but was less than in patients with a clinical psychiatric diagnosis (70.5% current, 68.2% past) ($P<0.01$). Unipolar mood disorders were most common psychiatric disorders in probable bvFTD.

Conclusion

Formally diagnosed psychiatric disorders are not overrepresented in probable bvFTD, suggesting that psychiatric misdiagnosis in bvFTD can be avoided by strictly applying diagnostic criteria. In suspected bvFTD close collaboration

between neurologists and psychiatrists will advance diagnostics and subsequent treatment.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is the most prevalent form of FTD and is associated with progressive degeneration of the frontal lobes, anterior temporal lobes, or both.[1 2] Alterations in social cognition represent the earliest and core symptoms of bvFTD resulting in emotional disengagement and socially inappropriate responses or activities. As is apparent in revised consortium criteria, neuropsychiatric symptoms including apathy, stereotyped and impulsive behaviour overshadow cognitive disabilities.[3 1 4 5] Consequently, both other neurodegenerative diseases and psychiatric disorders are crucial in the challenging differential diagnosis.

The distinction between bvFTD and Alzheimer's disease (AD) has become easier by the use of biomarkers that are able to identify underlying AD pathology, such as the amyloid-β (Aβ) and tau.[6 7] Differentiating bvFTD from psychiatric disorders however is still difficult, particularly since biomarkers for bvFTD are less robust.[8] However, the current clinical criteria require that "if behavioral disturbance is better accounted for by a psychiatric diagnosis, a diagnosis of bvFTD has to be excluded".[5] Previous studies indicate that as a result of symptomatic overlap between bvFTD and psychiatric disorders, bvFTD patients are clinically often mistaken for psychiatric patients and vice versa.[9 10 11 12] One study found that in comparison to other neurodegenerative diseases, bvFTD patients receive a prior psychiatric diagnosis significantly more often (50.7%) than patients with Alzheimer disease (23.1%), semantic dementia (24.4%) or progressive nonfluent aphasia (11.8%).[13] Although psychiatric misdiagnosis is a well-known phenomenon in bvFTD, a systematic evaluation of standardised criteria for a psychiatric disorder in bvFTD patients is still missing, potentially leading to a clinical under- or overestimation of psychiatric disorders in bvFTD patients. Additionally, though specifically psychotic disorders and bipolar disorders emerged as relatively common psychiatric misdiagnoses in bvFTD, this has never been systematically evaluated through applying the DSMIV and ICD-10 criteria.[11 13 14]

Recent studies showed increased rates of psychiatric symptoms prior to clinical Alzheimer's disease, suggesting that especially depressive symptoms appear before a threshold of neurodegeneration is passed.[15 16] A similar mechanism might be present in bvFTD, with the presence of prominent psychiatric and behavioral

symptoms before clinical onset of bvFTD described as mild behavioral impairment (MBI), but this has not been studied so far. [17] [18]

In this study we aimed at defining the frequency of current psychiatric disorders according to DSMIV and ICD-10 criteria in patients with probable bvFTD in comparison to patients with possible bvFTD, other neurodegenerative diseases, and psychiatric diagnoses, all exhibiting a late-onset frontal lobe syndrome. We also set out to determine the specific psychiatric disorders in these groups. Additionally we aimed at studying the frequency and character of past psychiatric disorders according to DSMIV and ICD-10 criteria in these groups.

MATERIALS AND METHODS

Patients

Subjects were participants of the ongoing late-onset frontal lobe (LOF) study, a longitudinal multicentre prospective follow-up study aiming to identify (prodromal) bvFTD among a cohort of patients with frontal neuropsychiatric features. An objective of the LOF study is to enforce early diagnosis of bvFTD and to discern the bvFTD prodrome from a broad spectrum of clinically relevant differential diagnosis.[19] All patients were recruited through the memory clinic of the Alzheimer center VUmc Amsterdam and the Old Age Psychiatry Department of GGZinGeest Amsterdam, the Netherlands (inpatient and outpatient) between April 2011 and June 2013. Patients were directed to these specialized health care institutions by primary care physicians or a medical specialist. Patients were only included if they were aged between 45 and 75 and if they had a Frontal Behavior Inventory score of 11 of higher and/or a Stereotype Rating Inventory of 10 or higher. Exclusion criteria were as follows: 1. an already established diagnosis of dementia or a psychiatric diagnosis that could explain behavior problems. 2. Mini Mental State Exam score less than 18. 3.traumatic brain injury, mental retardation or drug or alcohol abuse in medical history. 4. lack of reliable informant. 5. insufficient communicative skills of either patient or the closest informant 6. acute onset of behavioral problems. 7. clinically apparent aphasia or semantic dementia 8. MRI contra-indications.[19]

A total of 137 patients were included. Patients with other neurologic or general diseases like multiple sclerosis or obstructive sleep apnea but without a neurodegenerative or clinical psychiatric diagnosis were excluded in this study (n=8), as were patients with subjective complaints or relational problems without a

formal diagnosis (n=7). Two participants did not complete the MINI-Plus due to patients tiredness and logistic problems. The remaining 120 patients were included. Out of these patients 43 patients had probable bvFTD, 10 patients had possible bvFTD and 23 patients had another neurodegenerative disease. A total number of 44 patients received a clinical psychiatric diagnosis by the neurologist and the geriatric psychiatrist.

Diagnostic procedure

Before inclusion, informed consent was obtained from all participants or, in case of incompetence of giving a fully informed consent, obtained from the caregiver or legal representative. All patients underwent a standardized assessment, including medical history and family history, informant-based history, physical, neurological and psychiatric examinations, neuropsychological assessment, laboratory tests, and Magnetic Resonance Imaging (MRI) of the brain acquired on a 3T Signa HDxt scanner (GE Medical Systems, Milwaukee, WI) following a standard MRI protocol for dementia. In case of normal or insufficiently explanatory MRI results (not explaining frontosubcortical dysfunction), a [18F]FDG-PET scan was performed EXACT HRþ scanner (Siemens/CTI, Knoxville, TN). Neurological and psychiatric evaluation was done by both a neurologist as well as an experienced geriatric psychiatrist (YP,NP,PS,AD,CK,MS). In a multidisciplinary consensus meeting the neurologist and psychiatrist determined the diagnosis, specifically if a diagnosis of *probable bvFTD, possible bvFTD, other neurodegenerative disease* or a *psychiatric disorder* was applicable. Diagnoses were based on the National Institute on Aging- Alzheimer's Association guidelines for Alzheimer disease, the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l 'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia, the International Consensus Diagnostic Criteria for dementia with Lewy bodies, *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for psychiatric disorders and the International bvFTD Criteria Consortium criteria for bvFTD.[20 21 22 23] A diagnosis of possible bvFTD was only applied when a clinical psychiatric diagnosis was excluded.

Measurements

The MINI-International Neuropsychiatric Interview (MINI-Plus) is a structured diagnostic interview, developed to assess the psychiatric diagnoses of patients according to DSMIV and ICD-10 criteria. It contains 16 DSMIV psychiatric

disorders including inter alia unipolar and bipolar mood disorders, psychotic disorders like schizophrenia and anxiety and obsessive compulsive disorders. It does not include autism spectrum disorders and personality disorders besides the antisocial personality disorder. The MINI-International Neuropsychiatric Interview (MINI-Plus) incorporates both criteria for current psychiatric disorders according to DSMIV and ICD-10 (present psychiatric disorders) as well as criteria for past psychiatric disorders according to DSMIV and ICD-10 criteria (psychiatric disorders in previous history).

All included patients underwent a MINI-Plus interview, performed by trained clinicians who were blind for the clinical diagnosis (FG,WK). These clinicians did not have information about previous medical history neither other advance medical information. They worked separately from the clinicians involved in the diagnostic procedures. The MINI-Plus result was not included in the clinical evaluation.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows; IBM, Armonk, NY), version 21. Group differences on sociodemographic variables were investigated using independent t-tests and X^2tests. For the main analysis, the clinical diagnoses was the independent variable and the formal psychiatric disorder was the independent variable. Differences between groups for categorical variables were evaluated using X^2tests and Fisher's exact tests. A p-value of <0.05 was considered statistically significant, except otherwise indicated. After chi-square test of independence, post hoc Pearson chi-square analyses with Bonferroni correction were performed.

Ethical considerations

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam. All participants signed a written consent form.

RESULTS

Patient characteristics

Demographic data of the diagnostic groups are displayed in table 1. Patients were predominantly Caucasian (>90%) and male (> 60%). Regarding mean age at presentation, disease duration and gender, the groups did not differ *(*$p > 0.05$*).*

	Probable bvFTD n=43	Possible bvFTD n=10	OND n=23	Psychiatric diagnoses n=44	p value
Age (years) mean (SD)	62.4 (6.6)	61.4 (7.7)	63.5 (6.4)	61.1 (6.8)	*ANOVA* 0.91, df 27, F 0.64
Gender % male	65.1	80.0	65.2	77.3	X^2 0.51, df 3
Disease duration (years) mean (SD)	5.1 (5.1)	4.3 (3.7)	2.9 (2.3)	4.1 (4.6)	*ANOVA* 0.27, df 3, F 1.33

Table 1. Demographics.
OND other neurodegenerative disease, SD standard deviation

Fulfilment of DSMIV and ICD-10 criteria for current psychiatric disorder

The overall frequency of probable bvFTD patients who fulfilled criteria for a current psychiatric disorder according to DSMIV and ICD 10 criteria was 23.3%. This frequency did not differ from patients with other neurodegenerative diseases (17.4%) or possible bvFTD (20%), but was significantly lower than patients with a clinical psychiatric diagnosis (70.5%) ($p<0.01$) (table 2a).

Probable bvFTD patients fulfilled the formal criteria most common for unipolar mood disorders (13.9%) and anxiety and obsessive compulsive disorders (9.3%). Some patients fulfilled criteria for multiple psychiatric disorders according to DSMIV and IC-10 criteria at the same time.

Fulfilment of DSMIV and ICD-10 criteria for past psychiatric disorder

The overall frequency of any past psychiatric disorder according to DSMIV and ICD 10 criteria in probable bvFTD was 20.9%. This did not differ significantly from patients with other neurodegenerative diseases (13.0%) or possible bvFTD (40.0%), but was significantly less than patients with a clinical psychiatric diagnosis (68.2%) ($p<0.01$) (table 2b).

Unipolar mood disorders were by far the most prevalent past psychiatric disorder in probable bvFTD (16.3%), but this was not significantly different from patients with other neurodegenerative diseases or possible bvFTD. As shown in table 2b, some patients fulfilled DSMIV and ICD-10 criteria for multiple past psychiatric disorders.

	Probable bvFTD n=43	Possible bvFTD n=10	OND n=23	PDx n=44	p value		
					Probable bvFTD vs possible bvFTD	Probable bvFTD vs OND	Probable bvFTD vs PDx
Unipolar disorders n(%)	6 (13.9)	0 (0)	1 (4.3)	17 (38.6)	*F* 0.58, df 1	*F* 0.41, df 1	*F* 0.01, df 1
Bipolar disorders n(%)	1 (2.3)	1 (10.0)	0 (0)	8 (18.2)	*F* 0.35, df 1	*F* 1.00, df 1	*F* 0.03, df 1
Anxiety and OCD n (%)	4 (9.3)	1 (10.0)	0 (0)	8 (18.2)	*F* 1.00, df 1	*F* 0.29, df 1	*F* 0.35, df 1
Psychotic disorders n(%)	1 (2.3)	0 (0)	0 (0)	4 (9.1)	*F* 1.00, df 1	*F* 1.00, df 1	*F* 0.36, df 1
Somatoform disorders n(%)	1 (2.3)	0 (0)	1 (4.3)	0 (0)	*F* 1.00, df 1	*F* 1.00, df 1	*F* 0.49, df 1
Any psychiatric disorder n (%)	10 (23.3)	2 (20.0)	2 (17.4)	31 (70.5)	*F* 1.00, df 1	*F* 0.19, df 1	*F* <0.001**,**df 1

Table 2a. Current psychiatric disorder according to DSM IV criteria.
OND other neurodegenerative disease, OCD obsessive compulsive disorders, PDx= psychiatric diagnosis

DISCUSSION

Contrary to our expectations we found that despite large clinical symptomatic overlap between bvFTD and psychiatric disorders, formal psychiatric disorders are not overrepresented in probable bvFTD. Of 120 patients with a late-onset frontal syndrome, the overall frequency of psychiatric disorders according to DSMIV and ICD 10 criteria in 43 probable bvFTD patients (23.3%) did not differ from patients with other neurodegenerative diseases (n=23) or possible bvFTD (n=10), but was less than in patients with a clinical psychiatric diagnosis (n=44). Previous literature

showed that bvFTD is still underdiagnosed and often initially mistaken for psychiatric illnesses.[24] [25] [13] It was found that consensus criteria for bvFTD and other neurodegenerative diseases are crucial to differentiate bvFTD from other dementias, but psychiatric misdiagnoses must still be ruled out.[25] [26] In contrast to a previous study reporting that 50.7% of bvFTD patients receive a prior psychiatric diagnosis as found by retrospective chart review[13], our results show that correctly applying DSMIV and ICD-10 criteria in bvFTD gives a lower rate of formal psychiatric disorders in bvFTD (23.3%). This suggests that by correctly applying DSMIV and ICD-10 criteria in patients with suspected bvFTD, psychiatric misdiagnosis can be reduced.

The most common psychiatric disorders according to DSMIV and ICD-10 criteria that probable bvFTD patients fulfilled were unipolar mood disorders (13.9%). A recent meta-analysis including 29 studies showed that depressive mood and its manifestations are recognized in approximately one third (33%) of patients with bvFTD.[27] However, the majority of these studies about the prevalence of (comorbid) depression in bvFTD are based upon reports of depressed mood only.[28] Studies applying formal DSMIV and ICD-10 criteria are limited and suggest lower rates.[29] [30] Lopez et al. prospectively evaluated DSM-IIIR criteria in 20 patients with frontotemporal dementia (six autopsy-proven) and found that 25% (n=5) met DSM-III-R criteria of a major depression.[30] Gregory et al. found three bvFTD patients out of 15 who reported sadness, but only one met criteria for DSM-IV major depression.[29] The discrepancy between prevalence of depressive mood in bvFTD and the prevalence of depressive and dysthymic disorder according to DSMIV and ICD-10 criteria may highlight the risk of overdiagnosing depressive disorder in bvFTD when not using formal criteria.

Previous studies found that patients with bvFTD who are initially misdiagnosed with a psychiatric diagnosis are more likely to receive diagnoses of schizophrenia or bipolar disorder than patients with other neurodegenerative diseases.[11] [13] [14] The results of the current study show that by correctly applying DSMIV and ICD-10 criteria, the prevalence of these psychiatric disorders in bvFTD is not higher than in patients with other neurodegenerative diseases.

Regarding past psychiatric disorders, results show that patients with probable bvFTD fulfil DSMIV and ICD-10 criteria for a past psychiatric disorder less often than patients with a clinical psychiatric diagnosis (20.9% vs 68.2%), but remarkably not more than patients with other neurodegenerative diseases or

possible bvFTD. Previous studies suggested that many patients develop neuropsychiatric symptoms before impending dementia.[15 16] One study found that in the presence of cognitive decline, mild behavioral impairment (MBI) and neuropsychiatric symptoms have similar risks to convert to FTD as AD.[17] This is the first study about preceding psychiatric disorders according DSMIV and ICD-10 criteria in a frontal cohort, revealing that formal preceding psychiatric disorders are as present in bvFTD as in comparison to other neurodegenerative diseases, but not redundant.

In addition, we found that depression and dysthymic disorder were the most frequent past DSMIV and ICD-10 disorders among probable bvFTD patients. This is an intriguing result, especially in the context of recent findings about the prodromal phase of bvFTD and Alzheimer's disease. Mendez et al. already suggested that depression may be a prodrome of frontotemporal dementia and a possible familial risk factor.[28] Similar to studies of late-onset Alzheimer's disease and autosomal dominant Alzheimer's disease, our results suggest increased rates of depression prior to onset of bvFTD or when a threshold of neurodegeneration is passed.[15 16] These findings have implications for the early detection and treatment of patients with probable bvFTD and might influence pathogenic concepts on the concurrence of bvFTD and psychiatric disorders.

There are some limitations in this study. First of all, although the MINI- Plus for psychiatric diagnosis was performed from sections A till Z, autism spectrum disorders and personality disorders beside the antisocial personality disorder are not categorized in this interview. For this reason patients clinically diagnosed with a psychiatric diagnosis did not meet criteria for a DSMIV disorder in more than 70.5% of cases. It is conceivable that more bvFTD patients or patients with another neurodegenerative disease would meet criteria for a psychiatric disorder if the MINI-Plus interview included more personality disorders and autism spectrum disorders. Besides, the period of time from the clinical diagnosis to the past psychiatric disorder was not always exactly known. Future studies focusing on the prodromal phase of bvFTD are warranted to better understand whether these past psychiatric disorders represent a prodromal stage or comorbidity.

Acknowledging the limitations, this is the first study systematically and prospectively defining that formal psychiatric disorders are not overrepresented in probable bvFTD. Despite large clinical symptomatic overlap between bvFTD and psychiatric disorders, misdiagnosis in bvFTD can be limited by correctly applying diagnostic criteria for psychiatric disorders. In suspected bvFTD close

collaboration between neurologists and psychiatrists will advance diagnostics and treatment.

REFERENCES

1. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2006;77(1):4-7. doi:10.1136/jnnp.2005.072496.
2. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140-143. doi:10.1192/bjp.180.2.140.
3. Mendez MF, Perryman KM. Neuropsychiatric Features of Frontotemporal Dementia: Evaluation of Consensus Criteria and Review. *J Neuropsychiatry Clin NeurosciThe J Neuropsychiatry Clin Neurosci*. 2002;144(14):424-429. doi:10.1176/jnp.14.4.424.
4. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: Prevalence and review. *Dement Geriatr Cogn Disord*. 2008;25(3):206-211. doi:10.1159/000113418.
5. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
6. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128. doi:10.1016/S1474-4422(09)70299-6.
7. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12(2):207-216. doi:10.1016/S1474-4422(12)70291-0.
8. Pasquier F, Lebert F, Lavenu I, Guillaume B. The clinical picture of frontotemporal dementia: diagnosis and follow-up. *Dement Geriatr Cogn Disord*. 1999;10 Suppl 1(suppl 1):10-14. doi:51206.
9. Ducharme S, Dickerson BC, Larvie M, Price BH, et al. Differentiating frontotemporal dementia from catatonia: a complex neuropsychiatric challenge. *J Neuropsychiatry Clin Neurosci*. 2015;27(2):e174-e176. doi:10.1176/appi.neuropsych.14070157.
10. Gigi A, Pirrotta R, Kelley-Puskas M, Lazignac C, Damsa C. [Behavior disturbances in emergency psychiatry or fronto-temporal dementia diagnosis? A challenge for psychiatrists]. [French] Troubles du comportement aux urgences, ou demence fronto-temporale? Un defi pour les psychiatres. *Encephale*. 2006;32(5 Pt 1):775-780.
11. Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. *Br J Psychiatry*. 2009;194(4):298-305. doi:10.1192/bjp.bp.108.057034.

12. Gossink F, Dols A, Kerssens CJ, Scheltens P, Stek ML, Pijnenburg YA. [The behavioural variant of frontotemporal dementia: a challenging diagnosis]. *Ned Tijdschr Geneeskd*. 2013;157(42):A6370. http://www.ncbi.nlm.nih.gov/pubmed/24128597.

13. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011. doi:10.4088/JCP.10m06382oli.

14. Kerstein AH, Schroeder RW, Baade LE, Lincoln J, Khan AY. Frontotemporal dementia mimicking bipolar disorder. *J Psychiatr Pract*. 2013;19(6):498-500. doi:10.1097/01.pra.0000438190.04786.16.

15. Ringman JM, Liang LJ, Zhou Y, et al. Early behavioural changes in familial Alzheimer's disease in the Dominantly Inherited Alzheimer Network. *Brain*. 2015;138(4):1036-1045. doi:10.1093/brain/awv004.

16. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease : A longitudinal analysis. *Neurology*. 2015;84(6):617-622. doi:10.1212/WNL.0000000000001238.

17. Taragano FE, Allegri RF, Krupitzki H, et al. Mild behavioral impairment and risk of dementia: A prospective cohort study of 358 patients. *J Clin Psychiatry*. 2009;70(4):584-592. doi:10.4088/JCP.08m04181.

18. Hallam BJ, Silverberg ND, LaMarre AK, Mackenzie IRA, Feldman HH. Clinical Presentation of Prodromal Frontotemporal Dementia. *Am J Alzheimers Dis Other Demen*. 2008;22(6):456-467. doi:10.1177/1533317507308781.

19. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.

20. American Psychiatric Association. *DSM-IV*.; 2000.

21. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-260. doi:10.1212/WNL.43.2.250.

22. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.

23. Mckeith IG. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2006;66(September 2004):1455; author reply 1455. doi:10.1212/01.wnl.0000224698.67660.45.

24. Pasquier F, Deramecourt V, Lebert F. [From Pick's disease to frontotemporal dementia]. *Bull Acad Natl Med*. 2012;196(2):431-433. http://www.ncbi.nlm.nih.gov/pubmed/23420961.

25. Pasquier F. New behavioural variant FTD criteria and clinical practice. In: *Revue Neurologique*. Vol 169. ; 2013:799-805. doi:10.1016/j.neurol.2013.08.002.
26. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol*. 2010;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
27. Sepehry A, Chakrabarty T JC. Prevalence of depressive mood in frontotemporal dementia (FTD): a meta-analyses of studies from 2000 to present. *Alzheimer's &Dementia J Alzheimer's Assoc*. 2013;9(4):607.
28. Mendez MF, Lauterbach EC, Sampson SM. An Evidence-Based Review of the Psychopathology of Frontotemporal Dementia: A Report of the ANPA Committee on Research. *J Neuropsychiatry Clin Neurosci*. 2008;20(2):130-149. doi:10.1176/jnp.2008.20.2.130.
29. Gregory CA, Hodges JR. Frontotemporal dementia: Use of consensus criteria and prevalence of psychiatric features. *Neuropsychiatry, Neuropsychol Behav Neurol*. 1996;9(3):145-153.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1996208799.
30. Lopez OL, Gonzalez MP, Becker JT, Reynolds III CF, Sudilovsky A, DeKosky ST. Symptoms of depression and psychosis in Alzheimer's disease and frontotemporal dementia. Exploration of underlying mechanisms. *Neuropsychiatry, Neuropsychol Behav Neurol*. 1996;9(3).

3. Psychosis in behavioral variant frontotemporal dementia

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ABSTRACT

Background

Dementia is generally characterized by cognitive impairment which can be accompanied by psychotic symptoms. Visual hallucinations are a core feature of dementia with Lewy bodies and delusions are often seen in Alzheimer's disease. However, for bvFTD, studies into the broad spectrum of psychotic symptoms are still missing. The aim of the study was to systematically and prospectively subtype the wide spectrum of psychotic symptoms in probable and definite bvFTD.

Methods

We employed a commonly used and validated clinical scale which quantifies the broad spectrum of psychotic symptoms (Positive and Negative Symptom Scale, PANSS) in patients with probable and definite bvFTD (n=22) and patients with a primary psychiatric disorder (n=35) in a late onset frontal lobe cohort. Median symptom duration was 2.8 years and patients were prospectively followed over two-years.

Results

Delusions, hallucinatory behavior and suspiciousness were present in 22.7% of bvFTD patients, while the majority exhibited negative psychotic symptoms such as social and emotional withdrawal and blunted affect (95.5%) and formal thought disorders (81.8%). *Difficulty in abstract thinking* and *stereotypical thinking* (formal thought disorders) differentiated bvFTD from psychiatric disorders. The combined predictors *difficulty in abstract thinking, stereotypical thinking, anxiety, guilt feelings* and *tension* explained 75.4% of the variance in diagnosis of bvFTD versus psychiatric diagnoses ($p<0.001$).

Conclusions

Delusions, hallucinatory behavior and suspiciousness are present in one fifth of bvFTD patients, while negative psychotic symptoms such as social and emotional withdrawal, blunted affect, and formal thought disorders are more frequently present. This suggests that negative psychotic symptoms and formal thought disorders have an important role in the psychiatric misdiagnosis in bvFTD. Misdiagnosis in bvFTD might be reduced by systematically exploring the broad spectrum of psychiatric symptoms.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is the second most common early-onset dementia and the most prevalent form of frontotemporal lobar degeneration (FTLD).[1 2] The clinical presentation of bvFTD has a wide range of symptoms, including prominent neuropsychiatric symptoms that often mimic psychiatric disorders.[3 4] Various studies described the overlapping symptoms between bvFTD and psychiatric disorders resulting in frequent misdiagnoses, with psychosis as one of the most common.[5 6 7 8]

While in Alzheimer's disease delusions are often seen and visual hallucinations are a core feature of dementia with Lewy bodies, studies into the broad spectrum of psychotic symptoms in bvFTD are still missing.[9 10]As defined by classification criteria, symptoms of psychosis are divided into positive and negative symptoms and formal thought disorders.[11] Positive psychotic symptoms refer to an excess or distortion of normal functions (e.g, paranoia or hearing voices), negative symptoms reflect a diminution or loss of normal functions (e.g. reduced motivation or reduced emotion) and formal thought disorders implicit a disorganization of thought.[12 13 14]

Previous studies on psychotic symptoms in bvFTD were only focused on positive psychotic symptoms (hallucinations, delusions and paranoia) and found that these psychotic features were present in 10-32% of bvFTD patients.[3 15 16 17] Even though negative psychotic symptoms and formal thought disorders have led to frequent misdiagnosis of psychosis in bvFTD patients, comprehensive studies into the full spectrum of psychosis in bvFTD are lacking.[5 8 18 19 20] Whereas the distinction between bvFTD and psychiatric disorders is a major diagnostic dilemma especially in early stages of disease,[3,5, 21] knowledge about psychotic symptoms in bvFTD based on this common broad definition of psychosis cannot be omitted. From a diagnostic perspective, it would help the clinician in daily practice considerably when it is clarified whether specific psychotic symptoms distinct bvFTD from psychiatric disorders and vice versa.

The aim of our study was twofold. First, we investigated whether specific psychotic symptoms characterize bvFTD. Second, we studied whether despite clinical overlap, specific psychotic symptoms could distinguish bvFTD from a psychiatric disorder. We employed a commonly used and validated clinical scale for psychosis and schizophrenia symptoms (the Positive and Negative Symptom Scale-PANSS) which quantifies the broad spectrum of psychotic symptoms including positive and negative psychotic symptoms and formal thought

disorders.[21] As the PANSS is originally created to prospectively evaluate psychotic symptomatology over time, it also includes a general subscale, wherein symptoms such as tension and anxiety are included.[21 22] In this study we aimed to define psychotic symptoms in patients with probable and definite bvFTD in comparison to patients with a psychiatric disorder, all exhibiting a late-onset frontal lobe syndrome. At baseline we set out to determine the broad spectrum of psychotic symptoms including positive and negative psychotic symptoms, formal thought disorders and general symptoms. All patients were followed during a period of 2 years and the clinical diagnosis after 2 years was used as the gold standard.

METHODS

Patients

Subjects were participants of the late-onset frontal lobe (LOF) study, a longitudinal multicentre prospective follow-up study aiming to identify (prodromal) bvFTD among a cohort of patients with frontal neuropsychiatric features. All patients were recruited through the memory clinic of the Alzheimer Center VUmc Amsterdam and the Old Age Psychiatry Department of GGZinGeest Amsterdam, the Netherlands (inpatient and outpatient) between April 2011 and June 2013. Inclusion and exclusion criteria have been described previously.[21] Patients aged 45 and over were included when behavioral symptoms consisting of apathy, disinhibition, and/or compulsive behavior dominated the clinical picture.

Diagnostic procedure

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam. Before inclusion, informed consent was obtained from all participants or, in case of incompetence of giving a fully informed consent, obtained from the caregiver or legal representative. All patients underwent a standardized assessment, including medical history and family history, informant-based history, physical, neurological and psychiatric examinations, neuropsychological assessment, laboratory tests, and Magnetic Resonance Imaging (MRI) of the brain acquired on a 3T Signa HDxt scanner (GE Medical Systems, Milwaukee, WI) following a standard MRI protocol for dementia. In case of normal or insufficiently explanatory MRI results (not explaining frontosubcortical dysfunction), a [18F]FDG-PET scan was performed EXACT HRþ scanner (Siemens/CTI, Knoxville, TN). Neurological and psychiatric evaluation was done

by both a neurologist as well as an experienced geriatric psychiatrist. In a multidisciplinary consensus meeting the neurologist and psychiatrist determined the diagnosis. These diagnoses were based on *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for psychiatric disorders and the International bvFTD Criteria Consortium criteria for bvFTD.[11 25] All subjects were genetically screened for the presence of a C9orf repeat expansion, given the great symptomatic overlap with psychiatric disorders and long disease courses that have been described in this mutation type.[23 24] All patients received at least 2 years of clinical follow-up and the clinical diagnosis after 2 years was used as the gold standard.

In order to compare bvFTD with the most relevant diagnostic group concerning psychotic symptoms, out of all patients in the LOF study (n=137) we selected the group of patients with probable and definite bvFTD (n=22) and patients with a primary psychiatric disorder (n=35). Patients with other neurodegenerative, neurological or general diseases and patients with vascular cognitive impairment, relational problems or possible bvFTD were therefore not taken into account. We excluded fifteen patients who did not complete the PANSS, due to motivational and logistic problems. Out of 22 patients diagnosed with probable and definite bvFTD, 4 patients were diagnosed with *definite* bvFTD consisting of two C9orf72 hexanucleotide repeat expansion, one progranulin mutation and one histopathologically-confirmed tauopathy. Out of thirty-five patients with a clinical psychiatric diagnosis 2 patients had schizophrenia, 11 were diagnosed with a major depressive disorder, 4 with minor depressive disorder, 6 with a bipolar disorder, 3 with an autism spectrum disorder, 1 with obsessive compulsive disorder, 1 with a general anxiety disorder and 7 with personality problems.

Measurements

At baseline we measured 30 symptoms, including positive psychotic symptoms, negative psychotic symptoms, formal thought disorders and general psychopathology, in patients diagnosed with probable and definite bvFTD and patients diagnosed with a psychiatric disorder, using the *Positive and Negative Symptom Scale (PANSS).*[21] Of the 30 items included in the PANSS, 7 items represent *positive psychotic symptoms* (*Delusions, Conceptual disorganization, Hallucinatory behavior, Excitement, Grandiosity, Suspiciousness, Hostility*), 7 items represent *negative psychotic symptoms* (*Blunted affect, Emotional withdrawal, Poor rapport, Passive/apathetic social withdrawal, Difficulty in*

abstract thinking, Lack of spontaneity, Stereotypical thinking) and 16 items represent *general psychopathology* (*Somatic concern, Anxiety, Guilt feelings, Tension, Mannerisms & posturing, Depression, Motor retardation, Uncooperativeness, Unusual thought content, Disorientation, Poor attention, Lack of judgement/insight, Disturbance of volition, Poor impulse control, Preoccupation, Active social avoidance*). Formal thought disorders are defined by the items of *conceptual disorganization, difficulty in abstract thinking, lack of spontaneity and stereotypical thinking.*[21]

The *PANSS* is widely used in patients with neuropsychiatric symptoms and it has been found to have good sensitivity and specificity for psychosis and schizophrenia.[25 26 27]

The PANSS was administered as an approximately 45-minute clinical interview. Patients were rated by a trained clinician regarding the 30 different symptoms, based on the interview with the patient as well as reports of family members about how the patients had functioned during the last week.[21 22] The symptoms were rated on a 1-7 point scale whereby 1 represents the absence of symptoms and 7 corresponds with severe interference with daily live activities.[21 22] All included patients underwent the PANSS, performed by trained clinicians who were blind for the clinical diagnosis (WK, FG). These clinicians did not have information about previous medical history neither other advanced medical information. The PANSS scores were not included in the clinical evaluation.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows; IBM, Armonk, NY), version 21. Group differences on sociodemographic variables were investigated using independent t-tests and χ^2tests. Overall percentages of patients with psychotic symptoms were defined by counting all patients who had symptoms at the positive or negative subscale above score of $\geq$3, as a rating of 3 is indicative of a symptom whose presence is clearly established and interferes in day-to-day functioning.[28 22]

Group differences on symptoms of *PANSS* were measured with Mann-Whitney U test (MW). A p-value of <0.01 was considered statistically significant. Furthermore, we performed univariate logistic regression analyses with diagnosis as dependent variable. We selected variables showing p-values < 0.01 and in the next step we combined these variables into a multivariate model to investigate the explained variance. Potential multicollinearity was investigated for the

multivariable model using the variance inflation factor <5 for each of the independent variables in the multivariable model using linear regression analyses.

RESULTS

Clinical and demographic data

Demographic data of the diagnostic groups are displayed in table 1. Patients were predominantly Caucasian (>90%) and male (> 60%). Regarding symptom duration, education, the total score at the Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB) and Frontal Behavioral Inventory (FBI) the groups did not differ *(*p >0.05). Patients with probable and definite bvFTD were significantly older (p 0.03) and had a higher total score at the Stereotypy Rating Inventory (SRI) than patients with a psychiatric diagnosis (p <0.001).

Psychotic symptoms in bvFTD and psychiatric disorders

In 95.5% of patients with probable and definite bvFTD at least one of the psychotic symptoms was present (score ≥3) (table 1). BvFTD patients were not characterized by positive psychotic symptoms, but by negative psychotic symptoms and formal thought disorders (*blunted affect*, *emotional withdrawal*, *poor rapport*, *apathetic social withdrawal*, *difficulty in abstract thinking* and *stereotypical thinking*) and items from the general subscale (table 2). *Delusions*, *hallucinatory behavior* and *suspiciousness* were seen in 22.7% of bvFTD patients while the majority of bvFTD patients exhibited negative psychotic symptoms (95.5%) and formal thought disorders (81.8%) (table 1). In 97.1% of patients with a psychiatric disorder psychotic symptoms were present, both from the positive as well as the negative subscale (table 1). Symptoms from the general subscale were also present in patients with a psychiatric disorder (table 2).

	bvFTD n=22	Psychiatric diagnosis n=35	Statistics X^2/T-test/ MW (df) P value
Age, mean (SD)	63.04 (6.18)	58.95 (6.67)	0.84 (55) 0.03
Gender %male	63.64	80.00	1.87 (1) 0.17
Symptom duration, median (IQR)	3.00 (5.50)	3.00 (1.00)	0.68
Education, % low % middle % high	18.18 50.00 31.82	21.43 57.14 21.43	0.69 (2) 0.71
MMSE mean (SD)	26.14 (2.80)	25.91 (2.54)	0.36 (55) 0.76
FAB mean (SD)	14.29 (4.20)	15.41 (2.64)	0.11 (53) 0.23
SRI median (IQR)	16.50 (15.00)	4.00 (8.00)	<0.001
FBI mean (SD)	26.14 (10.86)	24.77 (8.70)	0.48 (55) 0.60
PANNS Total score mean (SD, range) Total positive subscale median (SD, range) Total negative subscale median (IQR, range) Total general subscale median (SD, range)	 59.5 (14.0, 35-87) 10.32 (2.9, 7-18) 21.0 (13.0, 8-34) 28.0 (6.1, 19-42)	 61.1 (13.6, 37-108) 11.66 (3.5, 7-25) 18.0 (6.0, 9-33) 32.0 (7.7, 18-58)	 0.03 (55) 0.67 0.36 (55) 0.14 MW 0.041 0.57 (55) 0.046
n (%) with psychotic symptoms (PANNS P N ≥3)	21 (95.5)	34 (97.1)	0.11 (1) 0.74
n (%) with delusions, hallucinatory behavior and/or suspiciousness [a]	5 (22.7)	15 (42.9)	2.40 (1) 0.12
n (%) negative psychotic symptoms [b]	21 (95.5)	34 (97.1)	0.11 (1) 0.74
n (%) with formal thought disorders [c]	18 (81.8)	23 (65.7)	1.74 (1) 0.19

Table 1. Demographics

Legend: SD=Standard Deviation, IQR=Inter Quartile Range, df=degrees of freedom, KW=Kruskal-Wallis Test, Education: low= less than four years of low or average level secondary education, middle= four years of low or average level secondary education, high= five years of high level secondary education or university degree, MMSE=Mini-Mental State Examination, FAB=Frontal Assessment Battery, SRI=Stereotypy Rating Inventory, FBI=Frontal Behavioral Inventory a PANSS P1, P3 and/or P6 ≥ 3, b PANSS N≥ 3, c PANSS P2, N5, N6 and/or N7 ≥ 3

Psychotic symptoms in bvFTD versus psychiatric disorders

The total score of the positive subscale of the PANSS was not different between bvFTD patients and patients with a psychiatric disorder. The total score of the negative subscale of the PANSS was significantly higher in patients with bvFTD than in patients with a psychiatric disorder (21.0 versus 18.0, p 0.041) (table 1)

Using logistic regression, a diagnosis of probable or definite bvFTD was associated with difficulty in abstract thinking (OR 1.86, 95% CI 1.22-2.84, p 0.004) and stereotypical thinking (OR 1.83, 95% CI 1.21-2.76, p 0.004), which both represent formal thought disorders. These symptoms distinguished patients with bvFTD from patients with a psychiatric disorder (table 3).

General psychopathological symptoms in bvFTD versus psychiatric disorders

Specific symptoms from the general subscale of the PANSS did not distinguish patients with probable and definite bvFTD from patients with a psychiatric disorder. Nonetheless, the total score of the general subscale of the PANSS was significantly higher in patients with a psychiatric disorder than in bvFTD (32.0 versus 28.0, p 0.046). Patients with a psychiatric disorder were characterized by anxiety (OR 0.32, 95% CI 0.14-0.72, p 0.006), guilt feelings (OR 0.41, 95% CI 0.20 -0.84, p 0.015) and tension (OR 0.26, 95% CI 0.12- 0.58, p 0.001) which distinguished them from bvFTD patients.

Symptoms median (IQR) range	bvFTD n=22	Pdx n=35	p value
Positive psychotic symptoms			
P1 *Delusions*	1 (0) 1-3	1 (1) 1-5	MW=0.05
P2 *Conceptual disorganisation*	2 (2) 1-4	1 (2) 1-5	MW=0.18
P3 *Hallucinatory behavior*	1 (0) 1-2	1 (0) 1-4	MW=0.54
P4 *Excitement*	1 (2) 1-4	3 (2) 1-4	MW=0.03
P5 *Grandiosity*	1 (1) 1-4	1 (0) 1-3	MW=0.02
P6 *Suspiciousness*	1 (0) 1-4	2 (2) 1-5	MW=0.05
P7 *Hostility*	1 (0) 1-3	1 (1) 1-3	MW=0.03
Negative psychotic symptoms			
N1 *Blunted affect*	3 (2) 1-7	3 (1) 1-7	MW=0.78
N2 *Emotional withdrawal*	3 (1) 1-6	3 (1) 1-6	MW=0.78
N3 *Poor rapport*	4 (3) 1-6	3 (1) 1-6	MW=0.10
N4 *Apathetic social withdrawal*	3 (2) 1-5	3 (2) 1-6	MW=0.56
N5 *Difficulty in abstract thinking*	3 (3) 1-6	1 (2) 1-4	**MW=0.004**
N6 *Lack of spontaneity*	1 (3) 1-5	1 (1) 1-5	MW=0.41
N7 *Stereotypical thinking*	3 (4) 1-7	1 (1) 1-5	**MW=0.005**
General subscale			
G1 *Somatic concern*	1 (1) 1-5	1 (2) 1-6	MW=0.37
G2 *Anxiety*	1 (0) 1-3	2 (2) 1-5	**MW=0.001**
G3 *Guilt feelings*	1 (0) 1-3	2 (2) 1-6	**MW=0.003**
G4 *Tension*	1 (0) 1-3	3 (2) 1-6	**MW=0.000**
G5 *Mannerisms& posturing*	1 (0) 1-3	1 (0) 1-3	MW=0.74
G6 *Depression*	1 (2) 1-5	3 (4) 1-7	MW=0.015
G7 *Motor retardation*	1 (2) 1-4	1 (2) 1-4	MW=0.78
G8 *Uncooperativeness*	1 (2) 1-5	1 (1) 1-4	MW=0.82
G9 *Unusual thought content*	1 (0) 1-3	1 (0) 1-3	MW=0.81
G10 *Disorientation*	1 (0) 1-6	1 (1) 1-3	MW=0.57
G11 *Poor attention*	1 (1) 1-4	1 (2) 1-5	MW=0.69
G12 *Lack of judgement/insight*	3 (1) 1-6	3 (2) 1-6	MW=0.02
G13 *Disturbance of volition*	1 (2) 1-4	1 (0) 1-5	MW=0.64
G14 *Poor impulse control*	3 (2) 1-5	3 (1) 1-5	MW=0.34
G15 *Preoccupation*	3 (3) 1-5	2 (2) 1-5	MW=0.12
G16 *Active social avoidance*	1 (2) 1-3	2 (2) 1-6	MW=0.15

Table 2. Psychotic symptoms in bvFTD patients and patients with a psychiatric diagnosis
Legend: MW= Mann-Whitney U test, Pdx= Psychiatric diagnosis

Predictive symptoms

The combined predictors difficulty in abstract thinking, stereotypical thinking, anxiety, guilt feeling and tension explained 75.4% of the variance in diagnosis of bvFTD versus psychiatric diagnoses (χ 32.26, df 5, $p<0.001$).

Multivariate logistic regression showed that patients with an increased tension (score ≥ 3) had a significant higher chance of having a psychiatric disorder and a lower chance of having bvFTD (OR 0.18, 95% CI 0.05 – 0.75, p 0.02).

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	p	OR (95%CI)	p
Difficulty in abstract thinking	**1.86 (1.22 - 2.84)**	**0.004**	1.62 (0.84 – 3.12)	0.15
Stereotyped thinking	**1.83 (1.21 - 2.76)**	**0.004**	1.74 (0.82 – 3.68)	0.15
Anxiety	**0.32 (0.14 – 0.72)**	**0.006**	1.77 (0.44 – 7.09)	0.42
Guilt feeling	**0.41 (0.20 – 0.84)**	**0.015**	0.53 (0.23 – 1.23)	0.14
Tension	**0.26 (0.12 – 0.58)**	**0.001**	**0.18 (0.05 – 0.75)**	**0.02**

Table 3. Univariate logistic regression and forward multivariate logistic regression
Dependent Variable: Psychiatric diagnosis =0, Probable and definite bvFTD= 1

DISCUSSION

This is the first study thoroughly exploring the broad spectrum of psychotic symptoms in bvFTD, revealing that 95.5% of bvFTD patients exhibits at least one psychotic symptom, although not commonly the typical positive psychotic symptoms (delusions, hallucinations and suspiciousness) but formal thought disorders and negative psychotic symptoms such as social and emotional withdrawal and blunted affect. *Difficulty in abstract thinking* and *stereotypical thinking* differentiated bvFTD patients from patients with a psychiatric diagnosis in this well phenotyped cohort of patients exhibiting a frontal lobe syndrome. Patients with a psychiatric diagnosis were characterized by the presence of *anxiety*, *guilt*

feelings and *tension* (general subscale), which distinguished them from bvFTD patients.

Despite frequent misdiagnosis with schizophrenia, the finding that bvFTD patients are not mainly characterized by typical positive psychotic symptoms (hallucinations, delusions and suspiciousness/ paranoia) is partially in line with previous studies. It has been found that although frontotemporal dementia can mimic schizophrenia, it rarely manifests with delusions and hallucinations.[17 29 30 31] In a clinicopathological investigation and review of cases it was found that delusions, hallucinations and paranoia are mainly present in young-onset frontotemporal dementia (in up to a third of bvFTD patients aged 30 years or under).[3] This may partly explain why we found a lower prevalence (22.7%) in our cohort, which was characterized by a higher mean age of bvFTD patients (58.95 years). A recent retrospective study about delusions, hallucinations and paranoid ideas in neuropathologically verified bvFTD patients also revealed a relatively high prevalence of these positive psychotic symptoms (32%): 20.6% of patients had paranoid ideas, and 17.5% had hallucinations and delusions in equal measure.[15] As discussed by the authors of this study, psychotic symptoms may be present during a short period only or occur later during disease course thereby explaining the relative high rates in their retrospective study. The variation in the prevalence of positive psychotic symptoms in different studies may also be associated with sample size. An association with the amount of genetic mutations cannot be excluded. Psychotic symptoms have repeatedly been described in progranulin and C9ORF72 mutation carriers.[32 33 34] As the present study cohort contained only three patients with a genetic mutation (13.6% of bvFTD patients), the percentage of known genetic variants was lower compared to other studies (percentages of approximately 20-50% of hereditary etiologies found in other studies).[32 33]

It is noteworthy that our bvFTD patients tend to have a lower total score at the positive subscale of the PANSS than found in studies into schizophrenia (respectively 9.5 in our bvFTD patients versus 18.2 in schizophrenia patients).[21 22]This suggests that these positive psychotic symptoms are not the most prominent symptoms in the clinical overlap of bvFTD and psychotic disorders.

Interestingly, we found that the median score on the negative subscale of the PANSS was significantly higher in patients with bvFTD than in patients with a psychiatric diagnosis (predominantly mood disorders) in our late onset frontal lobe cohort, but comparable to patients with schizophrenia as measured previously.[21 22]

[27] This finding suggests that negative psychotic symptoms may have an important contributory role in psychotic misdiagnosis in bvFTD.
With a closer look at the specific negative psychotic symptoms that characterize bvFTD we saw that the presence of *blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, difficulty in abstract thinking* and *stereotypical thinking* characterize bvFTD. It has been described previously that stereotypies or compulsive acts are often among the earliest and most salient presenting symptom of bvFTD and these symptoms evolved into the FTDC consensus criteria.[35] [36] Impairment of abstract thinking in bvFTD patients has been described previously as associated with the cognitive profile of predominately executive dysfunction in bvFTD.[37] The discriminatory power of stereotypical thinking in bvFTD versus psychiatric disorders also fits with our finding concerning the total scores at the *Stereotypical Rating Inventory* (SRI) as discriminating between bvFTD patients and patients with a psychiatric disorder, and with previous studies regarding the *Stereotypical Rating Inventory* in a similar cohort (submitted Vijverberg et al., 2016*)*.

Beyond the original aim of our study, we found that patients with a psychiatric diagnosis had a higher total score at the general subscale of the PANSS and that the presence of *anxiety, guilt feelings* and *tension* distinguished psychiatric patients from bvFTD patients in this late onset frontal lobe syndrome cohort. This suits with previous findings about psychiatric disorders, especially in mood disorders and anxiety disorders as these features are all expressions of distress.[38] [39] [40] This is the first time tension has been found as a predictor for a psychiatric diagnosis in a group of patients with late onset behavioral disturbances. The low tension in bvFTD is probable associated with lack of distress of bvFTD patients.[2] Impaired insight has been described as typical for bvFTD, and this also includes impairment in emotional awareness as defined by the lack of expression of concern of distress when confronted by difficulties.[2]

There are some limitations in this study. First of all, from our study we cannot draw conclusions about psychotic symptoms that differentiate bvFTD from schizophrenia. This limitation arises from the heterogeneity of the psychiatric patient group and the small number of schizophrenia patients in the LOF cohort. This is a consequence of our design which is symptom-based instead of aetiology-based. Nevertheless, we are also convinced that this symptom-based design is a

strength as it resembles clinical practice. Besides, it has been acknowledged that there is an overrepresentation of psychotic symptoms in bvFTD with a known genetic background.[23 32] We see it as a strength that our cohort represents daily clinical practice as it was not enriched for genetic bvFTD. As a consequence, only three patients with a genetic mutation were included in the cohort, and it was not possible to do statistical analyses on these patients in particular. Another limitation is that neuropathological confirmation was obtained in only one bvFTD case. The diagnostically gold standard of two years approximates diagnostic certainty but misdiagnosis after two years of diagnostic follow up cannot be excluded.

Acknowledging the limitations, this is the first study systematically and prospectively subtyping the broad spectrum of psychotic and general symptoms in bvFTD patients and patients with a psychiatric diagnosis within a late onset frontal lobe cohort. Our data indicate that classic psychotic symptoms are infrequently present in bvFTD, however negative psychotic symptoms such as social and emotional withdrawal and blunted affect and formal thought disorders are present. It suggests that negative psychotic symptoms may contribute to the pitfall of psychotic misdiagnosis in bvFTD. From the negative subscale of the PANSS *difficulty in abstract thinking* and *stereotypical thinking* are associated with probable and definite bvFTD while *anxiety*, *guilt feeling* and *tension* (general subscale) are associated with a psychiatric diagnosis. The combinations of these symptoms explained three-quarter of the variance in diagnosis of bvFTD versus psychiatric diagnoses. Misdiagnosis in bvFTD can therefore be reduced by systematically exploring the broad spectrum of psychiatric symptoms.

REFERENCES

1. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2006;77(1):4-7. doi:10.1136/jnnp.2005.072496.
2. Snowden JS. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140-143. doi:10.1192/bjp.180.2.140.
3. Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. *Br J Psychiatry*. 2009;194(4):298-305. doi:10.1192/bjp.bp.108.057034.
4. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol*. 2010;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
5. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011;72(2):126-133. doi:10.4088/JCP.10m06382oli.
6. Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical Approach to the Differential Diagnosis Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders.
7. Da Ponte G, Paiva A LM et al. Mania like symptoms in frontotemporal dementia. *Eur Psychiatry*. 2010;25(563).
8. Stone J, Griffiths TD RS. Non-Pick's frontotemporal dementia imitating schizophrenia in a 22-year-old man. *J Neurol*. 2003;250:369-370.
9. Ropacki SA, Jeste D V. Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry*. 2005;162(11):2022-2030. doi:10.1176/appi.ajp.162.11.2022.
10. Cagnin A, Gnoato F, Jelcic N, et al. Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry*. 2012:1-6. doi:10.1136/jnnp-2012-304095.
11. American Psychiatric Association. *DSM-IV*.; 2000.
12. Gaebel W, Zielasek J. Focus on psychosis. *Dialogues Clin Neurosci*. 2015;17(1):9-18. doi:10.1097/BOR.0b013e32834b5457.
13. Harvey PD WE. *Positive and Negative Symptoms in Psychosis: Description, Research, and Future Directions*. Routledge
14. Holshausen K, Harvey PD, Elvevåg B, Foltz PW, Bowie CR. Latent semantic variables are associated with formal thought disorder and adaptive behavior in older inpatients with schizophrenia. *Cortex*. 2014;55(1):88-96. doi:10.1016/j.cortex.2013.02.006.

15. Waldö ML, Gustafson L, Passant U, Englund E. Psychotic symptoms in frontotemporal dementia: a diagnostic dilemma? *Int Psychogeriatrics*. 2015;27(4):531-539. doi:10.1017/S1041610214002580.

16. Mendez MF, Perryman KM. Neuropsychiatric Features of Frontotemporal Dementia: Evaluation of Consensus Criteria and Review. *J Neuropsychiatry Clin NeurosciThe J Neuropsychiatry Clin Neurosci*. 2002;144(14):424-429. doi:10.1176/jnp.14.4.424.

17. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: Prevalence and review. *Dement Geriatr Cogn Disord*. 2008;25(3):206-211. doi:10.1159/000113418.

18. Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal Dementias: A Review. *Ann Gen Psychiatry*. 2007;6(1):15. doi:10.1186/1744-859X-6-15.

19. Swartz JR, Miller BL, Lesser IM, et al. Behavioral phenomenology in Alzheimer's disease, frontotemporal dementia, and late-life depression: a retrospective analysis. *J Geriatr Psychiatry Neurol*. 1997;10(2):67-74. doi:10.1177/089198879701000206.

20. Khan BK, Woolley JD CS et al. Schizophrenia or neurodegenerative disease prodrome? Outcome of a first psychotic episode in a 35-year old woman. *Psychosomatics*. 2012;53(280).

21. Kay SR, Fiszbein A OL. The Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276. doi:10.1093/schbul/13.2.261.

22. Kay SR, Opler LA FA. *Positive and Negative Syndrome Scale (PANSS) Rating Manual*. Social and Behavioral Sciences Documents.; 2007.

23. Galimberti D, Fenoglio C, Serpente M, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: Late-onset psychotic clinical presentation. *Biol Psychiatry*. 2013;74(5):384-391. doi:10.1016/j.biopsych.2013.01.031.

24. Shinagawa S, Naasan G, Karydas a. M, et al. Clinicopathological Study of Patients With C9ORF72-Associated Frontotemporal Dementia Presenting With Delusions. *J Geriatr Psychiatry Neurol*. 2014;28(2):99-107. doi:10.1177/0891988714554710.

25. Keshavan MS, Rabinowitz J, Desmedt G, Harvey PD, Schooler N. Correlates of insight in first episode psychosis. *Schizophr Res*. 2004;70(2-3):187-194. doi:10.1016/j.schres.2003.11.007.

26. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

27. Milak MS, Aniskin DB ED et al. The negative syndrome as a dimension: factor analyses of PANSS in major depressive disorder and organic brain disease compared with negative syndrome structures found in the schizophrenia literature. *Cogn Behav Neurol*. 2007;20:113-120.

28. Figuerido JL, Gutierrez M, Gonzalez Pinto A, et al. [Predictors of rehospitalization in schizophrenia]. *Predict rehospitalizacion en la esquizofrenia*. 1997;25(4):217-224.

29. Le Ber I, Guedj E GA et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain*. 2006.
30. Gregory CA. Frontal variant of frontotemporal dementia: a cross-sectional and longitudinal study of neuropsychiatric features. *Psychol Med*. 1999;29(5):S0033291799008934. doi:10.1017/S0033291799008934.
31. Passant U, Elfgren C, Englund E, Gustafson L. Psychiatric symptoms and their psychosocial consequences in frontotemporal dementia. *Alzheimer Dis Assoc Disord*. 2005;19 Suppl 1(3950):S15-S18.
32. Kertesz A, Cyn Ang L, Jesso S, et al. Psychosis and Hallucinations in FTD with C9ORF72 mutation: A detailed clinical cohort. *Cogn Behav Neurol*. 2013;26(3):146-154. doi:10.1097/WNN.0000000000000008.
33. Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009;73(18):1451-1456. doi:10.1212/WNL.0b013e3181bf997a.
34. Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol*. 2011;24(6):542-549. doi:Doi 10.1097/Wco.0b013e32834cd442.
35. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
36. Luzzi S, Fabi K, Pesallaccia M, Cafazzo V, Silvestrini M PL. To clap or not to clap? Applause sign in apathetic and disinhibited/stereotypical behavioural variants of FTD. *J Neurol Neurosurg Psychiatry*. 2014.
37. Poletti M, Lucetti C, Logi C, et al. Cognitive correlates of negative symptoms in behavioral variant frontotemporal dementia: implications for the frontal lobe syndrome. *Neurol Sci*. 2013;34(11):1893-1896. doi:10.1007/s10072-013-1400-2.
38. Watson D, Clark LA, Carey G. Positive and negative affectivity and their relation to anxiety and depressive disorders. *J Abnorm Psychol*. 1988;97(3):346-353.
39. Gilbert P. The relationship of shame, social anxiety and depression: the role of the evaluation of social rank. *Clin Psychol Psychother*. 2000;7(3):174-189. doi:10.1002/1099-0879(200007)7:3
40. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. *Int Classif*. 1992;10:1-267.

Section 2. Differentiating behavioral variant frontotemporal dementia from other neurodegenerative diseases and psychiatric disorders

4. Social cognition differentiates behavioural variant frontotemporal dementia from other neurodegenerative diseases and psychiatric disorders

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ABSTRACT

Introduction

While deficits in social cognition are established as core features in bvFTD, it remains unresolved if impaired social cognition distinguishes bvFTD from the broad differential diagnosis in clinical practice. Our aim was to study whether social cognition discriminates bvFTD from other neurodegenerative diseases and psychiatric disorders in patients presenting with late onset frontal symptoms. Next we studied the association of social cognition with frontal symptoms and cognitive functioning.

Methods

In this longitudinal multicenter study, besides clinical rating scales for frontal symptoms, social cognition was determined by the *Ekman 60 Faces test* and *Faux Pas* in addition to neuropsychological tests for other cognitive domains in patients with probable and definite bvFTD (n=22), other neurodegenerative diseases (n=24) and psychiatric disorders (n=33). Median symptom duration was 2.8 years and patients were prospectively followed over two-years.

Results

Total scores at *Ekman 60 Faces test* were significantly lower in bvFTD than in other neurodegenerative diseases and psychiatric disorders. *Ekman 60 Faces test* explained 91.2% of the variance of psychiatric disorders and other neurodegenerative diseases versus bvFTD (χ 11.02, df 1, p 0.001) and was associated with all other cognitive domains. *Faux Pas* and the other cognitive domains did not differ between these diagnostic groups.

Conclusion

In this clinical sample the *Ekman 60 Faces test* distinguished bvFTD successfully from other neurodegenerative diseases and psychiatric disorders. Although associated to social cognition, other cognitive domains were not discriminative. This study provides arguments to add the *Ekman 60 Faces test* to the neuropsychological examination in the diagnostic procedure of bvFTD.

INTRODUCTION

The behavioural variant of frontotemporal dementia (bvFTD) is an insidious neurodegenerative disorder associated with progressive degeneration of the frontal lobes, anterior temporal lobes, or both.[1 2] The disease is a leading cause of early-onset dementia and the third most common form of dementia across all age groups.[3 4] Alterations in social cognition represent the earliest and core symptoms of bvFTD resulting in emotional disengagement and socially inappropriate responses or activities.[5 6 7] As part of their impaired social cognition, bvFTD patients are often unconcerned about their relatives, unable to adjust to their environment, lacking moral restraint, and unable to recognize and attribute mental states to self and others. Consequently, dissolution of social attachment can be profound and the implications on patients' life and their relatives are far-reaching.[8 9 10]

In clinical practice, both other neurodegenerative diseases and psychiatric disorders are crucial in bvFTD's challenging differential diagnosis. Whereas the distinction between bvFTD and Alzheimer's disease (AD) has become easier by the use of biomarkers indicative of underlying amyloid pathology, differentiation of bvFTD from psychiatric disorders is still challenging, particularly when imaging results are not supportive.[11 12 13] In clinical practice, impaired social cognition may point to bvFTD but other neurodegenerative diseases and psychiatric disorders can be associated with diminished social cognition as well. [7 14 15 16] Whilst findings on social cognition in AD are inconsistent, deficits in recognizing emotional expressions in AD were found in more than one study.[14 17] It was also found that social cognition can be impaired in various psychiatric disorders, such as schizophrenia, autism and bipolar disorder.[15 18 19 20 21]

The clinical dilemma is that although deficits in social cognition are a core feature in bvFTD,[2 7 22] it is still unresolved if an impairment of this cognitive domain discriminates bvFTD from patients with other neurodegenerative diseases and patients with a psychiatric disorder in clinical practice. Previous studies with comparisons between diagnostic groups were aimed at the comparison between bvFTD and healthy controls, AD patients or specific psychiatric disorders only.[8 23 24 25 26] A comparison of social cognition between bvFTD and all clinically relevant differential diagnoses has never been performed, though all important in daily practice.[8] In addition, the diagnostic value of specific instruments testing social

cognition within this differential diagnosis is needed but has not been elucidated so far.

Besides social cognition, studies into cognitive function in bvFTD show that executive deficits are considered a core feature in bvFTD as well.[27 28 29] Revised consortium criteria emphasize that the neuropsychological profile in bvFTD is characterized by "deficits in executive tasks and relative sparing of episodic memory and visuospatial skills". [27] In this respect, it is interesting to know if social cognition in bvFTD is related to executive functioning or possibly to other cognitive domains. Moreover, for clinical practice it is relevant to have knowledge if social cognition is associated with other cognitive domains or specific clinical parameters.

Our study had three aims. First, we investigated how social cognition is characterized in patients with probable and definite bvFTD as measured by *Ekman 60 Faces test* and *Faux Pas*, and if these tests discriminate bvFTD from patients with other neurodegenerative diseases and patients with a psychiatric disorder in a late onset frontal lobe syndrome cohort. The *Ekman 60 Faces test* and *Faux Pas* are common instruments for the measurement of social cognition.[8 30] Second, as other cognitive domains including *executive functioning*, *memory*, *visuospatial functioning and attention/concentration/mental speed* are often tested in neuropsychological examinations, we studied if social cognition is associated with these cognitive domains and if these other domains distinguished bvFTD from patients with other neurodegenerative diseases and patients with a psychiatric disorder.[27 31 32] Next we studied the association of frontal behavioural symptoms and social cognition.

METHODS

Patients

Subjects were participants of the late-onset frontal lobe (LOF) study, a longitudinal multicentre prospective follow-up study aiming to identify (prodromal) bvFTD among a cohort of patients with frontal neuropsychiatric features. All patients were recruited through the memory clinic of the Alzheimer Center VUmc Amsterdam and the Old Age Psychiatry Department of GGZinGeest Amsterdam, the Netherlands (inpatient and outpatient) between April 2011 and June 2013. Inclusion and exclusion criteria have been described previously.[33] Patients aged

between 45 and 75 years were included when behavioural symptoms consisting of apathy, disinhibition, and/or compulsive behaviour dominated the clinical picture.

Diagnostic procedure

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam. Before inclusion, informed consent was obtained from all participants or, in case of incompetence of giving a fully informed consent, obtained from the caregiver or legal representative. All patients underwent a standardized assessment, including medical history and family history, informant-based history, physical, neurological and psychiatric examinations, neuropsychological assessment, laboratory tests, and Magnetic Resonance Imaging (MRI) of the brain acquired on a 3T Signa HDxt scanner (GE Medical Systems, Milwaukee, WI) following a standard MRI protocol for dementia. In case of normal or insufficiently explanatory MRI results (not explaining frontosubcortical dysfunction), a [18F]FDG-PET scan was performed EXACT HRþ scanner (Siemens/CTI, Knoxville, TN). Both a neurologist as well as an experienced geriatric psychiatrist performed a clinical evaluation. In a multidisciplinary consensus meeting the neurologist and psychiatrist together determined the diagnosis. Diagnoses were based on the National Institute on Aging- Alzheimer's Association guidelines for Alzheimer disease, the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l 'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia, the International Consensus Diagnostic Criteria for dementia with Lewy bodies, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for psychiatric disorders, and the International bvFTD Criteria Consortium criteria for bvFTD. [11 34 35 36 11] Included subjects were genetically screened, especially for C9orf repeat expansion, given the great symptomatic overlap with psychiatric disorders and long disease courses that have been described in this mutation type.[37] All patients were diagnostically followed during a period of at least 2 years and the clinical diagnosis after 2 years was used as the golden standard.

Out of all patients in the LOF study (n=137) we included 22 patients with probable and definite bvFTD, 24 patients with other neurodegenerative diseases and 33 patients with a psychiatric disorder. We excluded 4 patients with probable bvFTD, 3 patients with other neurodegenerative diseases and 8 patients with a psychiatric disorder who did not complete the *Ekman Faces test* (equally distributed among

diagnostic groups, p 0.65). Patients with subjective complaints or relational problems (n=11), possible bvFTD (n=3), different neurological or general diseases like multiple sclerosis (n=8) and patients with vascular mild cognitive impairment (n=3) were also excluded. Fifteen patients were excluded due to loss of follow up and three patients died without post mortem verification or a clear clinical diagnosis.

After two years, out of the 22 patients diagnosed with probable and definite bvFTD, 4 patients were diagnosed with *definite* bvFTD by the presence of a C9orf72 hexanucleotide repeat expansion (n=2), a progranulin mutation (n=1) and a histopathologically-confirmed tauopathy (n=1). Out of thirty-three patients with a clinical psychiatric diagnosis 2 patients had schizophrenia[38], 12 were diagnosed with a major depressive disorder, 4 with minor depressive disorder, 7 with a bipolar disorder, 3 with an autism spectrum disorder, 1 with obsessive compulsive disorder, 1 with a general anxiety disorder and 7 with personality problems. Out of all patients with other neurodegenerative diseases 6 patients were diagnosed with AD, 4 with vascular dementia, 4 with dementia with Lewy bodies, 5 with progressive supranuclear palsy, 2 with semantic dementia, 1 with corticobasal degeneration, 1 with Huntington's disease, and 1 with cerebellar degeneration.

Measurements

Clinical measurements

At baseline we set out to determine the *Mini Mental State Examination (MMSE)*, *Frontal Assessment Battery (FAB)*, *Frontal Behavioural Inventory (FBI)* and *Stereotypical Rating Inventory (SRI)* in patients with probable and definite bvFTD, other neurodegenerative diseases and patients diagnosed with a psychiatric disorder.[39 40 41 42]

Social cognition

At baseline, we measured social cognition in the diagnostic groups by using the *Ekman 60 Faces test* and *Faux Pas test*. To test the *Ekman 60 Faces Test* a range of photographs from the *Facial Expressions of Emotion: Stimuli and Tests (FEEST)* was used.[43 44] From this series, the faces of 10 actors (6 female, 4 male) were chosen, each displaying six basic emotions (happiness, sadness, disgust, fear, surprise and anger). The maximum test score indicating best performance is 60 for all six emotions and 10 for each basic emotion. The computer software for the test was available on CD-ROM. Patients were allowed unlimited time for the response.

Immediately prior to testing, we verified that patients semantically understood the words anger, disgust, fear, happiness, sadness and surprise. A cut-off score of 46 out of 60 points was found in a previous study to discriminate bvFTD patients from healthy controls (97% diagnostic accuracy).[8]

The *Faux Pas* tests the theory of mind, using stories that contain a "faux pas", an embarrassing social mistake.[44] [45] [46] For each *Faux Pas* story, the patient gets 1 point for each question answered correctly. The maximum score indicating best performance was 10. Different stories were used and the patient was asked whether someone in the story said something that he or she should not have said or whether a character said something inappropriate. Then was asked what emotion the other character would feel. Control stories and control questions were also included in this test.

Cognitive functioning

At baseline, we also set out to determine *executive functioning, memory, attention/concentration/mental speed* and *visuospatial functioning* in the diagnostic groups. These cognitive domains were formed by the scores of carefully chosen cognitive tests. The cognitive domain score of *executive functioning* was calculated by averaging the z-scores of *Trail Making Test part B (TMT B), Dutch version of the COWAT (Controlled Word Association Test)* and similarities of the *WAIS III (Wechsler Adult Intelligence Scale).* These tests are explained elsewhere.[47] [48] [49] [50] *Memory* as a cognitive domain was formed by the mean score of the z-scores from the *Word Memory test*[51] [52] and *Visual Association Test (VAT).*[53] The cognitive domain of *attention/concentration/mental speed* was calculated by averaging the z-scores of *Digit Span Forward and Backward of the WAIS III (Wechsler Adult Intelligence Scale*[54] and *Trail Making Test part A (TMT A).*[55] The score at the domain of *visuospatial functioning* was calculated by defining the mean score of the z-scores at the subtest Gestalt Completion *Groninger Intelligention Test (GIT),*[56] *Clock drawing,*[57] and *Rey Complex Figure Test.*[58] To calculate the z-score of a cognitive domain, the z-scores of the corresponding cognitive tests were logically converted into the same direction.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows; IBM, Armonk, NY), version 21. Group differences on sociodemographic variables were investigated using independent t-tests and χ^2tests. Group differences were measured with Mann-Whitney U test (MW) and T-test. Furthermore, we performed univariate logistic regression analyses with diagnosis as dependent variable. We selected variables showing p-values < 0.05 and in the next step we combined these variables into a multivariate model to investigate the explained variance. Potential multicollinearity was investigated for the multivariable model using the variance inflation factor <5 for each of the independent variables in the multivariable model using linear regression analyses. We used linear regression with Z-scores to test the association between social cognition with *FBI, SRI* and the different cognitive domains (*executive functioning, memory, attention/concentration/tempo, visuospatial functioning*). We calculated the best cut-off value with sensitivity and specificity. Receiver operating characteristic (ROC) curves were plotted for *Ekman Faces test* and *Faux pas* and we calculated the area under the curves with 95% confidence interval (CI). A p-value of < 0.05 was considered statistically significant.

RESULTS

Clinical and demographic data

Demographic data of the diagnostic groups are displayed in table 1. Patients were predominantly male (> 60%). Regarding symptom duration, education, the total score at the Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB) and Frontal Behavioral Inventory (FBI) at baseline the groups did not differ (p >0.05). Patients with probable and definite bvFTD had a higher total score at the Stereotypy Rating Inventory (SRI) than both patients with other neurodegenerative diseases and patients with a psychiatric diagnosis (p <0.001) (table 1). There was a difference regarding age among diagnostic groups (ANOVA p 0.01), but this difference was only present between other neurodegenerative diseases and psychiatric disorders (p<0.05) with patients with a psychiatric disorder having the lowest age (mean 59.2).

	bvFTD (n=22)	Psychiatric diagnosis (n=33)	Other neurodegenerative diseases (n=24)	Statistics X^2/KW/ANOVA (df) P value
Age, mean (SD)	62.8 (6.7)	59.2 (6.9)	64.7 (6.7)	4.9 (2) 0.0
Gender % male	59.1	84.9	62.5	5.4 (2) 0.1
Symptom duration, median (IQR)	3.00 (4.5)	3.0 (2.0)	2.50 (2.0)	KW 0.4
Education % low % middle % high	9.1 59.1 31.8	16.0 64.0 20.0	5.00 65.0 30.0	2.1 (4) 0.7
MMSE mean (SD)	26.1 (2.8)	26.4 (2.6)	25.4 (2.5)	0.9 (2) 0.4
FAB mean (SD)	14.2 (4.3)	15.3 (2.8)	13.4 (3.7)	1.8 (2) 0.2
SRI median (IQR)	15.0 (19.0)	4.0 (10.0)	2.0 (8.0)	KW 0.0
FBI mean (SD)	25.3 (10.5)	24.8 (8.8)	23.6 (8.9)	0.2 (2) 0.8

Table 1. Demographic and clinical characteristics at baseline

Legend: SD= Standard Deviation, IQR- Inter Quartile Range, df= degrees of freedom, KW=Kruskal-Wallis Test Education: low=less than four years of low or average level secondary education, middle= four years of low or average level secondary education, high=five years of high level secondary education or university degree, MMSE= Mini-Mental State Examination, FAB=Frontal Assessment Battery, SRI=Stereotypy Rating Inventory, FBI=Frontal Behavioral Inventory

Social cognition

The median score on the *Ekman 60 faces* test in all diagnostic groups was below 46, indicating impaired social cognition in all diagnostic groups. Patients with probable and definite bvFTD had a significantly lower score on this test than patients with other neurodegenerative diseases (p 0.04) and psychiatric disorders (p 0.001) (table 2). BvFTD patients performed significantly worse in recognition of negative emotions (anger, disgust, fear and sadness) (table 2).

The results of the *Faux Pas* test were comparable in all diagnostic groups. Although bvFTD patients tended to have a lower mean total score at the *Faux Pas*, this did not significantly differ from patients with other neurodegenerative diseases and psychiatric disorders. Also, the specific subtests of the *Faux Pas* did not significantly differ between diagnostic groups (table 2).

Ekman median (IQR)	bvFTD (n=22)	PDx (n=33)	OND (n=24)	bvFTD versus PDx		bvFTD versus OND	
				MW / T-test	Univariate logistic regression OR (95% CI), p	MW / T-test	Univariate logistic regression OR (95% CI), p
Total	31.5 (15)	41.0 (12)	38.5 (13)	**0.00**	**1.10 (1.1-1.2), 0.00**	**0.04**	**1.07 (1.0-1.2), 0.05**
Anger	4.0 (3)	7.0 (4)	6.0 (3)	**0.00**	**1.54 (1.2-2.0), 0.00**	**0.00**	**1.63 (1.2-2.3), 0.01**
Disgust	3.0 (4)	6.0 (4)	5.0 (5)	**0.00**	**1.49 (1.1-2.0), 0.00**	**0.03**	**1.27 (1.0-1.6), 0.05**
Fear	3.5 (3)	5.0 (3)	3.0 (4)	**0.04**	**1.38 (1.0-1.9), 0.04**	0.6	1.0 (0.8-1.3), 0.9
Happy	10.0 (1)	10.0 (0)	10.0 (1)	**0.02**	1.9 (0.9-3.7), 0.1	0.8	1.0 (0.6-
Sad	4.0 (3)	5.0 (3)	5.0 (2)	0.2	1.2 (0.9-1.5), 0.3	0.2	1.18 (0.9-1.6), 0.3
Surprise	8.0 (5)	8.0 (3)	7.5 (4)	0.2	1.3 (1.0-1.6), 0.1	0.6	1.08 (0.9-1.3), 0.5
Faux Pas mean (SD)							
Total	5.9 (2.8)	7.0 (2.2)	6.6 (2.4)	0.1	1.2 (0.9-1.6) 0.2	0.4	1.1 (0.8-1.5) 0.4
Good Faux pas	2.9 (1.8)	3.1 (1.6)	2.6 (1.9)	0.7	1.1 (0.7-1.6) 0.7	0.7	0.9 (0.6-1.3) 0.7
Non Faux Pas	3.1 (2.0)	3.7 (1.7)	4.0 (1.1)	0.2	1.2 (0.9-1.7) 0.2	0.1	1.5 (0.9-2.4) 0.1
Empathy in Faux Pas	1.9 (1.8)	2.4 (1.7)	1.5 (1.7)	0.4	1.2 (0.8-1.7) 0.4	0.5	0.9 (0.6-1.3) 0.5
Cognitive domain Zscore median (IQR)							
Executive functioning	-0.3 (1.6)	0.2 (0.9)	-0.5 (1.3)	0.1	1.8 (1.0 -3.4) 0.1	0.6	0.9 (0.5 - 1.7) 0.8
Memory	-0.1 (0.7)	0.3 (1.0)	-0.2 (0.7)	0.2	1.7 (0.8 -3.4) 0.1	0.8	0.9 (0.4 – 1.7) 0.7
Attention/ concentration/ tempo	0.1 (0.7)	-0.1 (0.8)	-0.1 (0.9)	0.3	0.7 (0.3 -1.4) 0.3	0.1	0.4 (0.2 – 1.1) 0.1
Visuospatial functioning	-0.0 (1.1)	0.4 (0.8)	-0.1 (1.5)	**0.04**	2.1 (0.9 – 4.7) 0.1	0.8	0.8 (0.4 - 1.6) 0.5

Table 2. Scores at Ekman faces, Faux pas and cognitive domains in diagnostic groups, between groups comparisons and univariate logistic regression

Legend: MW= Mann-WhitneyU, IQR= Inter Quartile Range, OR=Odds Ratio, OND= Other neurodegenerative Disesaes, PDx=Psychiatric Diagnosis, bvFTD = probable and definite bvFTD, SD= standard deviation, Coding logistic regression: 0=bvFTD 1=Respectively Psychiatric Diagnosis or Other Neurodegenerative Disease

Other cognitive domains and social cognition

The cognitive domains executive functioning, memory, attention/concentration/tempo and visuospatial functioning (z-cores) did not differ between bvFTD, other neurodegenerative diseases and psychiatric disorders, with the exception of visuospatial functioning which was significantly better in patients with a psychiatric disorder than in bvFTD (p 0.04) (table 3).

Using linear regression, an association was found between Ekman Faces total score and all cognitive domains: executive functioning (24.5%, F 24.61, df 1, p <0.001), memory (29.5%, F 18.81, df 1, p <0.001), attention/concentration/tempo (8.0%, F 6.61, df 1, p 0.012) and visuospatial functioning (14.4%, F 12.49, df 1, p 0.001) (table 3). The Stereotypy Rating Inventory (SRI) was also associated with the Ekman Faces test (12.0%, F 10.03, df 1, p 0.002), while the Frontal Behavioral Inventory (FBI) was not (F 1.33, df 1, p 0.25). The Faux Pas was also associated with the Ekman Faces test (24.0%, F 17.95, df 1, p <0.001).

	Ekman Faces Total score		
	R^2	F	p
SRI	0.1	10.0	**0.0**
FBI	0.0	1.33	0.3
Faux Pas	0.2	17.9	**0.0**
Cognitive domain			
Executive functioning	0.3	24.6	**0.0**
Memory	0.2	18.8	**0.0**
Attention/concentration/tempo	0.1	6.6	**0.0**
Visuospatial functioning	0.1	12.5	**0.0**

Table 3. Linear regression on Ekman Faces Test and FBI, SRI and cognitive domains based on Z tests

Legend: SRI=Stereotypy Rating Inventory, FBI=Frontal Behavioral Inventory

Diagnostic value

The predictor Ekman faces total score explained 91.2% of the variance in diagnoses other neurodegenerative diseases and psychiatric disorders versus bvFTD (χ 11.02, df 1, p 0.001). The optimal cut-off for Ekman Faces test for probable/definite bvFTD versus other neurodegenerative diseases and primary psychiatric disorders in our cohort was 34.5 with a sensitivity of 66.7% and specificity of 68.2%. A sensitivity of 100% for probable/definite bvFTD was found at a cut-off score of 20.0 out of 60 points and a specificity of 100% was found at a cut-off score of 46.5 out of 60 points at Ekman faces test. The ROC curve showed an area under the curve for Ekman Faces test of 0.73 (p 0.001, 95% CI 0.61-0.85).

The predictor Faux pas total score was not significant (χ 1.96, df 1, p 0.16 and AUC 0.60, p 0.24, 95% 0.44- 0.75).

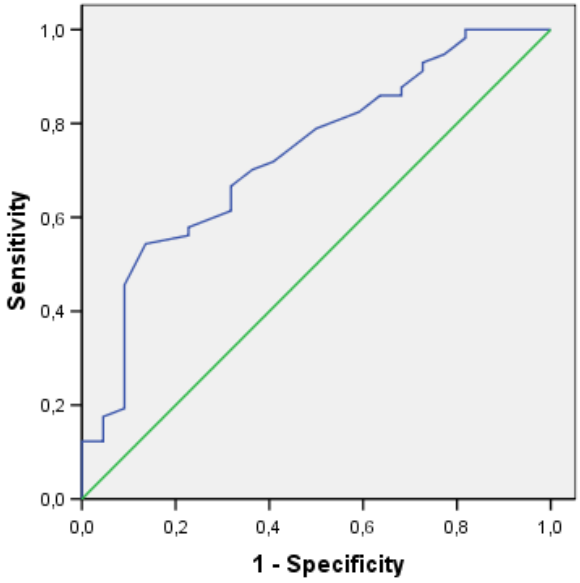

Figure 1.ROC curve of Ekman faces test for probable/definite bvFTD versus other neurodegenerative diseases and psychiatric disorders (AUC0.73 (p 0.001,95% CI 0.61-0.85)

DISCUSSION

Ekman 60 Faces test differentiates patients with bvFTD from patients with other neurodegenerative diseases and patients with psychiatric disorders with good diagnostic accuracy in our late onset frontal lobe cohort resembling clinical practice. In our sample, social cognition was associated with all other cognitive domains (*executive functioning, memory, attention/concentration/tempo and visuospatial functioning*) as well as stereotypical behaviour. *Visuospatial functioning* was different between bvFTD and psychiatric disorders, while the other cognitive domains were not different between diagnostic groups.

In accordance with previous literature, we found clear impairments in social cognition in probable and definite bvFTD patients.[7 5 22 59] Several studies have demonstrated that social cognition is markedly impaired in bvFTD when compared

to healthy controls[8 28] and AD patients.[60 61] A comparison of social cognition between bvFTD and psychiatric disorders has only been performed in two studies.[62 63] A comparison of social cognition between bvFTD and schizophrenia showed similar deficits in social cognition in schizophrenia patients as in bvFTD patients, using Theory of Mind (ToM) tests.[63] In another study, using the *Ekman 60 Faces test,* bvFTD patients displayed impaired social cognition compared to depressed patients.[62] In contrast to our study, patients in these two previous studies were not included based on similar symptom profile, but as depression and schizophrenia can present similarly, it subscribes clinical relevance.[8 64] The current study shows that besides bvFTD, also patients with other neurodegenerative diseases and psychiatric disorders presenting with frontal symptoms have impaired social cognition, but even with overlapping symptomatology, *Ekman 60 Faces test* is able to distinguish.

In our sample, all patients scored low on the *Faux Pas* but the test did not discriminate between the diagnostic groups. In this respect, it is conceivable that *Faux Pas* (a ToM test) is a very sensitive test for impaired social cognition, as it gives similar low results in bvFTD, other neurodegenerative diseases and psychiatric disorders. Previous studies found a disturbed *Faux Pas* in different psychiatric disorders, explicitly in autism spectrum disorder and schizophrenia.[46 63] It is conceivable that *Faux Pas* is a more sensitive method for measuring social cognition while *Ekman 60 Faces test* is a more specific method for bvFTD. As suggested in other studies, it is also conceivable that the recognition of positive emotions is limited to a certain 'maximum level' which makes it difficult to measure certain differences between diagnostic groups.[65]

One of the most striking results of the current study was the finding that despite the association of social cognition with all other cognitive domains (*executive functioning, memory, attention/concentration/tempo and visuospatial functioning*), the other cognitive domains except *visuospatial functioning* did not differentiate between diagnostic groups. The discriminative power of visuospatial functioning in the comparison of bvFTD with psychiatric disorders is a new finding as a comparison between both diagnostic groups has not yet been performed. Previous research revealed that difficulties in this domain in bvFTD can arise when a task relies heavenly on to down control of spatial processing.[66]

The association of social cognition with the other cognitive domains found in the current study is partially in line with earlier hypotheses.[32 67] Social cognition has been seen as a higher level of cognitive functioning, in which other cognitive domains are 'needed'.[68] It is conceivable that this is enhanced specifically in test situations due to its higher level of required performance when it also needs to be remembered and reproduced. Previous studies on executive functioning in bvFTD compared to controls are ambiguous but impairments in this domain have been found repeatedly.[69 70] In the current study, only social cognition measured with the *Ekman Faces* was able to distinguish bvFTD from both other neurodegenerative diseases and psychiatric disorders. The current bvFTD criteria emphasize the impairment of executive functioning in bvFTD,[27] whereas the results of the current study suggest that social cognition measured by *Ekman 60 Faces test* might even be more useful.

There are some limitations in this study. First of all, while we had 3 patients with a genetic mutation, neuropathological confirmation was obtained in only one bvFTD case. The diagnostic gold standard of two years approximates diagnostic certainty but misdiagnosis after two years of diagnostic follow up cannot be fully excluded. Second, as mentioned previously, the inclusion of our patients was symptom based instead of etiology based, which makes it impossible to draw conclusions on specific diagnostic groups within the psychiatric subgroup of patients and within the group of patients with a neurodegenerative disease. At the same time, we are convinced that this symptom-based design is also a strength as it resembles clinical practice. Another limitation is that many statistical tests were performed resulting in an increased risk for Type I errors. However, when the chance of incorrectly producing a difference on an individual test is reduced, the chance of making a type two error is increased, which implies that no effect or difference is declared, while in fact there is an effect. Thus, by reducing the chance of type one errors for individual tests, the chance of a type two errors is increased for all tests. As the chance that we have found a type one error is very small and the findings in our study are not unexpected, we have not made the Bonferroni correction.

Acknowledging the limitations, this is the first study measuring social cognition in bvFTD compared with its broad challenging differential diagnosis consisting of both other neurodegenerative diseases and psychiatric disorders. Neuropsychological tests are daily practice in diagnostics of bvFTD, and in line with recent literature our study provides new arguments for incorporation of social cognition in future diagnostic guidelines for bvFTD.[71]

REFERENCES

1. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2006;77(1):4-7. doi:10.1136/jnnp.2005.072496.
2. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140-143. doi:10.1192/bjp.180.2.140.
3. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615-1621. doi:10.1212/WNL.58.11.1615.
4. Bang J, Spina S, Miller BL. Frontotemporal dementia. *Lancet*. 2015. doi:10.1016/S0140-6736(15)00461-4.
5. Seeley WW, Crawford R, Rascovsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol*. 2008;65(2):249-255. doi:10.1001/archneurol.2007.38.
6. Lough S, Hodges JR. Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *J Psychosom Res*. 2002;53(2):639-646. doi:10.1016/S0022-3999(02)00433-6.
7. Kumfor F, Irish M, Leyton C, et al. Tracking the progression of social cognition in neurodegenerative disorders. *J Neurol Neurosurg Psychiatry*. 2014;85(10):1076-1083. doi:10.1136/jnnp-2013-307098.
8. Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. *Arch Clin Neuropsychol*. 2007;22(4):459-464. doi:10.1016/j.acn.2007.01.024.
9. Riedijk SR, De Vugt ME, Duivenvoorden HJ, et al. Caregiver burden, health-related quality of life and coping in dementia caregivers: A comparison of frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2006;22(5-6):405-412. doi:10.1159/000095750.
10. Mourik JC, Rosso SM, Niermeijer MF, Duivenvoorden HJ, Van Swieten JC, Tibben A. Frontotemporal dementia: Behavioral symptoms and caregiver distress. *Dement Geriatr Cogn Disord*. 2004;18(3-4):299-306. doi:10.1159/000080123.
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.
12. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol*. 2010;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
13. Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. doi:10.1136/jnnp-2015-310697.

14. Hargrave R, Maddock RJ, Stone V. Impaired recognition of facial expressions of emotion in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2002;14(1):64-71. doi:10.1176/appi.neuropsych.14.1.64.
15. Rowland JE, Hamilton MK, Vella N, Lino BJ, Mitchell PB, Green MJ. Adaptive associations between social cognition and emotion regulation are absent in schizophrenia and bipolar disorder. *Front Psychol*. 2013;3(JAN). doi:10.3389/fpsyg.2012.00607.
16. Balogh N, Égerházi A, Berecz R, Csukly G. Investigating the state-like and trait-like characters of social cognition in schizophrenia: A short term follow-up study. *Schizophr Res*. 2014;159(2-3):499-505. doi:10.1016/j.schres.2014.08.027.
17. Albert MS, Cohen C, Koff E. Perception of affect in patients with dementia of the Alzheimer type. *Arch Neurol*. 1991;48(8):791-795. doi:10.1001/archneur.1991.00530200027013.
18. Balogh N, Égerházi A, Berecz R, Csukly G. Investigating the state-like and trait-like characters of social cognition in schizophrenia: A short term follow-up study. *Schizophr Res*. 2014;159(2-3):499-505. doi:10.1016/j.schres.2014.08.027.
19. Samamé C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: Systematic review and meta-analytic approach. *Acta Psychiatr Scand*. 2012;125(4):266-280. doi:10.1111/j.1600-0447.2011.01808.x.
20. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci*. 2015;16(10):620-631. doi:10.1038/nrn4005.
21. Uljarevic M, Hamilton A. Recognition of emotions in autism: A formal meta-analysis. *J Autism Dev Disord*. 2013;43(7):1517-1526. doi:10.1007/s10803-012-1695-5.
22. Ibanez A, Manes F. Contextual social cognition and the behavioral variant of frontotemporal dementia. *Neurology*. 2012;78(17):1354-1362. doi:10.1212/WNL.0b013e3182535d0c.
23. Funkiewiez A, Bertoux M, de Souza LC, Lévy R, Dubois B. The SEA (Social Cognition and Emotional Assessment): A clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology*. 2012;26(1):81-90. doi:10.1037/a0025318.
24. Bertoux M, Delavest M, de Souza LC, et al. Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry*. 2012;83(4):411-416. doi:10.1136/jnnp-2011-301849.
25. Narme P, Mouras H, Roussel M, Devendeville A, Godefroy O. Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimer's disease. *J Clin Exp Neuropsychol*. 2013;35(7):728-744. doi:10.1080/13803395.2013.823911.
26. Gregory C, Lough S, Stone V, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*. 2002;125(Pt 4):752-764. doi:10.1093/brain/awf079.

27. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.

28. Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain*. 2009;132(5):1299-1309. doi:10.1093/brain/awp041.

29. Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology*. 2008;71(19):1481-1488. doi:10.1212/01.wnl.0000334299.72023.c8.

30. Allen-Walker L, Beaton AA. Empathy and perception of emotion in eyes from the FEEST/Ekman and Friesen faces. *Pers Individ Dif*. 2014;72:150-154. doi:10.1016/j.paid.2014.08.037.

31. Rascovsky K, Salmon DP, Ho GJ, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology*. 2002;58(12):1801-1808. doi:10.1212/WNL.58.12.1801.

32. Lough S, Gregory C, Hodges JR. Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. *Neurocase case Stud Neuropsychol neuropsychiatry, Behav Neurol*. 2001;7(2):123-130. doi:10.1093/neucas/7.2.123.

33. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.

34. American Psychiatric Association. *DSM-IV*.; 2000.

35. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-250. doi:10.1212/WNL.43.2.250.

36. Mckeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65:1863-1872. doi:10.1212/01.wnl.0000224698.67660.45.

37. Galimberti D, Fenoglio C, Serpente M, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: Late-onset psychotic clinical presentation. *Biol Psychiatry*. 2013;74(5):384-391. doi:10.1016/j.biopsych.2013.01.031.

38. Cora J. Kerssens, Welmoed A. Krudop, Niels D. Prins, Bart N. M. van Berckel, Annemieke Rozemuller, William W. Seeley, Philip Scheltens MLS& YALP. Schizophrenia as a mimic of behavioral variant frontotemporal dementia. *Neurocase*. 2016. doi:10.1080/13554794.2016.1187178.

39. Galea M, Woodward M. Mini-mental state examination (MMSE). *Aust J Physiother*. 2005;51(3):198. doi:10.1017/CBO9781107415324.004.

40. Dubois B, Slachevsky a, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626. doi:10.1212/WNL.57.3.565.

41. Milan G, Lamenza F, Iavarone A, et al. Frontal Behavioural Inventory in the differential diagnosis of dementia. *Acta Neurol Scand*. 2008;117(4):260-265. doi:10.1111/j.1600-0404.2007.00934.x.

42. Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res*. 2002;110(2):175-187. doi:10.1016/S0165-1781(02)00094-X.

43. Young a W, Perrett DI, Calder a J, Sprengelmeyer R, Ekman P. *Facial Expressions of Emotion: Stimuli and Tests (FEEST)*. Vol 126.; 2002. doi:10.1016/S0010-0277(97)00003-6.

44. Stone VE. Faux Pas Recognition Test Faux Pas Recognition Test (Adult Version). *J Cogn Neurosci Brain*. 2002;10(125):640-656.

45. Baron-cohen S, Riordan MO, Stone V, Jones R, Plaisted K. A new test of social sensitivity : Detection of faux pas in normal children and children with Asperger syndrome : *J Autism Dev Disord*. 1999;29:407-418.

46. Zalla T, Sav AM, Stopin A, Ahade S, Leboyer M. Faux pas detection and intentional action in asperger syndrome. A replication on a French sample. *J Autism Dev Disord*. 2009;39(2):373-382. doi:10.1007/s10803-008-0634-y.

47. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol*. 2000;22(4):518-528. doi:10.1076/1380-3395(200008)22:4;1-0;FT518.

48. Schmand B, Groenink SC, Van Den Dungen M. Letterfluency: psychometrische eigenschappen en Nederlandse normen. *Tijdschr Gerontol Geriat*. 2008;39:64-76. doi:http://dx.doi.org/10.1007/BF03078128.

49. Wechsler D. *WAIS-III Administration and Scoring Manual*.; 1997.

50. Basso MR, Carona FD, Lowery N, Axelrod BN. Practice effects on the WAIS-III across 3- and 6-month intervals. *Clin Neuropsychol*. 2002;16(1):57-63. doi:10.1076/clin.16.1.57.8329.

51. Rienstra A, Spaan PEJ, Schmand B. Reference data for the word memory test. *Arch Clin Neuropsychol*. 2009;24(3):255-262. doi:10.1093/arclin/acp035.

52. Goodrich-Hunsaker NJ, Hopkins RO. Word memory test performance in amnesic patients with hippocampal damage. *Neuropsychology*. 2009;23(4):529-534. doi:10.1037/a0015444.

53. Lindeboom J. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry*. 2002;73(2):126-133. doi:10.1136/jnnp.73.2.126.

54. Gregoire J, Van Der Linden M. Effect of age on forward and backward span tasks. *J Int Neuropsychol Soc*. 2004;10(4):475-481. doi:10.1017/S1355617704104037.

55. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19(2):203-214. doi:10.1016/S0887-6177(03)00039-8.
56. Luteijn F V der PH. *Handleiding Groninger Intelligentie Test (GIT)*. Lisse: Sweitz&Zeitlinger; 1983.
57. Shulman KI. Clock Drawing: Is It the Ideal Cognitive Screening Test? *Int J Geriatr Psychiatry*. 2000;15(March):548-561. doi:10.1002/1099-1166(200006)15:6<548::AID-GPS242>3.0.CO;2-U.
58. Estévez-González A, Kulisevsky J, Boltes A, Otermín P, García-Sánchez C. Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: Comparison with mild cognitive impairment and normal aging. *Int J Geriatr Psychiatry*. 2003;18(11):1021-1028. doi:10.1002/gps.1010.
59. Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*. 2006;44(6):950-958. doi:10.1016/j.neuropsychologia.2005.08.009.
60. Lavenu I, Pasquier F, Lebert F, Petit H, Van der Linden M. Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1999;13(2):96-101. http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=10372953.
61. Gregory C, Lough S, Stone V, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*. 2002;125(4):752-764. doi:10.1093/brain/awf079.
62. Bertoux M, Delavest M, de Souza LC, et al. Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry*. 2012;83(4):411-416. doi:10.1136/jnnp-2011-301849.
63. Kosmidis MH, Aretouli E, Bozikas VP, Giannakou M, Ioannidis P. Studying social cognition in patients with schizophrenia and patients with frontotemporal dementia: theory of mind and the perception of sarcasm. *Behav Neurol*. 2008;19(1-2):65-69. doi:10.1155/2008/157356.
64. Waldö ML, Gustafson L, Passant U, Englund E. Psychotic symptoms in frontotemporal dementia: a diagnostic dilemma? *Int Psychogeriatrics*. 2015;27(4):531-539. doi:10.1017/S1041610214002580.
65. Vaish A, Grossmann T, Woodward A. Not all emotions are created equal: The negativity bias in social-emotional development. *Psychol Bull*. 2008;134(3):383-403. doi:10.1037/0033-2909.134.3.383.
66. Possin KL, Laluz VR, Alcantar OZ, Miller BL, Kramer JH. Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. *Neuropsychologia*. 2011;49(1):43-48. doi:10.1016/j.neuropsychologia.2010.10.026.

67. Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. *J Neuropsychiatry Clin Neurosci*. 2011;23(1):74-82. doi:10.1176/appi.neuropsych.23.1.74.
68. Harvey PD, Penn D. Social cognition: the key factor predicting social outcome in people with schizophrenia? *Psychiatry (Edgmont)*. 2010;7(2):41-44.
69. Johns EK, Phillips N a, Belleville S, et al. Executive functions in frontotemporal dementia and Lewy body dementia. *Neuropsychology*. 2009;23(6):765-777. doi:10.1037/a0016792.
70. Access BA, Gleichgerrcht E, Torralva TT, Manes F. A neuropsychological battery to detect speci c executive and social cognitive impairments in early frontotemporal dementia ´. *Brain*. 2009. doi:10.1093/brain/awp041.
71. Kumfor F HJ. Social Cognition in Frontotemporal Dementia Proceedings: Special Lecture Neuropsychology Association of Japan 40th annual meeting. *Japanese J Neuropsychol*. 2017;33.

5. The diagnostic challenge of the late-onset frontal lobe syndrome: clinical predictors for primary psychiatric disorders versus behavioral variant Frontotemporal dementia

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ABSTRACT

Objective

Primary psychiatric disorders (PsD) can present with identical symptomatology as behavioral variant Frontotemporal dementia (bvFTD). To date, clinical guidelines do not provide a solution for this diagnostic challenge. The aim of our study was to prospectively determine which demographic, clinical, neuropsychological, neuroimaging and CSF biomarkers are important in distinguishing PsD from bvFTD.

Methods

Patients with late onset behavioral disturbances (aged 45-75 years, male 73%) were included based on their scores on the Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI) and followed for 2 years. Odds ratios (OR) were calculated with backward stepwise logistic regression analyses to investigate the association between baseline clinical and demographical variables and the two-year-follow-up diagnosis for PsD (n=46) (DSM-IV) versus *probable/definite* bvFTD(n=27) (Frontotemporal Dementia Consensus criteria (FTDC). We separately measured the association additional investigations and the two-year-follow-up diagnosis. Finally, we combined the selected variables to measure the predicted value of both clinical and additional investigations in a single model.

Results

Male gender (OR 5.9 CI 95%:1.3-26.0), less stereotypy (OR 0.08 CI 95%:0.02-0.34) and more depressive symptoms (OR 1.13 CI 95%:1.04-1.24) explained 49% of the variance predicting PsD versus bvFTD (Chi-square-test 29.4, df 3, $p<0.001$) and correctly classified 82.1% of the cases. Neuroimaging (OR 0.02 95%:0.002-0.123) explained 55% of the variance (Chi-test 37.5, df 1, $p<0.001$) and in combination with clinical variables 66.1% of the variance (Chi-square-test 44.06, df 3, $p<0.001$).

Conclusions

In this present study we demonstrated that PsD can be distinguished from *probable/definite* bvFTD with a thorough clinical evaluation by a psychiatrist and neurologist in addition with validated questionnaires for depression and stereotypy, and even more in combination with neuroimaging.

INTRODUCTION

Behavioral variant Frontotemporal dementia (bvFTD) is clinically characterized by insidious changes in personality, behavior and executive functions. It is the second most common early-onset dementia after Alzheimer's disease and accounts for approximately 10-20% of all patients with a neurodegenerative dementia.[1 2 3] Whereas bvFTD can be differentiated from other neurodegenerative disorders with a relatively good accuracy,[4 5 6 7] a major challenge lies in distinguishing bvFTD from primary psychiatric disorders (PsD) such as major depression, bipolar disorder and schizophrenia. These psychiatric disorders can present with identical symptomatology as bvFTD such as apathy, disinhibition and stereotyped/compulsive behaviour.[8 9]

The diagnosis of bvFTD is based on the International bvFTD Consortium Criteria (FTDC)(7), which include behavioral/cognitive features such as early disinhibition, apathy or inertia, loss of sympathy or empathy, stereotyped/compulsive behavior, hyperorality and a neuropsychological profile with predominately executive deficits (*possible* bvFTD). When these behavioral/cognitive features are accompanied by functional decline over time and neuroimaging abnormalities in the frontotemporal regions, the diagnostic certainty of bvFTD increases, and the clinical picture can be classified as *probable* bvFTD. However, the FTDC criteria also state that a diagnosis of bvFTD is excluded when 'behavioral disturbance is better accounted for by a psychiatric diagnosis'[7] and before diagnosing a PsD the Diagnostic and Statistical Manual of Mental Disorders (DSM)[10] states that a psychiatric disorder is excluded when 'the disturbance is attributable to another medical condition'. Using these guidelines in clinical practice results in a vicious circle and does not provide a solution how to solve this diagnostic challenge of clinical overlapping illnesses.

Getting an accurate, early PsD or bvFTD diagnosis is especially critical since most psychiatric disorders are treatable. A misdiagnosis of bvFTD or primary psychiatric disorder might cause inappropriate or delayed treatment and an increase in the burden for patients and caregivers.[11 12 13] In addition, the first and crucial step for a clinical intervention trail for bvFTD or PsD is the inclusion of highly accurate diagnosis.

In our previous published cross-sectional study,[14] we found that a positive history of psychiatric illness, male gender, lower SRI scores and higher MADRS scores

were predictive of PsD versus bvFTD. However, after two years of follow-up 50% of patients diagnosed which bvFTD at baseline changed diagnoses which is in contrast with a previous publication that more than 50% of the bvFTD cases primarily receives a psychiatric diagnosis(11). Furthermore, in this current study we include additional investigations such as neuropsychological profile, neuroimaging and cerebrospinal fluid (CSF). Therefore, to minimize the chance of misdiagnosis and so biased results, we now prospectively examined which specific clinical variables, demographic characteristics or additional investigations at baseline could predict PsD versus *probable/definite* bvFTD at follow-up in a cohort of patients with late onset behavior changes who were recruited from the Late Onset Frontal lobe syndrome (LOF) study.[15]

METHODS

Subjects

The late onset frontal lobe syndrome (LOF) study is a multi-center prospective study conducted between April 2011 and June 2015.[15] Patients were recruited from the Amsterdam Dementia Cohort[16] and the GGZInGeest Department of Old Age Psychiatry, Amsterdam, the Netherlands. Patients were eligible for inclusion when behavioral symptoms dominated the clinical presentation, the score on the Frontal Behavioural Inventory (FBI)[17] was ≥ 11 or the Stereotypy Rating Inventory (SRI)[18] score was ≥ 10 and they were aged between 45 and 75.[13]

From the original LOF cohort of 137 cases included at baseline, a total of 21 patients were excluded at follow-up. Three patients were diagnosed with a two-year follow-up diagnosis of *possible* bvFTD, as no other explanation could be found for their symptoms, cases that may be consider as bvFTD phenocopies. However, due to the open discussion on this subject, we excluded them from the final analysis. Furthermore, we excluded three patients which died without post mortem verification or a clear clinical diagnosis. Fifteen patients were lost to follow-up. For the current study we selected the patients with a two-year-follow-up multidisciplinary diagnosis of a primary psychiatric disorder (n=46) or *probable/definite* bvFTD (n=27) to investigate which combination of clinical characteristics and additional investigations measured on baseline could distinguish between PsD and *probable/definite* bvFTD (see figure 1). The Medical Ethical

Committee of the VU Medical Centre, Amsterdam, approved the study and all participants provided written informed consent.

Diagnostic procedure

All patients underwent full neurological and psychiatric examination at baseline, including a medical history, medical family history, use of medication, an informant based history, neuropsychological assessment and laboratory tests.[13] Furthermore, all patients underwent an Magnetic resonance imaging (MRI) scan of the brain, acquired on a 3T SignaHDxt scanner (GE Medical Systems, Milwaukee, WI) using a standard dementia Protocol.[14] In case of a normal or insufficiently explanatory MRI at baseline, an [^{18}F]-fluorodeoxyglucose-positron emission tomography ([^{18}F] FDG-PET) scan was performed using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN). An experienced neuroradiologist, unblinded for the study design and age but blinded to the patients' symptoms and medical history, evaluated the images with respect to global cortical atrophy (GCA), medial temporal lobe atrophy (MTA), and white matter hyperintensities (WMH) (Fazekas) according to established and validated visual rating scales.[19 20 21]

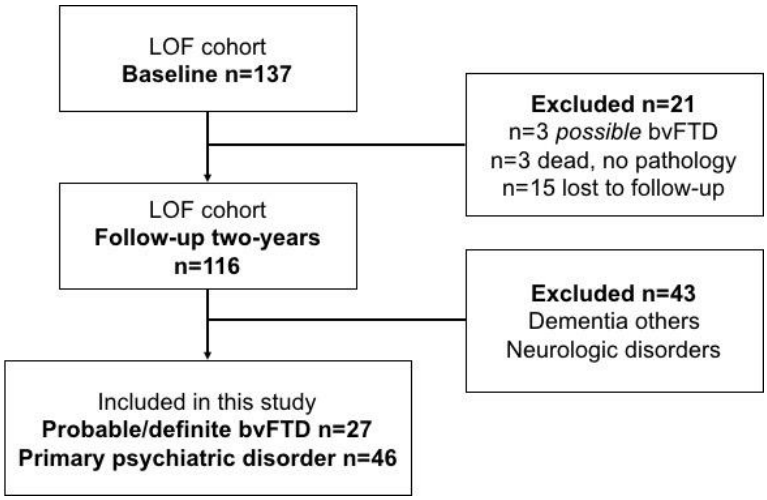

Figure 1. Flowchart

In addition, the neuroradiologist was asked to classify the MRI as consistent with frontotemporal dementia or not. When frontal and/or anterior temporal atrophy on MRI was present and discrepant with global cortical atrophy, this was considered as consistent with frontotemporal dementia. [^{18}F]FDG-PET-scans were assessed

visually and interpreted by an experienced nuclear medicine physician on frontal and/or anterior temporal hypometabolism based on the summed images of all the frames, unblinded for the study design and age, blinded to the patients' symptoms, complaints and medical history. Details about the results of neuroimaging in the LOF cohort are described elsewhere.[22]

Cerebrospinal Fluid (CSF) was obtained with a lumbar puncture. CSF was collected in polypropylene tubes and centrifuged within an hour. The supernatant was stored in 0.5 ml aliquots at -20 ºC. Laboratory analysis of levels of CSF total-Tau (CSF Tau), CSF phosphorylated Tau_{181} (pTau) and CSF Amyloid-β1-42 (CSF Aβ1-42) concentrations took place using sandwich ELISA's (Fujirebio/Innogenetics, Belgium) on a routine basis(16). A consensus diagnosis between the neurologist (YP, NP, PS) and the psychiatrist (AD, CK, MS) was made based upon the clinical information and additional investigations, including results of CSF biomarkers, MRI and [^{18}F]FDG-PET at baseline. Diagnoses were based on the consensus guidelines for dementia[16 23 24 25] and the psychiatric diagnoses were based on current psychiatric criteria.[26]

After two years of follow-up, neuropsychiatric examination, neuropsychological tests and the brain MRI were repeated, followed by establishment of the final multidisciplinary diagnosis. Again, diagnoses were based on the consensus guidelines for dementia[16 27 24 25] and the psychiatric diagnoses were based on current psychiatric criteria.[10] After two years of follow-up all subjects were screened for the C9orf72 expansion hexanucleotide repeat, given the great symptomatic overlap with psychiatric disorders and long disease courses that have been described in this mutation type.[15]

Clinical assessments

We assessed global cognition using the Mini Mental State Examination (MMSE, range 0-30)[28] and for the screening of 'frontal' executive functions we used the Frontal Assessment Battery(FAB, range 0-18).[29] We applied the Montgomery Asberg Depression Rating Scale (MADRS, range 0-60)[30] to evaluate 10 depressive symptoms, whereby higher scores on the MADRS indicated more depressive symptoms. To asses behavioral symptomatology we used the FBI[17] that has 24 items covering different aspects of abnormal behavior, each item can be rated 0 to 3 (range 0-72). The SRI[18] that covers five distinct stereotypical symptoms was rated by behavior and severity with a maximum of 12 per item (range 5 to 60). Higher scores on the FBI and SRI indicate more abnormal behavior or stereotypical

symptoms. All clinical assessments mentioned above were performed by trained clinicians who were blind for the clinical diagnosis (FG and WK). These clinicians did not have information about previous medical history or other medical information.

We included the additional investigations that are described in the FTDC: a neuropsychological assessment and neuroimaging, consisting of a MRI or MRI in combination with [^{18}F]FDG-PET. We also explored CSF biomarkers as potential predictors for primary psychiatric disorders versus *probable/definite* bvFTD, and included CSF biomarkers as additional investigation in the model. Additional investigations were categorized in positive and negative as follows: neuropsychological profile was rated positive when predominately executive deficits with relative sparing (more than 1 z-score higher between domains) of memory and visuospatial were found on the neuropsychological test battery, as stated in the FTDC criteria[7] Executive function was assessed by the Trail Making Test part B (TMT B),[31] Letter Naming fluency[32] and two subtests (Key Search and Rule Shift Cards) of the Behavioral Assessment of the Dysexecutive Syndrome (BADS).[33] For memory, the total immediate recall score of the Rey Auditory Verbal Learning Task (RAVT) for 15 words[34] and the Visual association test[35] was used. For the visuospatial domain, three subtests of the visual object and space perception battery (VOSP) were used; incomplete letters, dot counting and number location.[36] Neuroimaging was classified positive when findings were consistent with FTD based on the visual rating of the presence of frontal and/or anterior temporal atrophy on MRI or hypometabolism on [^{18}F] FDG-PET, according the FTDC criteria(7); CSF was rated positive with levels >375 pg/ml of CSF Tau, <550 pg/ml of CSF Aβ1-42 or >52 pg/ml of CSF pTau according to cut-off levels for abnormality.[37]

Statistical analyses

Data analysis was performed using IBM SPSS statistics version 22.0 (IBM SPSS Statistics, Armonk, NY) for Mac. Clinical and demographic baseline characteristics were compared between groups using independent student's t-tests for normally distributed continuous data. Assumptions for normality were checked and if not normally distributed after log-transformation, a Mann-Whitney test was used (SRI was log-transformed). For categorical data chi-square tests was used.

We used backward stepwise logistic regression analyses (predicts the probability that an observation falls into one of two categories of a dichotomous dependent

variable) to investigate the association between baseline clinical and demographical variables (based on our previous study[38] and the two-year-follow-up diagnosis for PsD versus *probable/definite* bvFTD (model 1) and we separately measured the association between the additional investigations and the two-year-follow-up diagnosis (model 2). Finally, we combined the selected variables from model 1 and 2 to measure the predicted value of both clinical and additional investigations in a single model (model 3). Associations were presented as odds ratios with 95% confidence intervals (CI). Selection method included backward stepwise selection with significance level of $p<0.10$ for all 3 models. The linearity of the associations was studied prior to the logistic regression for continuous data, and variables were categorized if necessary. Potential multicollinearity was investigated for the multivariable model using the variance inflation factor for each of the independent variables in the multivariable model using linear regression analyses and variables were removed if the variance inflation factor was >5.[39] A p-value of < 0.05 was considered statistically significant, except when indicated otherwise.

RESULTS

Clinical and demographic baseline data

The most common psychiatric disorders diagnosed at follow-up were major/minor depression (n=16, 21.9%), bipolar disorder (n=7, 9.6%), personality disorders (n=3, 4.1%) and autism spectrum disorders (n=3, 4.1%). Of the 27 patients in the bvFTD group, 4 (5.5%) patients were diagnosed with *definite* bvFTD consisting of two C9orf72 expansion hexanucleotide repeat, one progranulin mutation and one histopathologically-confirmed tauopathy (Table 1). Furthermore, table 1 illustrates that almost half of the initial bvFTD cases changed after follow-up, most were into psychiatric disorders or dementia others.

The patients' clinical and demographical characteristics at baseline from the included patients in the current study are shown in Table 2. Patients diagnosed with a psychiatric disorder after two years of follow-up used more antidepressants at baseline, had more often a psychiatric history, fewer stereotypy symptoms (lower total score on the SRI) and more depressive symptoms (higher score on the MADRS. The bvFTD group showed more frontotemporal atrophy or metabolism

changes on the baseline MRI and baseline [^{18}F] FDG-PET than psychiatric patients.

		Baseline		**Follow-up**	
		n	%	n	%
Possible bvFTD		10	7.3	3	2.2
Probable bvFTD		45	32.8	23	16.8
	FTD-ALS			4	
Definite bvFTD				4	2.9
	Histopathological				
	Tauopathy			1	
	Pathogenic mutation				
	C9orf72 expansion			2	
	GRN-mutation			1	
Primary Psychiatric disorders		44	32.1	46	33.6
	Schizophrenia			*1*	
	Major depression			*12*	
	Minor depression			*4*	
	Obsessive Compulsive Disorder			*1*	
	Bipolar Disorder			*7*	
	Autism Spectrum Disorder			*3*	
	Personality disorder			*3*	
	Other psychiatric disorders problems			*15*	
Dementia others		*8*	*5.8*	*30*	*21.9*
Neurologic diseases		*23*	*16.8*	*8*	*5.8*
Others		*7*	*5.2*	*5*	*3.6*
Lost to follow up		*(…)*		*18*	*13.2*
Total		*137*		*137*	

Table 1. Diagnoses at baseline and follow-up

Grey-zone: Patients included in the current study. Abbreviations: bvFTD= behavioural variant Frontotemporal Dementia; FTD-ALS = Frontotemporal Dementia-Amyotrophic lateral sclerosis; GRN-mutation = progranulin mutation.

FTD frontotemporal dementia; MADRS= Montgomery Asberg Depression Rating Scale; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance; PsD, primary psychiatric disorders.

	bvFTD (n=27)	PsD (n=46)	p-value
Age (years), mean (SD)	62.9 (6.7)	60.0 (6.4)	0.71
Male gender, n (%)	16 (59%)	37 (80%)	0.05§
Education (years), mean (SD)	10.2 (2.6)	9.9 (2.4)	0.63
Disease duration (years), mean (SD)	5.37 (5.1)	3.7 (2.6)	0.13
Positive psychiatric history, n (%)	5 (19%)	25 (53%)	<0.01§*
FBI, mean (SD)	26.3 (10.4)	25.9 (9.1)	0.87
SRI, median (IQR)	15 (16)	4 (8)	<0.01¶*
MADRS, mean (SD)	8.5 (6.1)	15.2 (10.2)	<0.01*
MMSE, mean (SD)	26.08 (2.7)	26.3 (2.8)	0.87
FAB, mean (SD)	14.4 (4.0)	14.8 (3.0)	0.72
Neuropsychological (executive dysfunction), n (%)	10 (37%)	9 (20%)	0.08§
MRI-brain (FT atrophy), n (%, missing)	19 (70%)	3 (6.8%, n=2)	<0.01§*
FDG-PET (FT hypometabolism), n (%, missing)	10 (91%, n=16)	12 (32.4%, n=9)	<0.01§*
CSF Tau positive >375 pg/ml, n (%, missing)	7 (30.4%, n=4)	5 (15.2%, n=13)	0.17§
CSF Abeta positive <550 pg/ml, n (%, missing)	4 (17.4%, n=4)	10 (30.3%, n=13)	0.27§
CSF pTau positive >52 pg/ml, n (%, missing)	0 (0%, n=4)	3 (9%, n=13)	0.14§
Use of sedatives, n (%)	0 (0%)	3 (7%)	0.17§
Use of antidepressants, n (%)	5 (19%)	23 (50%)	0.01§*
Use of antipsychotics, n (%)	0 (0%)	6 (13%)	0.48§

Table 2. Baseline clinical and demographical characteristics per diagnostic group at follow-up.

Abbreviations: CSF = Cerebrospinal Fluid; FAB = Frontal Assesment Battery; FBI = Frontal Behavioral Inventory; FDG-PET = [^{18}F]-fluorodeoxyglucose-positron emission tomography; FT= frontotemporal

Clinical/demographical predictors for primary psychiatric disorders

Variables for model 1 were age, gender, education, disease duration, psychiatric history, total FBI score, total SRI score, total MADRS score,
total MMSE score, and total FAB score. Psychiatric history was categorized. With backward stepwise logistic regression, the model consisted of male gender (OR 5.9 95% CI 1.3-26.0), less stereotypy measured with the SRI (OR 0.08 95% 0.02-0.34) and more depressive symptoms measured with the MADRS (OR 1.13 95% 1.04-1.24). The clinical and demographical variables psychiatric history, symptom duration, MMSE, education in years, age, FAB and the FBI were not significant in predicting PsD versus *probable/definite* bvFTD and were excluded from the model. The combination of these three predictorsexplained 49% (Nagelkerke R^2) of the variance (Chi-test 29.4, df 3, $p<0.001$) and correctly classified 82.1% of the cases (Table 3).

	OR (95% CI)	**p-value**
Model 1		
Male gender	5.91 (1.3-26.0)	0.019
MADRS	1.13 (1.04-1.24)	0.007
SRI (logtransformed)	0.08 (0.02-0.34)	0.001
Model 2		
Neuroimaging consistent with FTD	0.02 (0.002-0.123)	0.001
Model 3		
MADRS	1.10 (1.01-1.2)	0.030
SRI (logtransformed)	0.22 (0.04-1.18)	0.077
Neuroimaging consistent with FTD findings	0.02 (0.02-0.21)	0.001

Table 3. Results of backward stepwise logistic regression analyses for variables predicting Primary Psychiatric disorders versus behavioural variant Frontotemporal dementia.

Abbreviations: MADRS= Montgomery Asberg Depression Rating Scale; SRI = Stereotypy Rating Inventory. Data are presented as odd ratios (OR) with 95% confidence intervals (CI). Significant at p(0.1).

Additional investigations in predicting primary psychiatric disorders

For model 2, we selected the variables "Neuropsychological profile", "Neuroimaging", "CSF tau", "CSF pTau" and "CSF Aβ1-42". The final model included absence of changes in the frontotemporal region on neuroimaging (OR 0.02 95% 0.002-0.123). CSF Aβ1-42, neuropsychological profile, CSF pTau and CSF Tau were not significant as predictors for PsD versus *probable/definite* bvFTD and were excluded from the model. Model 2 explained 55% (Nagelkerke R^2) of the variance (Chi-test 37.5, df 1, $p<0.001$) and correctly classified 80.8% of the cases.

Combination of clinical/demographical and additional investigations predictors for primary psychiatric disorders

Gender, stereotypy (SRI), depressive symptoms (MADRS) and neuroimaging (frontal and/or anterior temporal atrophy on MRI or hypometabolism on [^{18}F] FDG-PET) were included in model 3. Neuroimaging was categorized. With backward stepwise logistic regression, the final model included neuroimaging at baseline (OR 0.02 95% 0.02-0.21), less stereotypy measured with the SRI (OR 0.08 95% 0.02-0.34) and more depressive symptoms measured with the MADRS (OR 1.13 95% 1.04-1.24). Model 3 explained 66.1% (Nagelkerke R^2) of the variance in diagnosis of PsD versus *probable/definite* bvFTD (Chi-test 44.06, df 3, $p<0.001$) and correctly classified 89.6% of the cases.

DISCUSSION

In this prospective study, we investigated which combination of clinical characteristics could distinguish between PsD and *probable/definite* bvFTD. We found that the variables male gender, less stereotypy based on a low score on the SRI, and more depressive symptoms with high scores on the MADRS have good predicting abilities for PsD versus *probable/definite* bvFTD in a cohort of patients with late onset behavior changes. Furthermore, we found that neuroimaging with absence of frontotemporal abnormalities predicted a PsD versus *probable/definite* bvFTD with a relatively good accuracy. The combination of clinical phenotyping and neuroimaging showed the most accurate prediction of PsD versus *probable/definite* bvFTD.

In comparison with our previous cross-sectional study, in which predictors of baseline diagnoses were explored, we found no significant association with

positive psychiatric history in predicting psychiatric disorders.[38] However, the clinical variables male gender, a low SRI score and high MADRS score were to be consistent predictors for a psychiatric diagnosis in our present study. In our and other previous studies, abnormal social behavioral changes such as decrease of emotional reactivity, loss of self-awareness and impulsivity were indicative for bvFTD compared to psychiatric disorders.[40] However, we found that stereotypical/compulsive behavior assessed with the SRI appeared to be better than other types of abnormal behavior measured with the FBI in predicting primary psychiatric disorders versus bvFTD.[41 42] This finding could be explained by the fact that in our present cohort primary psychiatric diagnosis presenting with stereotyped/compulsive behavioral such as schizophrenia or obsessive compulsive disorders[9] were underrepresented, which could clarify the strong association of the SRI with the bvFTD group.

Another finding was that depressive symptoms measured with the MADRS were predictive for PsD versus *probable/definite* bvFTD. This finding is probably driven by the fact that in our cohort predominately mood disorders were included. However, this is a remarkable finding as we also know that 33% of patients with bvFTD demonstrate depressive symptoms.[43] In addition, apathy is considered a bvFTD symptom,[7] however, can also be relatively often misinterpreted as a symptom of depression.[44 45] Consequently, both symptoms of depression or the misinterpretation of apathy contributes to the difficulty to distinguish between bvFTD or mood disorders in a daily clinical practice.[26] The MADRS as an instrument was designed to measure the course and severity of depressive symptoms but the current study shows that it can also have an important contributory role in distinguishing between PsD from bvFTD[30] by differentiating between symptoms of depression and apathy. More specific, patients with behavioral changes and a higher score on the MADRS are more likely to have a diagnose of PsD than bvFTD.

It is somewhat surprising that the total scores of the FBI and FAB, the clinically mostly used instruments, were found not to be able to differentiate between PsD and bvFTD. For the FAB, there are two likely explanations for this finding. First, executive dysfunction as measured with the FAB is not unique to bvFTD but also PsD have executive dysfunction both in an active or remitted psychiatric state.[46] Secondly, the FAB is previously found to be a poor discriminator, however, only analyzed between types of dementia.[47 48] Overall, it can thus be suggested that this

instrument is only useful to screen for executive dysfunction in brain disorders. Furthermore, that the FBI does not differentiate between PsD and bvFTD underscores the symptomatic overlap between these illnesses and explains our finding.

Male gender was associated with a psychiatric diagnosis in our predictive model 1 and lost its significance in model 3 due to the stronger associating of neuroimaging. However, 'Gender' as predictor for a PsD versus *probable/definite* bvFTD needs to be taken with caution, because FTD is considered to have an equal gender incidence,[49] with some studies reporting even an overrepresentation of male gender.[3 7] Psychiatric disorders, in contrast, show varying gender distributions across disorders.[50]

Neuroimaging with absence of frontotemporal abnormalities on the MRI or MRI and hypometabolism on [^{18}F] FDG-PET predicted relatively well a primary psychiatric disorder versus *probable/definite* bvFTD. This indicates that neuroimaging without frontotemporal abnormalities, is also relevant in the diagnostic process when distinguishing primary psychiatric disorders from bvFTD. The diagnostic certainty of bvFTD increases when frontotemporal abnormalities are found on neuroimaging.[4 7 51] However, model 2 did not explain 100% of the variance, indicating that several cases with a psychiatric disorder also showed frontotemporal abnormalities on neuroimaging. Furthermore, some bvFTD cases lack the specific frontotemporal neuroimaging abnormalities, especially genetic cases of bvFTD.[52 53]

The combination of clinical phenotyping and neuroimaging showed the most accurate prediction for PsD versus *probable/definite* bvFTD. Moreover, our group previously showed that neuroimaging and CSF biomarkers have impact on the diagnostic process in this clinically relevant neuropsychiatric cohort[54] and our study supports this finding by the increase of the explaining variance for PsD when using neuroimaging in combination with clinical phenotyping. The present finding that CSF biomarkers were not significantly contributing in predicting PsD versus *probable/definite* bvFTD was not surprising because the standard biomarkers used in this study have previously been described to be non-specific for *probable/definite* bvFTD or psychiatric disorders.[55] Furthermore, a neuropsychological profile with predominantly executive dysfunction had no significant value in predicting PsD versus *probable/definite* bvFTD disorders. This can be explained by fact that cognitive deficits are also found in PsD. Thus, our

data confirm that the best approach to establish a diagnosis of PsD in patients with behavioural disturbances is the combination of both qualitative and quantitative clinical assessment and neuroimaging.

The most important limitation of our study lies in the fact that we included only a few definite bvFTD cases, so we had to rely on the clinical consensus diagnosis and additional investigations. However, all patients underwent an extensive screening and were evaluated in a multidisciplinary panel in an academic memory-clinic. Secondly, due to relatively limited numbers of subjects, many missing data at baseline and the use of logistic regression analyses in this study, the generalizability must be taken with caution and our findings need to be replicated in an independent sample that included more psychiatric bvFTD mimics such as schizophrenia and obsessive compulsive disorder. And additional psychiatric symptoms, such as psychotic features, should be tested. We acknowledge that our study has to some extent an incorporation bias as most tests were part of the diagnostic procedure. However, by using a two-year follow-up diagnosis as dependent variable we attempted to avoid this. By dichotomizing the additional investigations in positive or negative, we ignored small differences in these variables between the diagnostic groups.

A major strength of this study is the inclusion of patients based on a symptom profile with late onset behavioural change, thereby reflecting the daily practice of a psychiatrist and neurologist and thereby providing clinically relevant results. Another important strength is the prospective design of our study, since retrospective rating of clinical characteristics or biomarkers is hampered by recollection bias and incomplete documentation.

In conclusion, this present study demonstrates that primary psychiatric disorders can be highly distinguished from *probable/definite* bvFTD with a thorough clinical evaluation by a psychiatrist and neurologist in addition with validated questionnaires for depression and stereotypy, and even more in combination with neuroimaging. Early recognizing of primary psychiatric disorders or bvFTD, and an early start with appropriate treatment and counselling for caregivers is to be gained. Furthermore, our findings suggest that more research is needed for complementary and disease specific biomarkers, which will increase the diagnostic specificity of primary psychiatric disorders and bvFTD.

REFERENCES

1. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. In: *Dementia and Geriatric Cognitive Disorders*. Vol 17. ; 2004:265-268. doi:10.1159/000077151.
2. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140-143. doi:10.1192/bjp.180.2.140.
3. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615-1621. doi:10.1212/WNL.58.11.1615.
4. Harris JM, Gall C, Thompson JC, et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology*. 2013;80(20):1881-1887. doi:10.1212/WNL.0b013e318292a342.
5. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007;64(6):830-835. doi:10.1001/archneur.64.6.830.
6. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. *Neurology*. 2009;72(8):732-737. doi:10.1212/01.wnl.0000343004.98599.45.
7. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
8. Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry.
9. Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical Approach to the Differential Diagnosis Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders.
10. American Psychiatric Association. *DSM-IV*.; 2000.
11. Shinagawa S, Catindig J, Block N, Miller B, Rankin K. When a little knowledge can be dangerous: False positive diagnosis of bvFTD among community clinicians. *Am J Neurodegener Dis*. 2014;3:374.
12. Diehl-Schmid J, Schmidt E-M, Nunnemann S, et al. Caregiver Burden and Needs in Frontotemporal Dementia. *J Geriatr Psychiatry Neurol*. 2013;26(4):221-229. doi:10.1177/0891988713498467.
13. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.
14. Van Der Flier WM, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: The Amsterdam dementia cohort. *J Alzheimer's Dis*. 2014;41(1):313-327. doi:10.3233/JAD-132306.

15. Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry*. 2012;83(4):358-364. doi:10.1136/jnnp-2011-301883.
16. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.
17. Milan G, Lamenza F, Iavarone A, et al. Frontal Behavioural Inventory in the differential diagnosis of dementia. *Acta Neurol Scand*. 2008;117(4):260-265. doi:10.1111/j.1600-0404.2007.00934.
18. Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res*. 2002;110(2):175-187. doi:10.1016/S0165-1781(02)00094
19. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *JNeurol*. 1995;242(0340-5354 (Print)):557-560. doi:10.1007/BF00868807.
20. Koedam ELGE, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YAL, Fox N et al. Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol*. 2011.
21. Fazekas F, Chawluk JB, Alavi A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Neuroradiol*. 1987;8(3):421-426. doi:10.2214/ajr.149.2.351.
22. Vijverberg EGB, Wattjes MP, Dols A, et al. Diagnostic Accuracy of MRI and Additional [18 F]FDG-PET for Behavioral Variant Frontotemporal Dementia in Patients with Late Onset Behavioral Changes. *J Alzheimer's Dis*. xx. doi:10.3233/JAD-160285.
23. Mckeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65:1863-1872. doi:10.1212/01.wnl.0000224698.67660.45.
24. Gorno-Tempini ML, Hillis a E, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1-10. doi:10.1212/WNL.0b013e31821103e6.
25. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-260. doi:10.1212/WNL.43.2.250.
26. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011. doi:10.4088/JCP.10m06382oli.

27. Mckeith IG. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2006;66(September 2004):1455; author reply 1455. doi:10.1212/01.wnl.0000224698.67660.45.
28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6.
29. Dubois B, Slachevsky a, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626. doi:10.1212/WNL.57.3.565.
30. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382-389. doi:10.1192/bjp.134.4.382.
31. Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276. doi:10.2466/PMS.8.7.271-276.
32. Benton A, Hamsher K. *Multilingual Aphasia Examinationle*.; 1983. doi:10.1076/clin.15.1.13.1911.
33. Wilson, B. Alderman, N., Burgess, P., Emslie, H., Evans J. Behavioural Assessment of the Dysexecutive Syndrome (BADS). *J Occup Psychol Employ Disabil*. 2003;5(2):33-37. doi:10.1080/09602010802622730.
34. Rey A. *L'examen Clinique En Psychologie.*; 1958.
35. Lindeboom J. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry*. 2002;73(2):126-133. doi:10.1136/jnnp.73.2.126.
36. Warrington EK, James M. *The Visual Object and Space Perception Battery*.; 1991.
37. Duits FH, Teunissen CE, Bouwman FH, et al. The cerebrospinal fluid "alzheimer profile": Easily said, but what does it mean? *Alzheimer's Dement*. 2014;10(6):713-723. doi:10.1016/j.jalz.2013.12.023.
38. Dols A, van Liempt S, Gossink F, et al. Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome. *J Clin Psychiatry*. 2016
39. Midi H, Sarkar SK, Rana S. Collinearity diagnostics of binary logistic regression model. *J Interdiscip Math*. 2010;13(3):253-267. doi:10.1080/09720502.2010.10700699.
40. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. 2008;69(1):60-73. doi:10.4088/JCP.v69n0109.
41. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand*. 2001;103(6):367-378. doi:ane236
42. Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. Compulsive behaviors as presenting symptoms of frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 1997;10:154-157.

43. Chakrabarty T, Sepehry AA, Jacova C, Hsiung GYR. The prevalence of depressive symptoms in frontotemporal dementia: A meta-analysis. *Dement Geriatr Cogn Disord*. 2015;39(5-6):257-271. doi:10.1159/000369882.
44. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. *J Am Geriatr Soc*. 2001;49(12):1700-1707. doi:10.1046/j.1532-5415.2001.49282.
45. Ishii S, Weintraub N, Mervis JR. Apathy: A Common Psychiatric Syndrome in the Elderly. *J Am Med Dir Assoc*. 2009;10(6):381-393. doi:10.1016/j.jamda.2009.03.007.
46. Meesters PD, Schouws S, Stek M, et al. Cognitive impairment in late life schizophrenia and bipolar i disorder. *Int J Geriatr Psychiatry*. 2013;28(1):82-90. doi:10.1002/gps.3793.
47. Castiglioni S, Pelati O, Zuffi M, Somalvico F, Marino L, Tentorio T et al. The Frontal Assessment Battery Does Not Differentiate Frontotemporal Dementia from Alzheimer's Disease. *Dement Geriatr Cogn Disord*. 2006.
48. Boban M. b, Malojčić B. b, Mimica N. c, Vuković S., Zrilić I. The frontal assessment battery in the differential diagnosis of dementia. *J Geriatr Psychiatry Neurol*. 2012;25(4):201-207. doi:10.1177/0891988712464821.
49. Rosso SM, Kaat LD, Baks T, et al. Frontotemporal dementia in The Netherlands: Patient characteristics and prevalence estimates from a population-based study. *Brain*. 2003;126(9):2016-2022. doi:10.1093/brain/awg204.
50. Kessler RC, McGonagle K a, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8-19. doi:10.1001/archpsyc.1994.03950010008002.
51. Vijverberg EGB, Dols A, Krudop WA, et al. Diagnostic accuracy of the frontotemporal dementia consensus criteria in the late-onset frontal lobe syndrome. *Dement Geriatr Cogn Disord*. 2016;41(3-4):210-219. doi:10.1159/000444849.
52. Beck J, Rohrer JD, Campbell T, et al. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. *Brain*. 2008;131(3):706-720. doi:10.1093/brain/awm320.
53. Whitwell JL, Boeve BF, Weigand SD, Senjem ML, Gunter JL, Baker MC et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. *Eur J Neurol*. 2015.
54. Krudop WA, Dols A, Kerssens CJ, et al. Impact of Imaging and Cerebrospinal Fluid Biomarkers on Behavioral Variant Frontotemporal Dementia Diagnosis within a Late-Onset Frontal Lobe Syndrome Cohort. *Dement Geriatr Cogn Disord*. 2016. doi:10.1159/000441023.
55. Schoonenboom NSM, Reesink FE, Verwey NA, Kester MI, Teunissen CE, van de Ven PM et al. Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology*. 2012.

Section 3. Disease course in the late onset frontal lobe syndrome

6. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia

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ABSTRACT

Introduction

The frontotemporal dementia (FTD) consortium criteria (2011) emphasize the importance of distinguishing possible and probable behavioural variant FTD (bvFTD). A significant number of possible patients with bvFTD do not show functional decline and remain with normal neuroimaging over time, thus exhibiting the bvFTD phenocopy syndrome. A neurodegenerative nature is unlikely but an alternative explanation is missing. Our aim was to detect psychiatric conditions underlying the bvFTD phenocopy syndrome after extensive evaluation.

Methods

We included patients with the bvFTD phenocopy syndrome whereby patients with probable bvFTD served as a control group. Patients had to have undergone both neurological and psychiatric evaluation. Their charts were reviewed retrospectively. Using both qualitative and quantitative methods, psychiatric and psychological conditions associated with the clinical syndrome were determined in both groups and their relative frequencies were compared.

Results

Of 181 suspected bvFTD cases, 33 patients with bvFTD phenocopy syndrome and 19 with probable bvFTD were included. Recent life events, relationship problems and cluster C personality traits were the most prevalent psychiatric/psychological conditions. The frequency of these conditions was higher in the group of patients with the bvFTD phenocopy syndrome (n=28) compared to the probable bvFTD group (n=9) ($\chi 2$ $p<0.05$).

Conclusions

This is the first study thoroughly exploring psychiatric causes of the bvFTD phenocopy syndrome, revealing that in most cases multiple factors played a contributory role. Our study gives arguments for neurological and psychiatric collaboration when diagnosing bvFTD. Prompt diagnosis of treatable psychiatric conditions is to be gained.

INTRODUCTION

The behavioural variant frontotemporal dementia (bvFTD) is the most prevalent form of FTD and is characterized by early and progressive changes in behaviour, personality and cognition. Disturbances in social cognition represent the earliest and core symptoms of bvFTD resulting in socially inappropriate responses or activities.[1 2] Patients also experience difficulty in adjusting behaviour and this often results in personality changes. The differential diagnosis of bvFTD is extensive and includes both other neurodegenerative diseases and psychiatric disorders. Whereas the distinction between bvFTD and Alzheimer's disease has become easier by the use of biomarkers, the distinction between bvFTD and psychiatric disorders is still difficult, particularly when frontotemporal atrophy on neuroimaging is absent.

In 2011 the International bvFTD Criteria Consortium established new diagnostic criteria whereby a degree of probability was assigned to the clinical diagnosis.[3] A diagnosis of *possible* bvFTD is based on the clinical hallmarks, whereas for a diagnosis of *probable* bvFTD, both functional decline and frontotemporal abnormalities on neuroimaging are required. Some patients with a diagnosis of possible bvFTD will develop changes on neuroimaging or will be found to have a genetic mutation and will therefore be re-classified as probable or definite bvFTD. Nevertheless, a significant number of possible bvFTD patients do not progress clinically to probable bvFTD and their neuroimaging results remain unchanged over time. This syndrome has been termed the benign bvFTD phenocopy syndrome.[4]

In terms of prognosis and treatment, the benign bvFTD phenocopy syndrome forms a substantial clinical dilemma. Studies of function and disease progression in bvFTD showed that these phenocopy patients do not decline cognitively or socially.[5 6] Importantly, after at least three years of follow up phenocopy patients demonstrated a significant longer survival to institutionalization and death.[7 8] In addition, cases diagnosed clinically as bvFTD without pathological changes at post mortem as reported in other studies highlighted again the importance of clinically detecting these phenocopy patients in an early stage.[9 10 11]

The aetiology of the bvFTD phenocopy syndrome has been reported to be variable, ranging from mood disorders, to autism spectrum disorders with decompensation due to altered life circumstances, but in the majority of cases its cause remains unknown.[12 13 14 15] Remarkably, although psychiatric factors have been suggested,

this has never been systematically explored. The purpose of our study was therefore to perform a quantitative and qualitative assessment of psychiatric conditions associated with the benign bvFTD phenocopy syndrome.

METHODS

Design

In this systematic retrospective chart review we studied bvFTD phenocopy syndrome patients and compared them to patients with probable bvFTD. Charts of patients with suspected bvFTD seen at the Alzheimer center VUmc Amsterdam and the psychiatry outpatient clinic for the elderly at GGZinGeest, from January 2002 to December 2011 were studied. Patients were directed to these specialized health care institutions by primary care physicians or a medical specialist. For the baseline diagnostic procedure, all patients underwent a standardized assessment, including medical history and family history, informant-based history, physical, neurological and psychiatric examinations, neuropsychological assessment, laboratory tests, and both MRI as well as PET or SPECT of the brain. Diagnoses were made by both a neurologist as well as a psychiatrist in a multidisciplinary consensus meeting. Through neuropsychiatric evaluation a descriptive diagnosis and if appropriate a categorical DSM4 diagnosis was made.[16]

In- and exclusion criteria

Patients were included if they retrospectively fulfilled the Rascovsky criteria for *possible* bvFTD without progression to probable or definite bvFTD over time (benign bvFTD phenocopy patients) or probable bvFTD (control group).[3] According to diagnostic criteria, patients with probable bvFTD had to have either supportive structural or functional imaging (or both), while benign bvFTD phenocopy patients had to have both normal structural (MRI) as well as functional (PET or SPECT) neuroimaging results. In addition, benign bvFTD phenocopy patients were only included if they did not exhibit functional decline during the course of their disease as measured by scores at *Mini Mental State Examination* and *Frontal Assessment Battery*. The course of disease had to be at least one year. To be included patients had to have undergone extensive neuropsychiatric evaluation by both an experienced geriatric psychiatrist as well as a neurologist in enhanced collaboration. Patients with frontal or temporal abnormalities on MRI/PET or SPECT like a tumour or gliosis were excluded.

As shown in figure 1, out of 181 patients with suspected bvFTD, 33 were identified as benign_bvFTD phenocopy syndrome cases and 60 as probable bvFTD cases, according to the Racovsky criteria.[3] Nineteen of the probable bvFTD patients had undergone extensive neurological and psychiatric evaluation and this group served as control group.

Data analysis

Data analysis was performed through a mixed methods approach: a combination of qualitative and quantitative analysis in a sequential procedure.[17 18 19 20] For exploratory purposes, analysis began with the qualitative method of producing themes out of included benign bvFTD phenocopy syndrome patients' DSM4 diagnoses and descriptive diagnoses.[16] Producing themes consisted of detecting both hard diagnosis (e.g. depression) as well as descriptive labeling (e.g. relationship problems), which were described by the neurologist and psychiatrist as underlying conditions for the benign bvFTD phenocopy syndrome. In this manner, out of the largely qualitative data (DSM4 diagnoses and descriptive diagnoses), a set of nominally scaled categories were formed. This framework of categories was used for quantitative analysis whereby the relative frequencies of the psychiatric and psychological conditions were compared between the benign bvFTD phenocopy syndrome group and the probable bvFTD group.

Descriptive statistical analyses were performed using the SPSS version 21. Differences between groups were analyzed using X^2 tests, Fisher's exact and t-tests.

Ethical considerations

The study was approved by the Medical Ethical Committee of the VU Medical Centre, Amsterdam.

RESULTS

Patient characteristics

Demographic data of the 33 benign bvFTD phenocopy syndrome patients and the group of 19 probable bvFTD patients are displayed in table 1. Whereas the groups did not differ with respect to disease duration, there was a strong male predominance in the benign bvFTD phenocopy syndrome only and patients in this group were significantly younger.

	bvFTD phenocopy syndrome n=33	Probable bvFTD n=19	**P value**
Demographics			
Gender % male	94	68	0.014 (X^2)
Mean Age at presentation (years) (SD)	59.9 (6.6)	65.0 (9.4)	0.047 (t-test)
Mean symptom duration (years) (SD)	3.8 (2.7)	2.6 (3.2)	0.704 (t-test)

Table 1. Demographics of bvFTD phenocopy syndrome patients and probable bvFTD patients

Psychiatric and psychological conditions

In the benign bvFTD phenocopy group, 85.2 % of patients had psychiatric or psychological conditions that mainly consisted of recent life events, relationship problems and cluster C personality traits. The psychiatric and psychological conditions that were identified in benign bvFTD phenocopy syndrome patients are presented in table 2 and table 3. Twelve patients (36.4%) had experienced a serious life event within two years before onset of symptoms including loss of a first degree family member and recent unemployment. By the patients or their spouses, these life events were referred to as very intrusive and affecting daily life. Ten benign bvFTD phenocopy patients experienced intense relationship problems at the moment of presentation (30.3%). The onset of these relationship problems ranged from eight years up to one year before the onset of bvFTD symptoms. The severity of relationship problems was such that one or both of the partners considered a divorce as an option. Mood disorders were diagnosed according to DSM4 criteria.[16] A mood disorder was present in 11 benign bvFTD phenocopy patients (33.3%), consisting of a current depressive episode and depression within two years before onset of symptoms in 7 patients (21.2%), and a bipolar disorder without a current depressive or manic episode and with adequate use of pharmacotherapeutic maintenance therapy (lithium or valproate) in 4 patients. Five out of seven patients with a depression had to deal with psychomotor agitation or retardation as part of their depression. Eight patients (24.2 %) were diagnosed as having Cluster C personality traits, defined as dependent or obsessive compulsive personality traits

according to DSM4.[16] Other codes had a smaller share: 3 patients (9.1%) were intellectually disabled (as concluded by neuropsychological test), and 2 patients (6.1%) had alcohol dependence at moment of presentation or within two years before onset of symptoms. Anxiety disorder occurred in 2 patients (6.1%), and Autism Spectrum Disorder was seen in only one patient. There were no patients with a psychotic disorder.

Among benign bvFTD_phenocopy patients the combination of either a mood disorder or recent intense life event with Cluster C personality traits turned out to be most notable (7 patients, 21.2%), followed by the combination of a recent intense life event together with a mood disorder or relationship problems (4 patients, 12.1%). As visualized in table 3, multiple conditions were present in 13 benign bvFTD_phenocopy patients (39.4%), highlighting again the complexity of the benign bvFTD phenocopy syndrome.

In the probable bvFTD group, 47.4 % of patients had psychiatric or psychological conditions that mainly consisted of a major depressive disorder and to a lesser extent alcohol abuse and relationship problems. The total number of subjects with a psychiatric or psychological condition was significantly lower than in the benign bvFTD phenocopy group (84.8%, *Fisher's exact P* 0.009). Frequencies of individual symptoms are indicated in table 2, 3 and 4.

Psychiatric or psychological condition, n (% of group)	**bvFTD phenocopy n=33**	**Probable bvFTD n=19**	**P value**
Bipolar Disorder	4 (12.1)	0 (0)	0.284 (F)
Major Depressive Disorder	7 (21.2)	6 (31.6)	0.305 (F)
Anxiety disorder	2 (6.1)	1 (5.3)	1.000 (F)
Alcohol abuse	2 (6.1)	2 (10.5)	0.617 (F)
Recent intense life event	12 (36.4)	1 (5.3)	0.018 (F)
Cluster C personality traits	8 (24.2)	0 (0)	0.021 (F)
Autism Spectrum Disorder	1 (3.0)	0 (0)	1.000 (F)
Intellectual Disability	3 (9.1)	0 (0)	0.291(F)
Relationship problems	10 (30.3)	2 (10.5)	0.172(F)
With psychiatric and psychological conditions	28 (84.8)	9 (47.4)	0.004 (X^2) 0.009 (F)

Table 2. Psychiatric and psychological conditions of bvFTD phenocopy patients and probable bvFTD patients

Patients n=33/ Psychiatric or psychological condition	**BD**	**MDD**	**AD**	**AB**	**RLE**	**PDC**	**ASS**	**ID**	**MP**	**WPPC**
Gender, age (years), symptom duration (years)										
Male, 59, 2.5	•									
Male, 71, 2.5	•									
Male, 62, 1	•					•				
Male, 65, 5	•				•					
Male, 54, 6		•	•		•				•	
Male, 61, 6		•	•		•	•				
Male, 46, 2.5		•				•		•		
Female, 70, 13		•								
Male, 57, 4		•								
Female, 70, 1		•								
Male, 57, 2		•								
Male, 58, 2.5					•	•				
Male, 53, 3					•	•				
Male, 66, 3					•	•				
Male, 47, 4					•					
Male, 65, 7					•		•			
Male, 61, 3					•					
Male, 63, 3					•					
Male, 52, 3.5					•			•	•	
Male, 65, 10				•	•	•				
Male, 53, 4						•		•	•	
Male, 64, 5									•	
Male, 57, 1				•					•	
Male, 56, 2									•	
Male, 64, 1									•	
Male, 57, 1									•	
Male, 55, 4									•	
Male, 63, 5									•	
Male, 50, 8										•
Male, 59, 2.5										•
Male, 65, 0.5										•
Male, 72, 2.5										•
Male, 59, 3.5										•

Table 3. Psychiatric and psychological conditions in 33 bvFTD phenocopy patients

Legend: BD=Bipolar Disorder, MDD=Major Depressive Disorder, AD=Anxiety Disorder, AB=Alcohol Abuse, RLE=Recent Life events, PDC=Traits personality disorder cluster C, ASS=AutismSpectrum Disorder, ID=Intellectual Disability, MP=Marital problems, WPPC=Without psychiatric/psychological condition

Patients n=19/ Psychiatric or psychological condition	**BD**	**MD**	**AD**	**AB**	**RLE**	**PDC**	**ASS**	**ID**	**MP**	**WPPC**
Gender, age(years), symptom duration(yrs)										
Male, 74, 2										•
Female, 50, 1		•								
Female, 60, 1										•
Male, 55, 1										•
Male, 57,3										•
Male, 60, 1.5									•	
Male, 63, 1.5		•								
Male, 63, 2.5		•								
Female, 83, 2										•
Female, 65, 1			•							
Male, 75,2				•	•					
Female, 70,2		•		•						
Female, 79,6		•								
Male, 56,2										•
Male, 77,2										•
Male, 68, 1.5										•
Male, 68, 2										•
Male, 56,15		•							•	
Male, 55,1										•

Table 4. Psychiatric and psychological conditions in 19 probable bvFTD patients
Legend: BD=Bipolar Disorder, MDD=Major Depressive Disorder, AD=Anxiety Disorder, AB=Alcohol Abuse, RLE=Recent Life events, PDC=Traits personality disorder cluster C, ASS=Autism Spectrum Disorder, ID=Intellectual Disability, MP=Marital problems, WPPC=Without psychiatric/psychological condition

DISCUSSION

This is the first study thoroughly exploring psychiatric causes of the bvFTD phenocopy syndrome, revealing that in the majority of cases a psychiatric or psychological explanation was present. In most cases of the benign bvFTD phenocopy syndrome, multiple conditions were present. According to previous research on the bvFTD phenocopy syndrome most of our included benign bvFTD phenocopy cases were men and they were younger than patients with probable bvFTD.[5 21 8] Psychiatric and psychological conditions were more prevalent in the benign bvFTD phenocopy syndrome than in probable bvFTD, thereby suggesting that these factors might indeed be contributory to the clinical syndrome.

At a closer look, in accordance with previous hypotheses mood disorders had a relatively large share in benign bvFTD phenocopy syndrome patients (both major depressive disorder as well as bipolar disorder).[13] A bipolar disorder seemed to be more often present in phenocopy patients than in probable bvFTD patients. However, the relative frequency of a depression among phenocopy patients wasn't higher than among probable bvFTD patients, but exceeded the community prevalence of depression in late life.[22] Previous studies suggested depressive traits in neurodegenerative bvFTD, ranging from 33% up to 47% which might explain why the phenocopy group and probable bvFTD group showed approaching frequencies of depression.[23 24] Relative frequencies of alcohol abuse among phenocopy patients and probable bvFTD cases were also approaching, possibly due to symptom overlap and comorbidity, as studies reported compulsive consummatory behaviours in bvFTD, including alcohol abuse.[25 26]

Striking in the results is the high proportion of cluster C personality traits, intense life events and relationship problems. Although an Autism Spectrum Disorder may resemble clinical features of frontotemporal dementia, especially together with altered life circumstances as was suggested by Hodges, we saw this only in one case of the benign bvFTD phenocopy syndrome.[27 4] In most patients with the benign bvFTD phenocopy syndrome different psychiatric and psychological conditions together were present. Knowledge of these patterns urges close neurological and psychiatric collaboration in the diagnosis of bvFTD. Prompt diagnosis of a treatable psychiatric condition is to be gained.

There are some limitations in this study. First of all, included patients with the benign bvFTD phenocopy syndrome did not have a pathological diagnosis, which is inherent to the benign nature of their disorder. Meanwhile, genetic information of these patients is absent while most patients were seen before the discovery of the C9ORF72 gene expansion. Nowadays it is known that very slow progression may be seen especially in subjects carrying a C9ORF72 hexanucleotide expansion.[28] Since the mean symptom duration of the benign bvFTD phenocopy syndrome was almost four years, however we are confident that we would have captured functional decline if present. Another limitation is referral bias for the probable bvFTD group. In accordance to patients with the benign bvFTD phenocopy syndrome, this probable bvFTD group had undergone extensive psychiatric evaluation. Due to the motive for extensive psychiatric evaluation these patients were more vulnerable of having psychiatric and psychological conditions than a general bvFTD group. Despite this issue, we still found higher frequencies of psychiatric and psychological conditions in subjects with the benign bvFTD phenocopy syndrome. By using qualitative analysis as part of the mixed methods, a subjective contribution is also not excluded.

A prospective study with evaluation of treatment of psychiatric disorders included, would strengthen our results. Besides, to follow patients fully systematically with standard instruments and with probable bvFTD patients as a control group, a prospective follow-up study of patients with late-onset behavioral disorders is needed.

REFERENCES

1. Seeley WW, Crawford R, Rascovsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol*. 2008;65(2):249-255. doi:10.1001/archneurol.2007.38.
2. Lough S, Hodges JR. Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *J Psychosom Res*. 2002;53(2):639-646. doi:10.1016/S0022-3999(02)00433-6.
3. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
4. Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome". *Curr Opin Neurol*. 2010;23(6):628-632. doi:10.1097/WCO.0b013e3283404309.
5. Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? *J Neurol Neurosurg Psychiatry*. 2009;80(6):591-593. doi:10.1136/jnnp.2008.163873.
6. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: Diagnosis, clinical staging, and management. *Lancet Neurol*. 2011;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
7. Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in Frontotemporal Dementia. *Group*. 2006;63(11):1627-1631. doi:10.1001/archneur.63.11.1627.
8. Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: Application of an MRI visual rating scale. *Dement Geriatr Cogn Disord*. 2007;23(5):334-342. doi:10.1159/000100973.
9. Piguet O, Halliday GM, Reid WGJ, et al. Clinical phenotypes in autopsy-confirmed pick disease. *Neurology*. 2011;76(3):253-259. doi:10.1212/WNL.0b013e318207b1ce.
10. Devenney, E., Forrest, S. L., Xuereb, J., Kril, J. J., & Hodges JR. The bvFTD phenocopy syndrome: a clinicopathological report. *J Neurol Neurosurg Psychiatry*. 2016.
11. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain*. 2005;128(9):1996-2005. doi:10.1093/brain/awh598.
12. Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome." *Curr Opin Neurol*. 2010;23(6):628-632. doi:10.1097/WCO.0b013e3283404309.

13. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol*. 2010;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
14. Rabinovici G, Miller B. *Frontotemporal Lobar Degeneration: Epidemiology, Pathophysiology, Diagnosis and Management*. Vol 24.; 2010. doi:10.2165/11533100-000000000-00000.Frontotemporal.
15. Rascovsky K, Grossman M. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. *Int Rev Psychiatry*. 2014;25(2):145-158. doi:10.3109/09540261.2013.763341.Clinical.
16. American Psychiatric Association. *DSM-IV*.; 2000.
17. Maudsley G. Mixing it but not mixed-up: Mixed methods research in medical education (a critical narrative review). *Med Teach*. 2011;33(2):e92-e104. doi:10.3109/0142159X.2011.542523.
18. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. *BMJ*. 2010;341(aug07_3):c4587. doi:10.1136/bmj.c4587.
19. Charmaz K. Constructing Grounded Theory: A Practical Guide through Qualitative Analysis. *Constr Grounded Theory A Pract Guid Through Qual Anal*. 2006:SAGE Publications Ltd. doi:10.1016/j.lisr.2007.11.003.
20. Creswell JW. *Research Design: Qualitative, Quantitative, and Mixed Methods Approaches*.; 2013. doi:10.1007/s13398-014-0173-7.2.
21. Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in Frontotemporal Dementia Identifying a Benign Behavioral Variant by Magnetic Resonance Imaging. *Arch Neurol*. 2006;63:1627-1631. doi:10.1001/archneur.63.11.1627.
22. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *BrJPsychiatry*. 1999;174:307-311.
23. Waldö ML, Gustafson L, Passant U, Englund E. Psychotic symptoms in frontotemporal dementia: a diagnostic dilemma? *Int Psychogeriatrics*. 2015;27(4):531-539. doi:10.1017/S1041610214002580.
24. Sepehry A, Chakrabarty T JC. Prevalence of depressive mood in frontotemporal dementia (FTD): a meta-analyses of studies from 2000 to present. *Alzheimer's &Dementia J Alzheimer's Assoc*. 2013;9(4):607.
25. Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(4):371-376. doi:10.1136/JNNP.73.4.371.
26. Crews FT, Boettiger CA. Impulsivity, frontal lobes and risk for addiction. *Pharmacol Biochem Behav*. 2009;93(3):237-247. doi:10.1016/j.pbb.2009.04.018.
27. Kipps CM, Hodges JR, Fryer TD, Nestor PJ. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. *Brain*. 2009;132(Pt 9):2566-2578. doi:10.1093/brain/awp077.

28. Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry*. 2012;83(4):358-364. doi:10.1136/jnnp-2011-301883.

7. Predicting progression in the late onset frontal lobe syndrome

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ABSTRACT

Background

A late onset frontal lobe syndrome (LOF) refers to a clinical syndrome with apathy, disinhibition or stereotypical behavior arising in middle or late adulthood. Diagnostics are challenging and both clinicians and patients need reliable predictors of progression to improve clinical guidance.

Methods

In this longitudinal multicentre and genetically screened prospective study, 137 LOF patients with frontal behavior (FBI score≥ 11) and/or stereotypical behavior (SRI≥ 10) were included. Progression was defined as institutionalisation, death or progression of frontal or temporal atrophy at MRI after two years of follow up. Absence of progression at MRI in addition to stable or improved MMSE and FAB scores after two years was indicative for non-progression.

Results

The presence of stereotypy and a neuropsychological profile with executive deficits at baseline were found to be predictive for progression, while a history and family history with psychiatric disorders were predictors for non-progression. The combination of these clinical markers had a predictive value of 80.4% ($p<0.05$).

Conclusion

In patients presenting with late onset behavioral symptoms, an appraisal of the rate of deterioration can be made by detailed mapping of clinical symptoms. Distinction of progressive discourses from non-progressive or treatable conditions is to be gained.

INTRODUCTION

The late onset frontal lobe syndrome (LOF) refers to a clinical syndrome associated with functional or structural changes in the frontal lobes leading to apathy, disinhibition or stereotypical behavior emerging in middle or late adulthood.[1] This syndrome gives rise to a broad differential diagnosis wherein the behavioral variant of frontotemporal dementia (bvFTD), other neurodegenerative diseases and psychiatric disorders are prominent. Highlighted by the fact that a large proportion of bvFTD patients initially receives a psychiatric diagnosis, identifying the appropriate etiology in LOF is often difficult.[1 2] In addition, patients with a *bvFTD phenocopy syndrome* add an extra level of complexity to the diagnosis as these patients present with possible bvFTD but do not convert to probable or definite bvFTD.[3]

Amidst these challenging diagnostics in LOF, guidance is needed regarding predictors that can determine progression and thereby prognosis. Hypotheses about predictors for progression in LOF can be distilled from research into underlying pathologies such as bvFTD and Alzheimer's Disease (AD), but whereas the differential diagnosis is broad and not always immediately clear, clinical markers able to distinguish a progressive discourse from non-progressive diseases in LOF are essential. In case of a non-progressive discourse, a curative treatment or at least symptomatic relief can be offered. As previous studies revealed caregivers' need for information about the course of illness (ref) insight in the expected disease course can also facilitate caregiver support.[4 5]

Previous studies on Alzheimer's disease revealed a higher age, higher education, being female, depression and a lower total score at the Mini Mental State Examination (MMSE) as clinical predictors for progression.[6] In a recent study about bvFTD and progression, it was found that a positive family history, memory impairment, clinical abnormalities (e.g. parkinsonism) and stereotypical behaviors were predictive for progression.[7 8] Although studies into predictors for progression in psychiatric disorders are scarce, early age of onset and high impulsivity are suggested as predictors for progression in some psychiatric disorders. [9]

The present study prospectively explored the outcomes in a multicentre and genetically screened cohort of patients presenting with LOF. We determined progression with both neuroimaging as well as clinical markers. First we studied the distribution of diagnoses among 'progressors' and 'non-progressors' after a two-year follow up, with the hypothesis that mainly neurodegenerative diseases

cause progression and psychiatric disorders show non-progression. Secondly, independent from the diagnosis, we examined predictors for progression to provide prognostic tools for clinical practice.

METHODS

Design and inclusion criteria

In this multicentre prospective follow-up study we included patients presenting with apathy, impulsive and/or stereotypy between 45 and 75 years of age. Patients were only included if they had a *Frontal Behavior Inventory* (FBI) score of 11 or higher and/or a *Stereotype Rating Inventory* (SRI) of 10 or higher. Other inclusion criteria are described elsewhere.[1] Patients were recruited through the memory clinic of the Alzheimer Center VUmc Amsterdam and the Old Age Psychiatry Department of GGZinGeest Amsterdam, the Netherlands between April 2011 and June 2013. All patients were diagnostically followed during 2 years.

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam and all patients signed a written consent form.

Progressors versus non-progressors

Progression after 2 years was defined as institutionalisation, death or progression of frontal or temporal atrophy at Magnetic Resonance Imaging (MRI) according to the medial temporal lobe atrophy (MTA) scale and the global cortical atrophy (GCA) scale. [10] [11] In order to strictly compare 'progressors' to patients who did not progress clinically or at imaging, non-progression was defined as the absence of progression at MRI in addition to stable or improved MMSE and Frontal Assessment Battery (FAB) scores.[12] [13]

Diagnostic procedure

At baseline and during follow-up all patients had undergone a standardized assessment, including medical and informant-based history, physical, neurological and psychiatric examinations, neuropsychological assessment and laboratory tests. MRI of the brain was acquired on a 3T Signa HDxt scanner (GE Medical Systems, Milwaukee, WI). In case of normal or insufficiently explanatory MRI results (not explaining frontosubcortical dysfunction), a [18F]FDG-PET scan was performed. Diagnostic evaluation were based on current guidelines and done by a neurologist

and an experienced geriatric psychiatrist in a multidisciplinary consensus meeting. Included subjects were genetically screened, especially for C9orf repeat expansion, given the long disease courses that have been described in these mutation types. [14]

Predictors for progression

To limit the number of variables in this relatively small sample size, based on predictors for progression found in AD, bvFTD and psychiatric disorders, [6 7] hypotheses were generated about predictors in LOF and these variables were measured in all patients. It was also examined whether patients fulfilled bvFTD international consensus criteria (table 1).[15]

Data analysis

Statistical analyses were performed using SPSS for Windows; IBM, Armonk, NY. Group differences were investigated using χ^2tests, independent t-tests and Mann-Whitney test. We performed univariate and multivariate logistic regression analyses with 'progressor'/ 'non-progressor' as dependent variable. Variables with *P*-values <0.05 were selected, and in the next step, these variables were combined with a multivariate model to investigate the explained variance. A p-value of <0.05 was considered statistically significant.

RESULTS

Included patients and demographic data

A total of 137 patients were included at baseline. After two years, 9 patients were dead, 5 were admitted to a nursing home and 21 showed progression of frontal or temporal atrophy at MRI (n=35 *progressors*). Twenty-eight patients did not progress at MRI and their score at MMSE and FAB remained stable or improved (n=28 *non-progressors*). Thirty-five patients did not progress at MRI but did clinically decline at MMSE or FAB and were therefore excluded. Thirty-nine patients did not have neuroimaging results after two years due to lost of follow up (n=15) or logistical problems or refusal of MRI (n=24) and were excluded. Demographic data are displayed in table 1.

	Progressor* n=35	**Non progressor* n=28**	**T-test/ X^2 (df)/P value**	**OR (95% CI)**	**P value**
Age, mean years (SD)	63.4 (6.67)	59.3 (6.53)	**0.04 (61) 0.02**	0.90 (0.84-0.99)	**0.02**
Sex (% male)	62.9	78.6	1.82 (1) 0.18	2.17 (0.70-6.73)	0.18
Symptom duration mean years (SD)	5.06 (5.01)	3.93 (2.54)	8.60 (61) 0.28	0.93 (0.81-1.06)	0.29
Education (%) Low Middle High	 13.8 51.7 34.5	 24.0 56.0 20.0	1.82 (2) 0.40	0.57 (0.25-1.31)	0.19
MMSE mean (SD)	25.8 (2.79)	26.1 (2.92)	0.03 (61) 0.70	1.04 (0.87-1.24)	0.70
FAB mean (SD)	14.0 (3.74)	14.6 (3.18)	1.15 (61) 0.50	1.05 (0.91-1.22)	0.50
SRI median (IQR), log	11.0 (16.0)	3.00 (6.0)	**0.62 (51) 0.04**	0.26 (0.07-0.98)	**0.047**
FBI mean (SD)	25.9 (8.35)	22.5 (9.94)	1.92 (61) 0.15	0.96 (0.91-1.02)	0.15
MADRS mean (SD)	10.4 (9.72)	10.5 (9.10)	0.03 (41) 0.97	1.00 (0.94-1.07)	0.97
Gait disturbances (%)	3.23	0	0.85 (1) 1.00	0.00 (0.00-1.00)	1.00
Tremor (%)	6.45	0	1.74 (1) 0.50	0.00 (0.00-1.00)	1.00
Corticospinal tract disturbance (%)	6.45	0	1.74 (1) 0.50	0.00 (0.00-1.00)	1.00
Lateralization (%)	9.68	0	2.66 (1) 0.24	0.00 (0.00-1.00)	1.00
History of psychiatric disorder (%)	28.6	57.1	**5.24 (1) 0.022**	3.33 (1.17- 9.51)	**0.02**
Family history psychiatric disorder (%)	17.1	42.9	**5.04 (1) 0.025**	3.63 (1.14-11.50)	**0.03**
Family history dementia (%)	37.1	35.7	0.01 (1) 0.91	0.94 (0.34-2.64)	0.91
Rascovsky (%) • Disinhibition • Apathy • Loss of empathy • Sterotypical behavior • Hyperorality • NPO	 71.4 74.3 77.1 62.9 74.3 35.3	 71.4 82.1 71.4 39.3 71.4 10.7	 0.02 (1) 1.00 0.56 (1) 0.46 0.27 (1) 0.77 3.47 (1) 0.06 0.06 (1) 0.80 **5.06 (1) 0.03**	 1.00 (0.33-3.00) 1.59 (0.47-5.44) 0.74 (0.24-2.31) 0.38 (0.14-1.06) 1.16 (0.38-3.53) 0.22 (0.06-0.88)	 1.00 0.46 0.61 0.07 0.80 **0.03**

Table1. Demographics and univariate logistic regression on variables in patients with and without progression.

* progression was defined as institutionalisation, progression of frontal or temporal atrophy at Magnetic Resonance Imaging (MRI) or death, non-progression was defined as the absence of progression at MRI in addition to stable or improved *Mini Mental State Examination (MMSE)* and *Frontal Assessment Battery (FAB)* scores.
Legend: SD=Standard Deviation, IQR=Inter Quartile Range, df=degrees of freedom, KW=Kruskal-Wallis Test, Education: low= less than four years of low or average level secondary education, middle= four years of low or average level secondary education, high= five years of high level secondary education or university degree, MMSE=Mini-Mental State Examination, FAB=Frontal Assessment Battery, SRI=Stereotypy Rating Inventory, FBI=Frontal Behavioral Inventory

Distribution of diagnoses

After two years, 82.9 % (n=29) of progressors had a neurodegenerative disease, while in the progressor group about half had a psychiatric disorder (53.6%, n=15), a quarter had a neurodegenerative disease (26.7%, n=4) and the remaining non-progressors had other 'diagnoses' including 'subjective cognitive impairment', 'possible bvFTD' and 'marital problems' (table 2).

	Progressor n=35	**Non progressor n=28**
Dementia		
Alzheimer's disease	4	0
Possible bvFTD	0	2
Probable bvFTD	14	1
Definite bvFTD	3	0
Vascular Dementia	1	0
Lewy Body Dementia	0	2
Progressive Supranuclear Palsy	2	0
Corticobasal Degeneration	1	0
Semantic Dementia	2	0
Other Dementias	2	1
Psychiatric disorder		
Major Depressive Disorder	0	3
Minor Depressive Disorder	0	1
Bipolar Disorder	1	2
Autism Spectrum Disorder	0	2
Personality Disorder	1	1
Other Psychiatric Disorders	0	6
Other		
Subjective Cognitive Impairment	0	3
Vascular Mild Cognitive Impairment	2	0
Marital problems	0	3
Neurologic disorders	2	1

Table 2. Diagnoses after two years of follow up in patients with progression and patients without progression
Legend: bvFTD= behavioral variant frontotemporal dementia

Predictors for progression and non-progression

Progressors were predicted by a higher total score on the SRI (OR0.26, 95% CI 0.07-0.98) and a neuropsychological profile with executive deficits and relative sparing of episodic memory and visuospatial functions (OR0.22, 95% CI 0.06-0.88). Predictors for non-progression were a positive history of psychiatric disorders (OR3.33, 1.17-9.51) and a positive family history of psychiatric disorders (OR3.63, 1.14-11.50) (table 1). The predictive value for progression of these 4 factors together was 80.4% ($p < 0.05$).

DISCUSSION

As hypothesized we found that progressors in LOF were mainly patients with a neurodegenerative disease, but contrary to our hypotheses a lack of progression did not prove a psychiatric diagnosis. In case of non-progression, several etiologies were found, including psychiatric disorders, marital problems and subjective cognitive impairment. Tools to predict progression in LOF were stereotypy and a neuropsychological profile with mainly executive deficits and relative sparing of episodic memory and visuospatial functions. A patients history and a family history with psychiatric disorders and a younger age were found to be predictors for non-progression.

While it can be seen as common sense that we mainly found neurodegenerative diseases inour progressor group and psychiatric diseases in the non-progressor group, this result is interesting in the context of recent studies into progression in psychiatric disorders. In the last decade evidence has accumulated that besides neurodegenerative diseases also psychiatric disorders can have a progressive course. In major depressive disorder cognitive decline and obvious hippocampal changes have been found, while in older bipolar patients several studies confirmed grey matter volume reduction and in schizophrenia changes in cortical white and grey matter were seen.[16] [17] Although indeed two patients with a psychiatric disorder in this LOF cohort showed progression at MRI, in general our study does not support these findings.

The complexity of diagnostics in LOF has been emphasized and the above mentioned bvFTD phenocopy syndrome is one of the complicating factors.[3] We limited the number of possible bvFTD diagnoses to only 4 patients due to diagnostics by both a neurologist and a psychiatrist already at baseline. The etiology of the bvFTD phenocopy syndrome was found to be variable ranging from mood disorders to autism and with multidisciplinary diagnostics these potential disorders were already accounted for. Two of these patients with possible bvFTD did not progress to probable or definite bvFTD (phenocopy syndrome patients). Interestingly, while MMSE and FAB improved, SRI and FBI worsened in these patients, implying an increase of reported behavioral changes by the family. The majority of patients had been genetically screened (1 patient had C9ORF repeat expansion and 1 patient progranuline mutation) but mutations were not found in phenocopy cases.

A higher score at the SRI as a predictor for progression in LOF is a new finding but fits previous study results on progression in bvFTD.[18] The current study prompts that beyond diagnosis, in late onset frontal disturbances, stereotypy might be seen as an early warning sign. Progression was also predicted by a neuropsychological profile with executive deficits with relative sparing of memory and visuospatial functions. It is remarkable that although more than half of the progressors had another disease than bvFTD in our cohort, this neuropsychological profile originating from FTDC criteria still had prognostic value.[15] These clinical markers together with age (mean age of progressors was 63 years, mean age of non-progressors was 59 years) and the absence of (family) history with psychiatric disorders were reasonably capable to distinguish a progressive from a non-progressive discourse.

There are some limitations in this study. First of all, the diagnostic gold standard of two years approximates diagnostic certainty but misdiagnosis cannot be fully excluded. Another limitation is an increased risk for Type I errors. In clinical practice the presence of progression in patients with LOF is indicative of a neurodegenerative disease whereas the absence of progression is in approximately half of patients indicative of psychiatric origin of symptoms. Acknowledging the limitations, this is the first study into predictors in LOF, revealing that much can be gained by a focus on clinical symptoms as it can distinguish treatable conditions from progressive discourses.

REFERENCES

1. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.
2. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011. doi:10.4088/JCP.10m06382oli.
3. Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome". *Curr Opin Neurol*. 2010;23(6):628-632. doi:10.1097/WCO.0b013e3283404309.
4. Diehl-Schmid J, Schmidt E-M, Nunnemann S, et al. Caregiver burden and needs in frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 2013;26(4):221-229. doi:10.1177/0891988713498467.
5. Wald C, Fahy M, Walker Z, Livingston G. What to tell dementia caregivers - The rule of threes. *Int J Geriatr Psychiatry*. 2003;18(4):313-317. doi:10.1002/gps.828.
6. Tifratene K, Robert P, Metelkina A, Pradier C, Dartigues JF. Progression of mild cognitive impairment to dementia due to AD in clinical settings. *Neurology*. 2015;85(4):331-338. doi:10.1212/WNL.0000000000001788.
7. Devenney E, Bartley L, Hoon C, et al. Progression in Behavioral Variant Frontotemporal Dementia: A Longitudinal Study. *JAMA Neurol*. 2015;72(12):1501-1509. doi:10.1001/jamaneurol.2015.2061.
8. Li J-Q, Tan L, Wang H-F, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J Neurol Neurosurg Psychiatry*. 2016;(6):1-9. doi:10.1136/jnnp-2014-310095.
9. Alloy LB, Urošević S, Abramson LY, et al. Progression along the bipolar spectrum: a longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. *J Abnorm Psychol*. 2012;121(1):16-27. doi:10.1037/a0023973.
10. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55(10):967-972. doi:10.1136/jnnp.55.10.967.
11. Harper L, Barkhof F, Fox NC, Schott JM. Using visual rating to diagnose dementia: a critical evaluation of MRI atrophy scales. *J Neurol Neurosurg Psychiatry*. 2015;86(11):1225-1233. doi:10.1136/jnnp-2014-310090.

12. Galea M, Woodward M. Mini-mental state examination (MMSE). *Aust J Physiother*. 2005;51(3):198. doi:10.1017/CBO9781107415324.004.
13. Dubois B, Slachevsky a, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626. doi:10.1212/WNL.57.3.565.
14. Solje E, Aaltokallio H, Koivumaa-Honkanen H, et al. The phenotype of the C9ORF72 expansion carriers according to revised criteria for bvFTD. *PLoS One*. 2015. doi:10.1371/journal.pone.0131817.
15. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
16. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol Psychiatry*. 2012;18(5):595-606. doi:10.1038/mp.2012.33.
17. Haller S, Xekardaki A, Delaloye C, et al. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. *J Psychiatry Neurosci*. 2011;36(6):391-401. doi:10.1503/jpn.100140.
18. Dols A, van Liempt S, Gossink F, et al. Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome. *J Clin Psychiatry*.

Section 3. Care and interventions in the late onset frontal lobe syndrome and bvFTD

8. An intervention program for caregivers of dementia patients with frontal behavioural changes: an explorative study with controlled effect on sense of competence

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ABSTRACT

Background

Caregivers of dementia patients experience high levels of burden, especially caregivers of dementia patients with behavioural problems. As intervention studies for these caregivers are still lacking, we conducted an explorative pilot study into the efficacy of a support program.

Methods

Participants were caregivers of dementia patients affected by apathy, disinhibition and/or stereotypical behaviour with a FBI score of 11 or higher. Caregivers were randomized to the intervention or control group (both n=15). The intervention consisted of psychoeducation, social support and behavioural cognitive therapy and was given during 6 months. Quantitative and qualitative data were collected at baseline and after the intervention.

Results

Increased sense of competence was found in the intervention group. Burden, perceived stress and depressive symptoms decreased, although not significantly different from the control group.

Conclusions

The sense of competence of caregivers improved by the support program and caregivers revealed comprehensive supportive effects. Further research into the efficacy of the program, on a larger scale, is recommended.

INTRODUCTION

Caregivers of dementia patients experience high levels of physical and psychological stress and burden.[1, 2] Research performed by health services research institute, Nivel, in the Netherlands revealed that 58% of informal caregivers runs the risk of emotional distress as a result of caring.[3] Burdened caregivers reported that the majority of the problems they experience are related to behavioural problems in dementia patients.[4, 5, 6] The indelible mark of behavioural disturbances on the determination of burden and stress in caregivers has been corroborated by several studies.[7, 8] Caregivers of patients with the behavioural variant of Frontotemporal dementia (bvFTD) are in particular dealing with frontal behavioural problems: apathy, disinhibition and/or stereotypical behaviour.[9] Associated with these frontal behavioural disturbances, different studies showed that caregiver burden in bvFTD is even higher than in Alzheimer's Disease, with obvious implications for caregiver health and well-being.[10, 11, 12, 13] Noteworthy, also other neurodegenerative diseases can cause frontal behavioural disturbances (apathy, disinhibition and/ or stereotypical behaviour), as can be apparent in semantic dementia (SD), Alzheimer's disease (AD), progressive non-fluent aphasia (PNFA), dementia with lewy bodies (DLB), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), with sizeable consequences for the caregivers involved.[14]

Worldwide, efforts have been made to develop intervention programs to support caregivers of dementia patients.[1, 15] A meta-analysis, including the results of 127 intervention studies on dementia caregivers, showed that interventions have, on average, small effects on burden and subjective well-being, but that elements of cognitive behavioural therapy, social support and psycho-educational interventions had at least some positive effects on caregiver stress and depression.[16] A lack in the literature exists regarding studies into support programs especially for caregivers dealing with dementia patients with mainly frontal behavioural problems. However, two small intervention studies have focused on the effects of a support program especially for bvFTD caregivers and had thereby a focus on behavioural problems. In one non-randomized study, nine patients received a program with cognitive appraisal and coping strategies in weekly two-hour group sessions over 15 weeks. The intervention group had an increase in their scores of functional responses and thereby learned how to apply problem-solving strategies, compared to the control group (n=12).[17] In the other study, performed by Mioshi and

colleagues, a cognitive appraisal and coping strategies program was performed, during 12 months. They found greater reductions in both caregiver's burden and reactions to patients' challenging behaviours in the intervention group (n=9) compared to the control group (n=12).[18] The results of these intervention studies are optimistic, but intervention studies especially aimed at support programs for caregivers of different dementia patients with frontal behavioural problems are still needed.

Aware of the high levels of burden, distress and depression in caregivers of dementia patients dealing with behavioural symptoms,[4, 5, 11, 12, 13] we set up an explorative pilot study on this subject. We performed a caregiver intervention program consisting of three elements: psychoeducation by a medical specialist, sharing of experiences and feelings with other caregivers (social support) and learning new coping strategies by behavioural cognitive therapy. Qualitative and quantitative data were collected to explore the possible benefits of the intervention program on caregiver burden, perceived stress, sense of competence and depression. Based on the study results future recommendations are made.

METHODS

Design

In an explorative pilot study the effect of the intervention program on caregivers of dementia patients with prominent frontal behavioural changes was investigated by means of a randomized controlled trial. Caregivers in the intervention group received the support program on top of care as usual and patients in the control group received only care as usual. The intervention program (in detail described below) was given in 5 sessions during a period of 6 months. Care as usual consisted of regular visits with a medical specialist in the context of patient's treatment and case management, which is mostly coordinated by a nurse specialized in dementia. Within one month prior and after the intervention the following outcomes were measured: caregiver burden, perceived stress, sense of competence and depressive symptoms. A qualitative assessment was taken after the intervention.

Subjects

Participants were caregivers of patients affected by serious frontal behavioural changes due to a neurodegenerative disease (bvFTD, SD, AD, PSP, CBD, PNFA).

Behavioural changes included apathy, disinhibition or stereotypical behaviour determined by a neurologist and measured with the Frontal Behavioural Inventory (FBI). Only caregivers of patients with a FBI of 11 or higher were included in the study. Caregivers were recruited through the memory clinic of the Alzheimer center VUmc Amsterdam and the Old Age Psychiatry Department of GGZinGeest Amsterdam, the Netherlands (inpatient and outpatient) between May and August 2014. Caregivers were either partner, sibling or child of the affected patient.
In this pilot a total of 30 participants were included. In accordance with a double blind randomized controlled trial design caregivers were randomized to the intervention group (n=15) and the control group (n=15). Caregivers were only included if they reported not to suffer from a mental illness and if they were not receiving treatment in mental healthcare for themselves.

The support program

During a period of six months five sessions of 2 hours were given with certain frequency, as based upon previous literature.[19] The intervention sessions were led by a community psychiatric nurse (RK) and a psychologist (AP). All 5 sessions had a fixed schedule with a specific theme: introduction of the frontal lobe syndrome, disinhibition, apathy, compulsive behaviour, and one session with an integration of the previous themes. Each session started with an exchange of experiences by the participants for 15 minutes whereby time was reserved for social support, followed by an interactive presentation of the medical specialist (neurologist (YP) or psychiatrist(AD)) focusing on one of the themes (disinhibition, apathy or stereotype/compulsive behaviour) for 30 minutes. After a coffee/tea break of 15 minutes, a case vignette of frontal behaviour challenging a caregiver was discussed by the psychologist using the ABC model (Action-Behaviour-Consequence) during 20 minutes.[20, 21] Participants were encouraged to discuss their own experiences, the psychologist aided the group in applying the ABC model to the new examples (approximately in 20 minutes). In the last 20 minutes there was time for questions and discussing exercises for the next week. The exercises consisted of further implementation of the ABC model in home situations and formulating a case in the context of the theme of the next meeting (disinhibition, apathy or compulsive behaviour).

Data collection

Quantative data collection

Within one month prior to the first session and within one month after the last session of the intervention all participants filled in questionnaires to measure caregiver burden, and indirect measurements of burden in the form of perceived stress, sense of competence and depressive symptoms. In patients, the scores at Frontal Behavioural Inventory (FBI) and the Neuropsychiatric Inventory (NPI) were measured at baseline. To follow the severity of patients' behavioural problems over time, FBI scores after two years of follow up were retrieved through chart review.

-Caregiver burden was measured using the short Zarit Burden Interview. We used the Dutch version which consists of 11 items, with a higher score meaning a higher burden. The Zarit Burden Interview is the most widely used measure in caregiver research, and short versions have proven to suit clinical settings.[22, 23] Caregiver burden was also measured using the Dutch version of the Involvement Evaluation Questionnaire (IEQ).[24] The IEQ is a questionnaire developed to measure the burden on the family. It is widely used in studies about the burden of family members.[25, 26] The validity and reliability of the IEQ have been studied in five European countries.[25, 26] Questions 1 till 31 were used, which are closed questions with answers on a 5 point Likert scale all of which relate to the period of the last four weeks. The questions are divided into the following modules: attention and care that were spent by the caregiver, the quality of the relationship between the patient and the caregiver and the concerns experienced by the caregiver. Higher scores indicating more burden.

-The Perceived Stress Scale was used for measuring the perception of stress. The validity and reliability has proven to be satisfactory in different studies.[27] It contains 10 items and each item is rated on a 5-point scale ranging from never (0) to almost always (4). Positively worded items are scored reversely, and the ratings are summed, with higher scores indicating more perceived stress.

-The short sense of competence questionnaire (SSCQ) was used to measure the sense of competence experienced by the caregiver.[28, 29] The SSCQ denotes caregivers' feelings of being capable of caring for a demented person and consists of 7 items. It has been indicated as potential for use in caregiver research in an evidence based European consensus on outcome measures for psychosocial intervention research in dementia care.[28, 29] A higher score indicates a better sense of competence.

-The Center for Epidemiologic Studies Depression scale (CES-D) was used to measure the extent of depressive symptoms in caregivers. The CES-D is widely

used as a screening instrument for clinical depression with satisfactory reliability and validity.[30, 31] The scale consists of 20 questions at a 4 point ordinal scale. The sum of the questions forms the total score with a high score meaning more depressive symptoms. A score $\geq$ 16 is used to determine a clinically relevant depression.[30, 31]

Qualitative data collection

Qualitative data collection consisted of evaluation forms, emails and oral information. In the evaluation forms caregivers were asked to answer the following open questions: "What was the best part of the intervention program?" and "What are your recommendations for future intervention programs for caregivers dealing with dementia patients with behavioural changes?" In the evaluation forms caregivers also assigned the following elements of the program with a grade (between 1 and 10, with a higher number indicating a better score): the given psychoeducation by a medical specialist, the part of sharing experiences with other caregivers, behavioural cognitive therapy, frequency of the meetings, duration of the program, the room where it was given, the course material and the accordance to previous expectations. Also all emails with feedback from caregivers given during, and in between, the sessions, as well as oral feedback, were gathered.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows; IBM, Armonk, NY), version 21. Group differences on sociodemographic variables were investigated using independent t-tests, X^2tests, *F* tests and Mann- Whitney-U test. Differences between groups on primary outcome measures were tested two-sided (alpha<0.05) using ANCOVA on posttest scores, with baseline scores as covariates. If a variable was not normally distributed log transformation was performed.

We calculated effectsizes to get an idea of the extent of possible differences between the groups during the posttest. Effect sizes were calculated with the following formula[32]:

$$d = \frac{\text{adjusted mean control group} - \text{adjusted mean intervention group}}{\text{SD pooled}}$$

$$\text{SD pooled} = \sqrt{\frac{(N_{\text{interventiongroup}}-1)SD_{\text{interventiongroup}}^2 + (N_{\text{controlgroup}}-1)SD_{\text{controlgroup}}^2}{N_{\text{interventiongroup}} + N_{\text{controlgroup}}}}$$

SD= SE √ N

An effectsize (d) of 0.5 was considered as moderate and d=0.8 was considered as large, according to Cohen's d.[32]

Ethical considerations

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam.

RESULTS

Patient and caregiver characteristics

Patients had a mean age of 66.6 years and a mean symptom duration of 6.3 years (table 1). The mean score at the Neuropsychiatric *Inventory (NPI)* was 23.6 (range 3.0-56.0), indicating that the majority of patients had a moderate severity of symptoms while 9 patients had mild symptoms and 1 patient severe symptoms. At baseline the mean score at the FBI in all patients was 27.6 (SD 8.3) (severe frontal behavioural problems) without a difference between intervention and control group. The mean score at the FBI retrieved from patients records after two years of patients' first presentation was 28.6 (SD 16.9) in all patients, revealing that behavioural problems did not decrease over time (table 1).

The most common neurodegenerative disease of patients was bvFTD (60% of patients). These variables, including the underlying neurodegenerative diseases, were not different between intervention and control group.

Caregivers were mostly the patient's partner (67.7%), on average 7 years younger (mean age of 59.6 years) and they were mainly female (73.3%). These variables did not differ between the intervention and control group.

	Total N=30	Control N=15	Intervention N=15	Statistics T-test/ X^2/ *F* (df) P value
Patient				
Age, mean (SD)	66.6 (8.7)	69.6 (8.3)	63.7 (8.3)	0.93 (28) 0.06
Symptom duration, median (IQR)	6.3 (5.4)	7.3 (6.5)	5.4 (5.3)	MW= 0.41
Neurodegenerative disease,% AD % bvFTD % SD % PSP % DLB	 16.7 60.0 13.3 6.7 3.3	 20.0 66.7 0 6.7 6.7	 13.3 53.3 26.7 6.7 0	 0.24 (1) 1.00 0.56 (1) 0.46 4.62 (1) 0.10 0.00 (1) 1.00 1.03 (1) 1.00
NPI	23.6 (15.3)	21.2 (16.6)	26.5 (13.7)	0.31 (22) 0.40
Caregiver				
Age, mean (SD)	59.6 (10.5)	60.1 (10.1)	59.1 (11.1)	0.91 (28) 0.80
Gender, % male	26.7	33.3	20.0	0.7 (1) 0.41
Living with patient, n (%)	23 (76.7)	12 (80.0)	11 (73.3)	0.18 (1) 0.66
Relationship, % partner	67.7	73.3	80	0.19 (1) 0.66
Education, % middle % high	43.3 56.7	46.7 53.3	40.0 60.0	0.14 (1) 0.71

Table 1. Patient and caregiver characteristics
SD=Standard Deviation, IQR=InterQuartile Range, df=degrees of freedom, W=Mann-Whitney U test, Education: middle= four years of low or average level secondary education, high= five years of high level secondary education or university degree

Caregiver burden at baseline

All caregivers showed high scores on the various instruments indicating high burden, perceived stress and depressive symptoms and low sense of competence. In the vast majority the CES-D scores were above 16 implying that caregivers had depressive symptoms to the extent of a clinically relevant depressive syndrome. The mean score at the Zarit Burden interview in both groups was also above cut off score of 13 indicating a high caregiver burden at baseline. At baseline, caregivers from the intervention and control groups did not differ regarding their mean scores at outcome measures (IEQ, Zarit, SSCQ, PSS and CES-D, P>0.05) (table 2).

Measurements after the intervention

Mean score at SSCQ (sense of competence) after the intervention, adjusted for baseline scores, was significantly higher in the intervention group than in the

control group, indicating a better sense of competence in the intervention group after the support program (large effect). Mean scores at Zarit (caregiver burden), PSS (perceived stress) and CES-D (depressive symptoms) decreased in the intervention group, which are all in a favourable direction, although not significant compared to the control group. The mean score at the IEQ (measuring caregiver burden) increased in the intervention group, while it decreased in the control group, as did the mean score on the SSCQ (sense of competence). The mean score at the Zarit (caregiver burden), PSS (perceived stress) and CES-D (depressive symptoms) increased in the control group (table 2).

Qualitative results

Participants in the intervention group reported their experiences in between the sessions orally and through email. The following feedback was given: "the session was helpful because I recognized myself in the stories of other caregivers and it was effective for me that examples were given how to cope with difficult situations in another way"; "it was emotional but at the same time very valuable because it was very recognizable"; "the cognitive behavioural therapy was supportive"; "the main thing for me was that it is so important to accept the situation because then it is possible to control my own behaviour in order to learn new coping strategies that can reduce stress"; "I tried to apply the exercises from the behavioural cognitive therapy several times in daily life and it helped me to experience more control in daily life". The caregivers in the intervention group took the initiative to organise an additional meeting to continue sharing experiences after the last session.

Evaluation of the sessions by the caregivers

The given psychoeducation by a medical specialist was scored 7.9 out of 10, the part of sharing experiences with other caregivers 7.2, behavioural cognitive therapy 8.7, frequency of the meetings 8.0, duration of the program 7.8, the course material 7.3 and accordance to individual previous expectations 7.0 (all mean scores).

Most caregivers (n=7) in the intervention group declared that they appreciated the internal support and mutual recognition between caregivers the most. The elements of psychoeducation and the behavioural cognitive therapy were considered as the most supportive part of the program by an equal number of caregivers (each n=4). Regarding the open question about advises for the future, most caregivers recommended that the intervention program should be available in an earlier stage, at any time when a caregiver would feel the need for it or more frequently (n=5).

	Intervention group		Δ mean (range) intervention group	Adjusted mean (Std. Error) intervention group	Control group		Δ mean (range) control group	Adjusted mean (Std. Error) control group	Statistics* F (df) P value	Effectsize
	Before	After			Before	After				
Zarit, mean (SD)	21.5 (6.2)	21.2 (7.2)	0.3 (-8 – 9)	20.68 (1.4)	19.8 (9.0)	20.9 (9.6)	-1.1 (-8 – 8)	21.35 (1.3)	0.12 (1) 0.73	0.14
IEQ, mean (SD)	77.2 (16.8)	78.4 (17.0)	-1.2 (-3 – 39)	78.18 (3.1)	71.4 (16.7)	66.9 (13.5)	4.5 (-32 – 51)	71.2 (3.0)	2.58 (1) 0.12	-0.71
PSS, mean (SD)	17.7 (7.1)	16.8 (6.4)	0.9 (-9 − 8)	16.8 (1.5)	17.2 (8.7)	18.1 (8.8)	-0.9 (-9 − 8)	18.0 (1.4)	0.4 (1) 0.56	0.23
SSCQ, mean (SD)	22.1 (6.1)	23.9 (6.0)	-1.8 (-9 − 10)	24.56 (1.16)	24.6 (7.4)	21.5 (6.1)	3.1 (-8 − 9)	20.85 (1.1)	**5.42 (1) 0.03**	**-0.92**
CES-D, mean (SD)	17.3 (6.5)	16.4 (6.7)	0.9 (-11 − 14)	16.6 (1.7)	16.9 (7.3)	17.2 (8.5)	-0.3 (-12 − 9)	17.0 (1.6)	0.04 (1) 0.85	0.08

Table 2. Caregiver's burden in intervention- and control group before and after intervention

IEQ=Involvement Evaluation Questionnaire, Zarit=Short Zarit Burden Inventory, SSCQ=Short Sense of Competence Questionnaire, PSS= Perceived Stress Scale, CES-D=Center for Epidemiologic Studies Depression Scale

* comparison of both groups after intervention with analysis of covariance (ANCOVA) with baseline results as covariate

DISCUSSION

This is the first explorative study focusing on an intervention program for caregivers of dementia patients dealing with frontal behavioural problems (apathy, disinhibition and/or stereotypical behaviour). We found that burden and depressive symptoms are highly prevalent among caregivers of these patients. An effect on sense of competence was found in caregivers who received the support program. Based on this study it annot be concluded that the support program improved the experience burden, perceived stress and depressed mood of caregivers who participated in the support program, though the results suggest that caregivers who received the support experienced also some benefit from it regarding their mood and perceived stress. Regarding burden a negative (non-significant) tendency was found in the(small) intervention group. Further research in a larger group will have to answer if this is a negative effect of the intervention.

The improvement in the caregiver's sense of competence in the intervention group is an interesting result that confirms some previous studies about support programs for caregivers of dementia patients who were not specifically selected on the base of dealing with behavioural problems. In a controlled study into the Meeting Centres Support Program which included informative meetings, discussion groups and social activities for caregivers of patients with mild to moderate severe dementia, performed in Amsterdam, the Netherlands, a significant positive effect on sense of competence in caregivers was also found.[33] A subsequent study with the same program implemented in other regions in the Netherlands did not confirm this positive effect on sense of competence.[34] In another study, a randomized controlled trial (n=138), wherein also the sense of competence of caregivers of dementia patients was studied, this time as an outcome of emotional and practical support during 4 hours a week during 10 months, no significant overall effect on change in primary caregiver's competence between pre- and posttest was found. However, the subgroup of female caregivers sharing a household with the dementia patient showed a significantly more favorable change in sense of competence in the intervention group compared to the control group.[15] It is conceivable that this subgroup of caregivers is indeed most sensitive to improvements on sense of competence by a support program, as we see in our included group of caregivers also more female caregivers and caregivers who live with the dementia patient (equally distributed in intervention group and control group).

The absence of any significant group effect on the other indicators of feelings of burden (caregiver burden, perceived stress and depressive symptoms) is a result that was also found in previous research into the effectiveness of caregiver support programs. Although caregivers who participated in these programs were satisfied with the support and managed to go on caring longer than caregivers who did not receive this support, a reduction of levels of burden could hardly be proved scientifically.[1, 15, 32] In the study of Mioshi with an intervention program performed in caregivers of patients with bvFTD, significant results on levels of burden were measured.[19] However, due to practical constraints, the participants in this study were not randomized, and the burden scores between the intervention group and control group differed at baseline (Zarit score of 26 in intervention group and 10.5 in control group at baseline) for which no correction was applied. As discussed by the authors, this lack of randomisation may have limited the results of their study, but the positive effects are hopeful. We recommend to replicate a randomized controlled design to re-test if positive effects on levels of burden can be found.

Another important aim of our study was the qualitative assessment of the intervention and to summarize recommendations for future caregiver interventions. After the intervention caregivers turned out to have high levels of satisfaction and they reported the various positive benefits in daily life. The appreciation of the three elements of this intervention, as was apparent in the psychoeducation, cognitive behavioural therapy and social support, are corroborating suggestions made by previous intervention studies and seem to be applicable in future studies.[16, 35, 36] Regarding recommendations made by caregivers themselves, an extension of the availability of the intervention program was suggested, either in an earlier stage of the disease or during a longer period. We recommend to test this on a larger scale in future studies.

At the same time, the question arises if the applied quantitative indicators of feelings of burden, such as perceived stress and depressive symptoms, are the most relevant and discriminating outcome measures in research into support programs for caregivers, or that more attention should be paid to other aspects that are crucial in well-being of caregivers and that can strengthen their coping strategies. In a recent study about the *European skills training and reskilling (STAR) project*, consisting of an online dementia care training both for informal and formal caregivers of dementia patients, significant effects were found on positive attitudes

of caregivers to dementia, and on empathic concern.[37] It was found that after following the course caregivers became better able to view situations from another's perspective (eg, a person with dementia) and that they showed more sympathy and concern, which may help them to provide better care for people with dementia.[37] This advocates that future research also takes into account outcome measures on approaches of caregivers regarding the relative with dementia and on empathy as well, as this may determine the well-being and coping skills of caregivers.

There are some limitations in this study. First of all, with a total number of 15 included patients per group we had a small sample size and therefore little statistical power to find significant differences between the groups. Second, follow up on patients behavioural symptoms was performed, but not exactly during the time of the intervention. However, severity of behavioural problems in patients did not decline over time whereby improvements in caregivers cannot be explained by a decrease of behavioural problems in patients. For a future effect study we therefore recommend to perform a randomised controlled trial in a larger sample of caregivers with a follow up on severity of patients symptoms.

Acknowledging the limitations, this first explorative pilot study for caregivers of dementia patients with behavioural changes, indicates the challenge and need for an effective intervention program in this highly burdened group of caregivers. We found a controlled effect on sense of competence in caregivers who received the support program, which consisted of psychoeducation, social support and behavioural cognitive therapy. Further research, on a larger scale, should conclude on the effectiveness of the support program for caregivers of early onset dementia patients with frontal behavioural changes.

REFERENCES

1. Cuijpers P, Hosman CM, Munnichs JM. Change mechanisms of support groups for caregivers of dementia patients. *Int Psychogeriatr*. 1996;8(4):575-587. doi:10.1017/S104161029600289X.
2. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: A review of the literature. *J Am Acad Nurse Pract*. 2008;20(8):423-428. doi:10.1111/j.1745-7599.2008.00342.x.
3. Peeters, JM, De Lange J, Van Asch I, Spreeuwenberg P, Veerbeek M, Pot AM F AL. Landelijke evaluatie van casemanagement dementia [National evaluation of case management dementia, the Netherlands]. *NIVEL, Utr*. 2012.
4. Bakker C, Vugt ME De, Vernooij-dassen M, et al. Needs in Early Onset Dementia : A Qualitative Case From the NeedYD Study. *Am J Alzheimer 's Dis Other Dementias*. 2010;25:634-640. doi:10.1177/1533317510385811.
5. Van Vliet D, De Vugt ME, Bakker C, Koopmans RTCM, Verhey FRJ. Impact of early onset dementia on caregivers: A review. *Int J Geriatr Psychiatry*. 2010;25(11):1091-1100. doi:10.1002/gps.2439.
6. Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatrics*. 2004;16(3):295-315. doi:10.1017/S1041610204000468.
7. Meiland FJM, Kat MG, van Tilburg W, Jonker C, Dröes R-M. The emotional impact of psychiatric symptoms in dementia on partner caregivers: do caregiver, patient, and situation characteristics make a difference? *Alzheimer Dis Assoc Disord*. 2005;19(4):195-201. doi:10.1097/01.wad.0000189035.25277.02.
8. de Vugt ME, Stevens F, Aalten P, Lousberg R, Jaspers N, Winkels I, Jolles J VF. Behavioural disturbances in dementia patients and quality of the marital relationship. *Int J Geriatr Psychiatry*. 2003;18(2):149-154.
9. Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.
10. Caceres BA, Frank MO, Jun J, Martelly MT, Sadarangani T, de Sales PC. Family caregivers of patients with frontotemporal dementia: An integrative review. *Int J Nurs Stud*. 2015;55:14. doi:10.1016/j.ijnurstu.2015.10.016.
11. Riedijk SR, De Vugt ME, Duivenvoorden HJ, et al. Caregiver burden, health-related quality of life and coping in dementia caregivers: A comparison of frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2006;22(5-6):405-412. doi:10.1159/000095750.

12. Mourik JC, Rosso SM, Niermeijer MF, Duivenvoorden HJ, Van Swieten JC, Tibben A. Frontotemporal dementia: Behavioral symptoms and caregiver distress. *Dement Geriatr Cogn Disord*. 2004;18(3-4):299-306. doi:10.1159/000080123.

13. Lima-Silva TB, Bahia VS, Carvalho VA, et al. Neuropsychiatric symptoms, caregiver burden and distress in behavioral-variant frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2015;40(5-6):268-275.

14. Kertesz A, Nadkarni N, Davidson W, Thomas a W. The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. *J Int Neuropsychol Soc*. 2000;6(4):460-468. doi:10.1017/S1355617700644041.

15. Dröes R-M, Breebaart E, Meiland FJM, Van Tilburg W, Mellenbergh GJ. Effect of Meeting Centres Support Program on feelings of competence of family carers and delay of institutionalization of people with dementia. *Aging Ment Health*. 2004;8(3):201-211. doi:10.1080/13607860410001669732.

16. Pinquart M, Sörensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? *Int Psychogeriatr*. 2006;18(4):577-595. doi:10.1017/S1041610206003462.

17. McKinnon C, OÇonnor CM, Savage S, Hodges JR ME. Qualitative results of a structured group program for carers of peopple with fronotemporal dementia. *Alzheimer Dis Assoc Disord*. 2013;27(1):84-86.

18. Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR. Improving burden and coping skills in frontotemporal dementia caregivers: a pilot study. *Alzheimer Dis Assoc Disord*. 2013;27(1):84-86. doi:10.1097/WAD.0b013e31824a7f5b.

19. Toseland RWE, Haigler DHE, Monahan DJE. Education and support programs for caregivers: Research, practice, policy. *Educ Support programs caregivers Res Pract policy*. 2011:85-105. doi:10.1007/978-1-4419-8031-1.

20. Chang BL. Cognitive-behavioral intervention for homebound caregivers of persons with dementia. *Nurs Res*. 1999;48(3):173-182.

21. Beck Judith S. *Cognitive Therapy: Basics and beyond*.; 1995. doi:10.1016/0005-7916(96)89143-9.

22. Zarit SH, Anthony CR BM. Interventions with caregivers of dementia patients: comparison of two approaches. *Psychol Aging*. 1987;2(3):225-232.

23. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: A New Short Version and Screening Version. *Gerontologist*. 2001;41(5):652-657. doi:10.1093/geront/41.5.652.

24. Schene AH VWB. *De Betrokkenen Evaluatie Schaal (BES) [The Dutch Version of the Involvement Evaluation Questionnaire (IEQ)*. Amsterdam; 1991.25. Moniz-25.

25. Cook E, Vernooij-Dassen M, Woods R, et al. A European consensus on outcome measures for psychosocial intervention research in dementia care. *Aging Ment Health*. 2008;12(1):14-29. doi:10.1080/13607860801919850.

26. Van Wijngaarden B SA. Caregiving consequences in The Netherlands and other european countries: the development and use of the family. *Fam Interv Ment Illn Int Perspect*. 2002.
27. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. *Soc Psychol Heal*. 1988;13:31-67. doi:10.1111/j.1559-1816.1983.tb02325.x.
28. Vernooij-Dassen JFJ, Felling JA, Brummelkamp E, Dauzenberg GH, van Geertrudis AM, Grol R. Assessment of caregiver's competence in dealing with the burden of caregiving for a dementia patient: A Short Sense of Competence Questionnaire (SSCQ) suitable for clinical practice. *J Am Geriatr Soc*. 1999;47(2):256.
29. Vernooij-Dassen MJFJ, Persoon JMG, Felling AJA. Predictors of sense of competense in caregivers of demented persons. *Soc Sci Med*. 1996;43(1):41-49. doi:10.1016/0277-9536(95)00332-0.
30. Miller WC, Anton HA, Townson AF. Measurement properties of the CESD scale among individuals with spinal cord injury. *Spinal Cord*. 2008;46(4):287-292. doi:10.1038/sj.sc.3102127.
31. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306.
32. Thalheimer W, Cook S. How to calculate effect sizes from published research: A simplified methodology. *Work Res*. 2002;(August):1-9. doi:10.1113/jphysiol.2004.078915.
33. Dröes R.M. *Amsterdamse Ontmoetingscentra; Een Nieuwe Vorm van Ondersteuning Voor Dementerende Mensen En Hun Verzorgers [Amsterdam Meeting Centres: A New Type of Support for People with Dementia and Their Carers]*. Amsterdam; 1996.
34. Dröes R.M, Meiland FJM, Schmitz MJ, van Tilburg W. Effect of the Meeting Centres Support Program on informal carers of people with dementia: results from a multi-centre study. *Aging Ment Health*. 2006;10(2):112-124. doi:10.1080/13607860500310682.
35. Brodaty H, Roberts K, Peters K. Quasi experimental evaluation of an educational model for dementia caregivers. *Int J Geriatr Psychiatry*. 1994;9(3):195-204. doi:10.1002/gps.930090304.
36. Brodaty H, Roberts K PK. Quasi-experimental evaluation of an educational model for dementia caregivers. *Int J Geriatr Psychiatry*. 1994;9(195):204.
37. Hattink B, Meiland F, Van Der Roest H, et al. Web-based STAR E-learning course increases empathy and understanding in dementia caregivers: Results from a randomized controlled trial in the netherlands and the United Kingdom. *J Med Internet Res*. 2015;17(10). doi:10.2196/jmir.4025.

9. Clinical guidance for pharmacological symptomatic interventions in behavioral variant frontotemporal dementia: A systematic review

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ABSTRACT

Objective

To provide a systematic overview of pharmacological interventions in the symptomatic treatment of behavioral variant of frontotemporal dementia (bvFTD), and thereby clinical guidance.

Methods

Medline (Pubmed), Embase & PsycINFO were searched systematically for all reports on pharmacological interventions for bvFTD published between 1970 and 2017, by using key indicators and relevant terms. Studies on pharmacological interventions in bvFTD were included if an objective outcome of the efficacy of the intervention on the symptoms of bvFTD was provided. We described the efficacy of pharmacological interventions by relevant symptom profiles according to the FTDC-criteria: Apathy, Disinhibition, Lack of empathy or sympathy, Hyperorality, Stereotypical behavior and Executive dysfunction. In addition, we explored the effect on depression because of the high prevalence of depressive symptoms in bvFTD.

Results

Twenty-three studies were included with 12 randomized controlled trials, 8 open-label studies and 3 case series reporting on 583 patients. 17 of the 23 studies were published in the past decennium and 16 described pharmacological interventions that improved symptoms in bvFTD. Based on the NPI measurement Trazodone has the greatest effect on the general symptoms of bvFTD followed by Rivastigmine and Citalopram.

Conclusion

This systematic review provides an overview of the pharmacological interventions that can be used to treat the main symptoms in bvFTD and gives thereby a solid guideline for clinical practice. Future research is needed to investigate pharmacological interventions for bvFTD by using a validated outcome as NPI to establish robust evidence for adequate symptomatic treatment.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is the most prevalent form of FTD and is associated with progressive degeneration of the frontal lobes, anterior temporal lobes or both. [1] [2] It is the second most common early-onset dementia after Alzheimer's disease (AD). [3] [4] [5] Progressive changes in social behavior, such as emotional disengagement and socially inappropriate responses or activities affect the personal identity of the patient with bvFTD, which has profound implications for the patient and family members. [6] [7]

There are several pathways in the pathogenesis of bvFTD and it is hypothesized that abnormal tau protein or TAR-DNA binding protein 43 (TDP-43) aggregates in bvFTD. Therapy specifically focusing on cure of bvFTD is still lacking, more specific no treatment has been described so far in which aggregation of abnormal tau or TDP-43 is inhibited. [8] [9] Promising treatments aimed at reduction of beta-amyloid aggregation, thereby reversing the pathological mechanism of Alzheimer's disease, are not effective in the treatment of FTD. [10]

As there is still no cure for bvFTD, pharmacological treatment is focused on managing the symptoms. Relieve of behavioral symptoms may improve the quality of life of bvFTD patients and their relatives.[3] [11] As many bvFTD patients are suffering from depressive symptoms, a reduction of depression also seems profitable. [12] [11]

Three previous systematic reviews into the effect of pharmacological therapeutics in bvFTD have been performed.[13] [14] [15] These systematic reviews all included randomized controlled trials (RCTs), while the first performed systematic review in this field [13] also included open label studies and case reports, and the latest systematic review [15] included open label studies besides RCTs. All previous systematic reviews described improvement in behavioral symptoms in bvFTD with serotonergic antidepressants. Preliminary evidence also supported a possible usefulness of dopaminergic compounds including Selegiline and Dextroamphetamine. [13] [14] [15] These previous systematic reviews provided a solid overview of the effect of pharmacological interventions in bvFTD, however a systematic summary of the effect of pharmacological interventions on specific symptom profiles of bvFTD including apathy, disinhibition, stereotypy, hyperorality, lack of empathy and executive dysfunction has not been performed yet. Previous systematic reviews were focused at performing an overview of the effect of specific drugs or pharmacological subgroups. This systematic review

aims to give an updated overview of the effect of pharmacological interventions on symptom profile in bvFTD, not limited to randomized controlled trials but also including open label studies and case series, as they can be very informative in the explorative phase of treatment options of bvFTD. It could be of great importance that clinicians are provided with as much relevant and updated information as possible in this pioneer stage of evidence based interventions to improve symptomatology in bvFTD. The key strength of this systematic review is to provide a guidance of clinical management focusing on symptom profile according to the FTDC criteria: Apathy, Disinhibition, Lack of empathy or sympathy, Hyperorality, Stereotypical behavior and Executive dysfunction.[16] Since depression is a well-known comorbidity in bvFTD with comprehensive effect on caregivers, we also report the effect of pharmacological interventions on depressive symptoms in bvFTD.[17] [11] Lastly, we summarize pharmacological interventions that have no effect on the symptoms of bvFTD.

METHODS

Search strategy

We used three databases: Medline (Pubmed), Embase & PsycINFO, to perform a search evaluating the pharmacological interventions for bvFTD by using key indicators and relevant terms. The search was completed on 9 September 2016.

Articles were retrieved by using the following Medical Subject Heading (MESH) terms, ‘’Frontotemporal Dementia"[Mesh] and "Drug Therapy"[Mesh]. In addition, keywords and synonyms of ‘’Frontotemporal Dementia’’ and ‘’ Drug Therapy’’ from journal article titles and abstracts were searched. The use of free text terms in title and abstract (tiab) resulted in a search term as follows: "Frontotemporal Dementia"[Mesh] OR frontotemporal dementia* [tiab] OR fronto-temporal dementi* [tiab] OR pick disease* [tiab] OR pick's disease* [tiab] OR "Frontotemporal Lobar Degeneration"[Mesh] OR frontotemporal lobar degeneration* [tiab] OR frontotemporal lobe degeneration* [tiab] OR fronto-temporal lobar degeneration* [tiab] OR fronto-temporal lobe degeneration* [tiab] OR (FTD [tiab] AND (dement* [tiab] OR degeneration*[tiab])))) AND ("Drug Therapy"[Mesh] OR drug therap* [tiab] OR drug treatment* [tiab] OR "drug therapy" [Subheading] OR pharmacotherap* [tiab] OR pharmacologic therap* [tiab] OR pharmacological therap* [tiab] OR pharmacological treatment* [tiab]

OR pharmacological strateg* [tiab] OR pharmacological management* [tiab] OR "Serotonin Uptake Inhibitors"[Mesh] OR SSRI* [tiab] OR serotonin uptake inhibitor* [tiab] OR serotonin reuptake inhibitor* [tiab] OR serotonin re-uptake inhibitor* [tiab] OR "Serotonin Uptake Inhibitors" [Pharmacological Action].

Study selection

For this systematic review, certain inclusion and exclusion criteria were established. This review only included studies that performed pharmacological interventions. These studies had to provide an objective outcome of the efficacy of the intervention on the symptoms of bvFTD, such as Neuropsychiatric Inventory (NPI) or Frontal Behavioral Inventory (FBI).

We excluded studies that were not related to our review based on the following exclusion criteria: 1. Studies not including bvFTD patients, 2. Studies with a non-pharmacological intervention, 3. Studies in non-humans, 4. Studies with a sample size less than 3 patients. 5. Studies written in languages other than English. 5. Studies focused at the effect of discontinuation of medication or tolerability of medication.

All citations of this search were firstly registered in an Endnote database. The citations were scanned for duplicates based on overlapping authorship, study description, number of participants and participant characteristics. Hereby, overlapping studies based on these characteristics were then removed.

Next, one reviewer (CT) screened the citations on title and abstract to determine if it should be included within the systematic review. Citations that were certified as ineligible were subsequently scanned by a second reviewer (FG) to ensure that no potentially relevant citations were excluded. Lastly, full-text articles were obtained and reviewed to determine whether the articles were in accordance with the predefined inclusion criteria.

Data extraction

All data were extracted from the eligible full-text articles. In this process, Microsoft Access was used as a storage database for the extracted data. The extracted data was categorized by the features of the study including: information of the study design, participants, drug used in study, duration of study and outcome of study.

Data analysis

Microsoft Access database included all eligible studies with the pharmacological treatment of bvFTD sorted by drug type, by dose, by methodology and by outcome. This database was then reviewed and compared by the symptoms of bvFTD, drug type and effectiveness of the medication, with NPI as main outcome. The NPI consist of 12 different elements, including Apathy, Disinhibition (Irritability, Agitation/Aggression), Hyperorality (Eating change) and Stereotypical behavior (Aberrant motor behavior), Depression (Anxiety) and Others (Delusions, Hallucinations, Sleep behavior change, Euphoria). We reviewed all studies with NPI measurements and organized the results for each symptom category per study (see *Table 2 Results*).

Quality assessment of included studies

Methodological quality was assessed by FG and CT using the Cochrane risk of bias tool.[18] The Cochrane risk of bias tool includes seven domains: random sequence generation, random allocation concealment, blinding, incomplete outcome data, selection outcome reporting, and other sources of bias. A judgement relating to the risk of bias was assigned for each entry in terms of 'low', 'high', or 'unclear' risk. Although not affecting the inclusion or exclusion of studies, the above domains were used to generate an overall quality score. Studies were rated as strong if they had no high risk of bias on any of the bias domains or if they had a maximum of one domains with 'unknown' risk of bias. A study was rated as moderate if 1 of 2 domains had a high risk of bias or if there were more than 2 domains with 'unknown' risk of bias. All other studies were rated as weak, implying that more than 2 domains had a high risk of bias.

Ethical considerations

This study has not been sponsored by medical health care institutes or pharmaceutical companies and none of the authors are currently affiliated with pharmaceutical institutes.

RESULTS

Systematic search

A total of 1476 citations were retrieved by our search strategy (see also *Figure 1 Flow diagram*). After the analysis for duplications, 224 citations were excluded

and 1252 citations remained. Within these 1252 citations, we retrieved 372 citations from Pubmed, 698 from Embase and 182 from PsycINFO. Next, 1204 citations were excluded after the titles and abstracts were reviewed, since it did not meet the inclusion criteria. Full-text copies of 23 potentially relevant citations were then obtained and reviewed (Figure 1).

Types of studies

Nearly all studies were published in the past decennium, except for 5 studies. Ten studies were employed in Europe, eight in the United States, two in Canada, two in Japan and one in China. Of all 23 studies in this systematic review, 12 were randomized controlled trials, 8 were open-label studies and 3 were case series (table 1).

Methodological quality

Of the included studies, methodological quality was rated as weak for 56.5 %, moderate for 26.1 %, and strong for 17.4 %.[18] (table 2)

Overall sample

The 23 published reports provided information on 583 patients (Table 1). Patients in the studies were diagnosed with (bv)FTD, according to either the Neary criteria or Lund-Manchester group criteria, except for nine studies, in which the diagnosis criteria were unclear. Only three studies also included patients with Primary Progressive Aphasia (PPA) or Semantic dementia (SD). The mean age of patients in all studies ranged from 54.4 year to 78.5 years. The sample size ranged from 3 to 76.

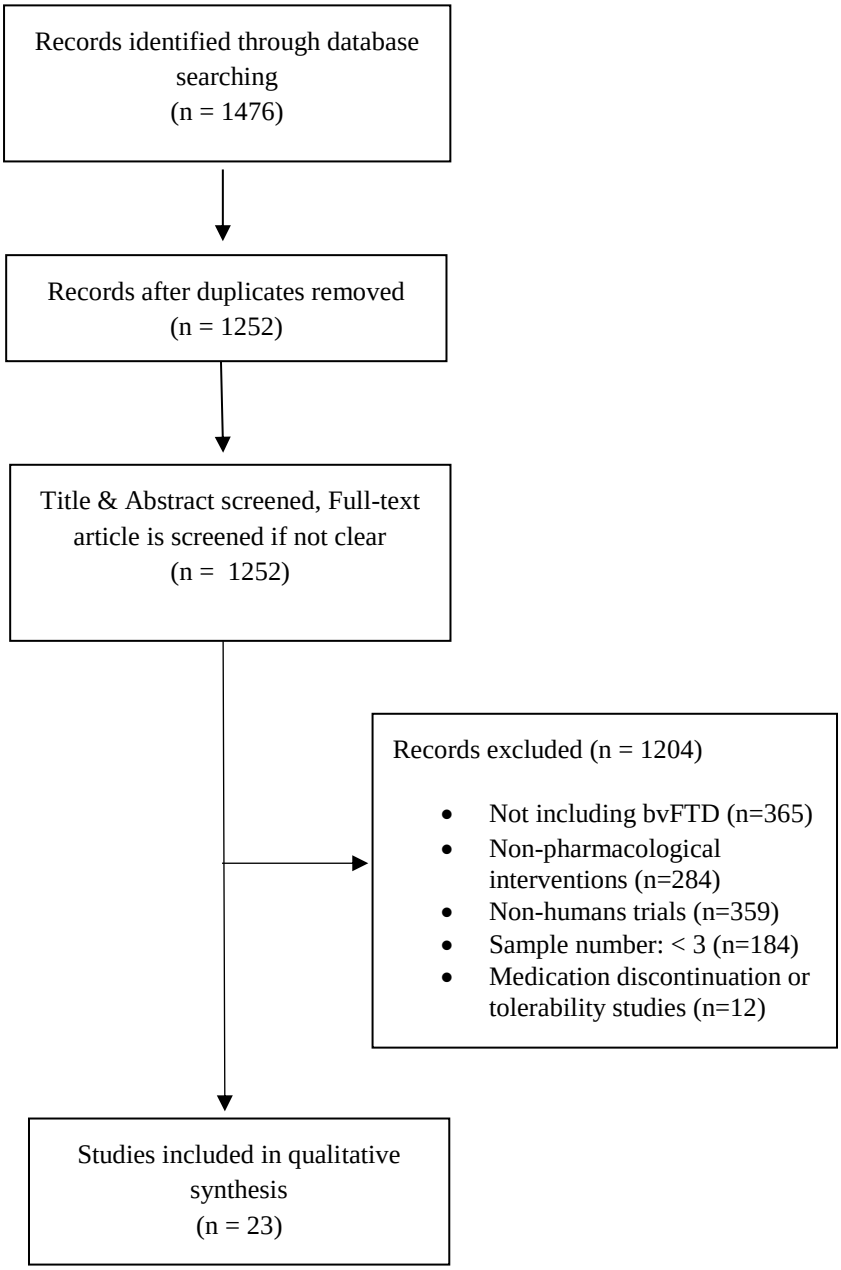

Figure 1. Flow Diagram of the study

Reference	Med	Control	Dosage	Study type	Incl	Treat period	Diagnosis	Measure	Effect
Callegari et al, 2016	Agomelatine	Melatonin	50 mg/d	RCT	24	20 weeks	bvFTD	FAB / NPI	No significant difference in FAB and NPI-D & Improvement in AES-C and NPI-A
Herrmann et al, 2012	Citalopram	-	40 mg/d	Open label	15	6 weeks	FTD (Neary)	NPI	Significant improvement of NPI and FBI
Furlan et al, 2014	Clomipramine	-	20 - 175 mg/d	Case series	3		bvFTD		Improvement in behavioral symptoms
Huey et al, 2008	Dexamphetam	Quetiapine	D: 20 mg/d Q: 150 mg/d	RCT	8	9 weeks	bvFTD	NPI	Significant improvement in NPI
Ikeda et al, 2004	Fluvoxamine maleate	-	50 - 150 mg/d	Open label	16	12 weeks	FTD & SD	SRI	Significant improvement in NPI and SRI
Kertesz et al, 2008	Galantamine	Placebo	8 - 24 mg/d	RCT	36	26 weeks	FTD / PPA (Neary)	FBI / CGI-S	No significant differences in FBI and CGI-S
Devanand et al, 2017	Lithium	-	300 - 600 mg/d	Case series	3		FTD	CGIS / CGIC	Improvement in behavioral symptoms
Boxer et al, 2009	Memantine	-	20 mg/d	Open-label	43	26 weeks	FTD	NPI / FBI	Improvement in total NPI at week 16 and not at week 26
Boxer et al, 2013	Memantine	Placebo	20 mg/d	RCT	76	26 weeks	bvFTD / SD (Neary)	NPI / CGIC	No significant difference in NPI or CGIC and Worse neuropsychological performance
Diehl-Schmid et al, 2008	Memantine	-	20 mg/d	Open-label	16	6 months	FTD Lund Manchester	CIBIC / NPI / FBI	No significant difference in NPI and FBI, significant increase in ADAS-cog
Gu et al, 2015	Memantine	-	2x 10 mg/d	Open label	76	3 years	bvFTD	MMSE	Worsening on all scales in cognitive and behavior performance

Table 1. Study information

Med=Medication group, Control=Control group, Measure=Measurement, Incl=included patients, mg/d = milligram per day; Treat period=treatment period, IU = International Units, RCT = Randomized controlled trials, bvFTD = behavioral variant frontotemporal dementia; SD = Sematic dementia, FAB = Frontal Assessment Battery; NPI = Neuropsychiatric Inventory; SRI = Stereotypy Rating Inventory; FBI = Frontal Behavioral Inventory; CGIS = Clinical Global Impression of Severity; CGIC = Clinical Global Impression of Change; CBIC(-Plus) = Clinician's Interview-Based Impression of Change (plus caregiver); MMSE = Mini Mental State Examinations; CANTAB = Cambridge Neuropsychological Test Automated Battery; IRI = Interpersonal Reactivity Index, CBI = Cambridge Behavioral Inventory; AES-C = Apathy Evaluation Scale; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; MDRS = Mattis Dementia Rating Scale; ZBI = Zarit Caregiver Burden Interview; DAD = Disability Assessment for Dementia; BEHAVE-AD = Behavioral pathology in Alzheimer's disease; RMET = Reading the Mind in the Eyes Test

Reference	Med	Control	Dosage	Study type	Incl	Treat period	Diagnosis	Measure	Effect
Swanberg et al, 2007	Memantine	Placebo	2x 10 mg/d	Case series	3	3 months	FTD	NPI	Improvement in NPI
Vercelletto et al, 2011	Memantine		2 x 10 mg/d	RCT	49	1 year	bvFTD (Neary)	CIBIC-Plus	No significant difference in CIBIC-Plus, MMSE, MDRS, NPI, ZBI, DAD
Rahman et al, 2006	Methylphenidate	Placebo	40 mg (1x)	(R)CT	8	1 - 2 weeks	FTD Lund Manchester)	MMSE / CANTAB	Improvement in behavioral symptoms
Finger et al, 2015	Oxytocin	Placebo	2 x 24, 48 or 72 IU	RCT	23	1 week	bvFTD / SD (Neary)	NPI / FBI / IRI	Significant improvement in NPI, FBI and IRI
Jesso et al, 2010	Oxytocin	Placebo	24 IU (1x)	RCT	20	3 weeks	bvFTD (Neary)	Emotion recognition	Significant improvement in NPI
Deakin et al, 2004	Paroxetine	Placebo	40 mg/d	RCT	10	9 weeks	FTD (Neary)	NPI / CBI	No significant difference on NPI & CBI
Moretti et al, 2002	Paroxetine	Piracetam	Pa: 20 mg/d Pi: 1,200 mg/d	RCT	16	14 months	FTD Lund Manchester	MMSE	Improvement in NPI and BEHAVE-AD
Moretti et al, 2004	Rivastigmine	-	3 - 9 mg/d	Open label	40	12 months	FTD Lund - Manchester	NPI	Significant improvement in NPI
Pardini et al, 2015	Souvenaid	Placebo	125 ml/d	Proof of concept	26	24 weeks	bvFTD	NPI / FAB	Significant improvement in NPI RMET and CGI-S
Lebert et al, 2004	Trazodone	AP	150 mg/d	RCT	26	12 weeks	FTD Lund Manchester	NPI	Significant improvement in NPI
Lebert et al, 2006	Trazodone	Placebo	300 mg/d	Open label	26	3 years	FTD Lund Manchester	NPI	Significant improvement in NPI
Kimura et al, 2010	Yokukansan	-	7,5 g/d	Open label	20	4 weeks	FTD (Neary)	NPI	Significant improvement in NPI and SRI

Table 1. Study information
Med=Medication group, Control=Control group, Measure=Measurement, mg/d = milligram per day; IU = International Units, RCT = Randomized controlled trials, bvFTD = behavioral variant frontotemporal dementia; SD = Sematic dementia, FAB = Frontal Assessment Battery; NPI = Neuropsychiatric Inventory; SRI = Stereotypy Rating Inventory; FBI = Frontal Behavioral Inventory; CGIS = Clinical Global Impression of Severity; CGIC = Clinical Global Impression of Change; CBIC(-Plus) = Clinician's Interview-Based Impression of Change (plus caregiver); MMSE = Mini Mental State Examinations; CANTAB = Cambridge Neuropsychological Test Automated Battery; IRI = Interpersonal Reactivity Index, CBI = Cambridge Behavioral Inventory; AES-C = Apathy Evaluation Scale; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; MDRS = Mattis Dementia Rating Scale; ZBI = Zarit Caregiver Burden Interview; DAD = Disability Assessment for Dementia; BEHAVE-AD = Behavioral pathology in Alzheimer's disease; RMET = Reading the Mind in the Eyes Test

Studies reporting effect on symptoms

Apathy

Seven studies reported the effect of medication on apathy: Agomelatine, [19] [20] Memantine,[21] Oxytocin,[22] [23] Souvenaid,[24] and Yokukansan.[25] Five studies were randomized controlled trials, one was an open label study and one was a case series, including in total 124 patients.

Twenty-four patients were randomized to either agomelatine (50 mg /day) or sustained release melatonin (10 mg/d) for 10 weeks.[19] The latter patients switched to agomelatine for an additional 10 weeks. Apathy, measured with Apathy Evaluation Scale clinical version (AED-C), was significantly decreased in the group receiving agomelatine, also in the patients that switched from melatonin to agomelatine. This study supports that agomelatine can be an effective treatment for apathy in bvFTD.

In 8 patients 20 mg of dextroamphetamine was compared to 150 mg of quetiapine.[20] A significant effect of dextroamphetamine was seen on the total NPI, including the NPI subscale for apathy.

In a case series three bvFTD patients improved on the total NPI score with memantine (twice 10 mg/d), with a most notable improvement in agitation, apathy and anxiety.[21]

Oxytocin was examined by two separate RCT studies, one prescribed three doses of intranasal Oxytocin (24, 48 and 72 IU) or placebo twice daily for 1 week to 23 patients[22] and in the other study twenty patients received a single dose of 24 IU of intranasal oxytocin or placebo.[23] Both studies observed a positive effect of Oxytocin on the Neuropsychiatric Inventory (NPI) and Frontal Behavioral Inventory (FBI), with a reduction of levels of apathy.

In a proof of concept study twenty-six patients with bvFTD were randomized to Souvenaid (125 ml/d) or placebo with a cross-over after 12 weeks.[24] There was a significant improvement for both NPI and RMET scores in the Souvenaid group. The overall NPI score for the Souvenaid group decreased, including NPI apathy, whereas NPI scores remained stable in the placebo group.

Twenty patients received a daily dosage (7,5 mg/d) of Yokukansan for 4 weeks in an open label study.[25] All patients completed the trial and the NPI score improved significantly in 90% of the patients, with an overall decrease of 13.4 points. Several NPI subscale decreased significantly, such as NPI apathy.

Due to the variability in study duration and lack on specific outcome reports, it is not possible to conclude which is best for the effect on apathy.

Disinhibition (Including: Agitation, Aggression, Irritability)

Twelve studies examined the effect of medication on disinhibition, including Citalopram,[26] Dexamphetamine,[20] Lithium, [27] Memantine, [21] Methylphenidate, [28] Oxytocin, [22] [23] Paroxetine,[29] Rivastigmine,[30] Souvenaid,[24] Trazodone[31] and Yokukansan.[25] Within these studies, 7 studies were randomized controlled trials, 3 were open labels studies and 2 were case series. These studies examined a total of 208 patients.

Eleven of the studies observed a positive effect of medication on disinhibition, whereas one study showed a negative side effect of medication, with an increased level of hypersexual behavior after the treatment of Oxytocin.[22] Of the eleven studies that observed a positive effect, four showed improvement on general disinhibition, 6 of the medication showed improvement on agitation, 2 on aggression, 5 on irritability and 1 on betting behavior.

Four studies reported outcome on general disinhibition. Fifteen bvFTD patients received a single dose of citalopram (30 mg), to assess central serotonergic function, followed by a 6-week treatment with a daily dose of Citalopram.[26] A significant decrease was found in the total NPI score and in several NPI subsets, such as NPI disinhibition. Additionally, there was a significant decrease in FBI scores over the 6-week period, with a decrease of FBI-Disinhibition.

In eight bvFTD patients treated with dexamphetamine, a positive effect was observed for disinhibition (see also *Apathy*).[20] A significant effect of dexamphetamine was seen on the total NPI ($p=0.05$), with a reduction of 2.4 points in NPI-Disinhibition.

A great improvement was observed in 20 patients treated with Yokukansan, with an overall NPI score reduction of 13.4 points (see also *Apathy)*.[25] Several behavioral symptoms improved significantly, such as NPI-Disinhibition ($p=0.0164$) and NPI-Agitation ($p=0.0018$).

Treatment with Souvenaid showed a significant improvement in 26 patients for both NPI and RMET scores in bvFTD (see also *Apathy & general Disinhibition*).[24] The overall NPI score decreased with 4.2 points for Souvenaid

Reference	*Random sequence generation*	*Allocation concealent*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
Callegari et al, 2016	+	+	+	?	+	+	?
Herrmann et al, 2012	-	-	-	-	+	-	?
Furlan et al, 2014	-	-	-	-	+	-	-
Huey et al, 2008	+	-	+	?	+	-	?
Ikeda et al, 2004	-	-	-	-	+	+	-
Kertesz et al, 2008	?	?	+	+	+	+	?
Devanand et al, 2017	-	-	-	-	+	-	-
Boxer et al, 2009	-	-	-	-	+	+	+
Boxer et al, 2013	+	+	+	+	+	+	?
Diehl-Schmid et al, 2008	-	-	-	?	+	+	+
Gu et al, 2015	-	-	-	-	?	+	?
Swanberg et al, 2007	-	-	-	-	?	-	-
Vercelletto et al, 2011	+	+	+	+	+	+	+
Rahman et al, 2006	+	?	+	?	?	+	?
Finger et al, 2015	+	?	+	?	+	+	-
Jesso et al, 2010	+	?	+	?	+	+	?
Deakin et al, 2004	+	?	+	+	?	+	-
Moretti et al, 2002	?	?	-	-	+	+	-
Moretti et al, 2004	-	-	-	-	+	+	-
Pardini et al, 2015	+	+	-	-	+	+	-
Lebert et al, 2004	?	?	+	?	+	+	-
Lebert et al, 2006	-	-	-	-	+	+	-
Kimura et al, 2010	-	-	-	-	+	+	-

Table 2. Cochrane Collaboration's tool for assessing riks of bias

Higgins, J. P. T., Altman, D. G., & Sterne, J. (2011). Chapter 8.5 The Cochrane Collaboration's tool for assessing risk of bias. *The Cochrane Collaboration. Higgins JPT, Green S, In: Cochrane Handbook for Systematic Reviews of Interventions. Version*, *5*(0). Legend: + = Low risk of bias, - = High risk of bias, ? = Unclear risk of bias

Reference	Medication	NPI	Apathy	Disinhibition	E	Hyperorality	Stereotyp.	Depression	Others
Herrmann et al, 2012	Citalopram	- 14*		↓ Disinhibition*				↓ Depression*	
Huey et al, 2008	Dexampheta	↓*	↓ (2,8 points)	↓ Disinhibition					
Ikeda et al, 2004	Fluvoxamine	- 11.0*					↓ Aberrant		
Devanand et al, 2017	Lithium	↓		↓ Aggression					
Boxer et al, 2009	Memantine	=							
Boxer et al, 2013	Memantine	=							
Diehl-Schmid et al,	Memantine	=							
Swanberg et al, 2007	Memantine	↓	↓	↓ Agitation				↓ Anxiety	
Vercelletto et al, 2011	Memantine	=							
Finger et al, 2015	Oxytocin	- 5,81	↓						
Jesso et al, 2010	Oxytocin	- 3.9*	↓	↓ Disinhibition		↓ Hyperorality		↓ Depression	
Deakin et al, 2004	Paroxetine	=							
Moretti et al, 2002	Paroxetine	- 8,25*		↓ Aggression		↓ Hyperorality		↓ Depression	↓ Sleeping
Moretti et al, 2004	Rivastigmine	- 15,1*		↓ Agitation* ↓ Irritability*		↓ Hyperorality*		↓ Anxiety*	↓ Delusions & Hallucinations*
Pardini et al, 2015	Souvenaid	- 4,2*	↓	↓Disinhibition ↓ Agitation ↓ Irritability					
Lebert et al, 2004	Trazodone	- 18,95*		↓ Agitation ↓ Irritability		↓ Hyperorality		↓ Depression	
Lebert et al, 2006	Trazodone	- 20,5*							
Kimura et al, 2010	Yokukansan	- 13,4*	↓*	↓ Disinhibition* ↓ Agitation* ↓ Irritability*			↓ Aberrant behavior*		↓ Delusions*

Table 3 Results on NPI for symptom categories

* = $p<0.05$ vs baseline, E=Empathy

group and was stable for the placebo group. The overall NPI score reduction was based on several subscales of NPI, under which NPI-Disinhibition.

Agitation / Aggression

Six studies reported specifically on agitation. Three patients with bvFTD presenting with agitation with or without psychotic features were treated with low-dose (300-600 mg/d with 0,2 - 0,8 mmol/L serum) lithium.[32] The short-term to intermediate-term follow up indicated that lithium was effective in treating agitation and other behavioral disturbances.

In twenty patients a significant reduction was seen in the overall NPI score during Day 1 following oxytocin administration (see also *Apathy*).[23] The improvement in the total NPI was driven by small reduction across multiple subscales in NPI including disinhibition. The effectiveness of intranasal oxytocin wore off after one week, because of the short half-life of oxytocin. Sixteen patients diagnosed with FTD were randomized into two homogeneous groups, matched for age and education levels.[29] Eight patients received Paroxetine up to 20 mg/d and eight patients received Piracetam up to 1200 mg twice a day for 14 months. Patients treated with Paroxetine showed statistically significant improvements on different behavioral symptoms, considering the NPI total score. The NPI total score reduced ($p<0,05$), with a reduction of aggression and agitation. In contrast, patients treated with Piracetam showed no improvements in any domain.

Forty patients received Rivastigmine (3-9 mg/d) or placebo for 12 months.[30] Patients were manually divided into two homogenous groups, of which 20 patients received Rivastigmine and 20 patients placebo. The control group received treatment with antipsychotics, benzodiazepines and selegiline. The Rivastigmine group improved significantly in NPI scores ($p<0,001$). In contrast, the control group worsened significantly in NPI scores ($p<0,001$). Rivastigmine had the greatest effect on agitation.

Treatment with Souvenaid showed a significant improvement in 26 patients for both NPI and RMET scores in bvFTD, with also an improvement of in agitation (see also *Apathy & general Disinhibition*).[24]

In a case series a reduction of the overall NPI score ($p<0,001$) was observed in 3 patients treated with memantine (see also *Apathy*).[21] Within the subscale score of NPI, agitation was one of the most notable improvements.

A gradual increased dose of Trazodone was administered to 26 patients with FTD.[31] Patients started with an initial 6 days-titration period with 50 and 100 mg/d

or matching placebo, followed by a 3 week period of 150 mg/d administration. If patients did not report side-effect, 300 mg/d of Trazodone was prescribed for the next 3 weeks. This cross-over showed a decrease of 50 % in NPI score 10 patients based on 4 NPI sub scales, of which agitation was one of them.

Irritability

Citalopram,[26] Yokukansan,[25] Trazodone,[31] Rivastigmine[30] and Souvenaid[24] were used in different trials and demonstrated efficacy in treating irritability in bvFTD, measured with NPI.

Abnormal risk taking behavior

Galantamine was used in 36 bvFTD patients in a double-blind, placebo-controlled study.[33] The key finding of this study was an attenuation of risk-taking and there were no significant side effects on memory function or executive tasks.

Loss of empathy or sympathy

Only two studies examined the effect on empathy or sympathy in bvFTD patients with Oxytocin[22] and Paroxetine[29] as medication.

In the RCT study of Finger et al (see also *Apathy & Disinhibition*),[22] results suggest that intranasal oxytocin may improve a subset of behavioral symptoms in bvFTD, including a significant improvement in expressions of empathy, resulting in improved patient care-giver interactions.

In an open label study by Moretti et al (see also *Disinhibition*)[29], Paroxetine treatment showed statistically significant improvements on different behavioral symptoms, with a reduction of social conduct.

Hyperorality

Six studies reported the effect of medication on hyperorality: Fluvoxamine maleate,[34] Oxytocin,[23] Paroxetine,[29] Rivastigmine, [30] Trazodone[31] and Yokukansan.[25] These studies were based on 3 randomized controlled trials and 2 open label studies, including in total 138 patient.

Fluvoxamine maleate was administered to 16 bvFTD patients for 12 weeks. [34] Dosage of Fluvoxamine ranged from 50 to 150 mg/d throughout the whole trial, with a mean dose of 110 mg/d. This study found a significant effect for the NPI and SRI total scores and revealed a significant time effect in the eating and cooking behaviors ($p=0.020$).

Twenty patients were observed during Oxytocin administration and improvement in overall NPI score was seen, based on multiple subscales in NPI including NPI-Appetite and eating disorders, with a reduction of 3.5 points (see also *Apathy & Disinhibition*). [23]

Sixteen patients treated with Paroxetine and statistically significant improvements were observed in different behavioral symptoms, with a reduction of eating problems (see also *Disinhibition & Loss of empathy or sympathy*).[29]

Rivastigmine was used as medication for FTD in an open label study and had an positive effect on eating disorders, measured by NPI (see also *Disinhibition*).[30]

Trazodone a reduced the total NPI score significantly, with the greatest behavioral benefit in severe eating disorders (see also *Disinhibition*).[31]

Yokukansan treatment improved several SRI subscales significantly, such as SRI-Eating and cooking, reduced with 1.5 points, p=0.0180 (see also *Apathy & Disinhibition*).[25]

Stereotypical behavior

Three studies examined the effect of medication on stereotypical behavior, including Clomipramine,[35] Fluvoxamine[34] and Yokukansan.[25] These studies included a total number of 39 patients.

Three cases diagnosed with probable bvFTD received a daily dosage of Clomipramine varying from 20 mg to 175 mg.[35] In all three patients improvement in compulsive behavior was noted with administration of clomipramine.

In 16 patients Fluvoxamine maleate was used as treatment (see also *Hyperorality*).[34] This study found a significant effect for the NPI and SRI (p=0.002). Among the NPI subscales, a significant effect in aberrant motor behavior (p=0.001) was observed. Among the SRI subscale, a significant effect in roaming (p=0,010), speaking (p=0.018), movements (p=0.006) and daily rhythm (p=0.020) was observed.

In an open label study with 20 patients by Kimura et al.,[25] Yokukansan treatment improved several NPI and SRI subscales significantly, such as NPI-Aberrant behavior (2.9 points, p=0.0009) , SRI-Speaking (1.6 points, p=0.0117) and SRI-Movements (1.5 points, p=0.0117) (see also *Apathy, Disinhibition & Hyperorality*).

Depression

Citalopram,[26] Oxytocin,[23] Paroxetine[29] used in RCT and Trazodone[31] in an open label study showed efficacy in treating depression in bvFTD, measured by NPI-Depression or Cornell Scale for Depression.

Memantine tested in a case series[21] and Rivastigmine tested in an open label study showed efficacy in treating anxiety in bvFTD[30], measured by NPI-Anxiety.

Executive dysfunction

There was no study that reported an effect on reducing executive dysfunction. However, two studies showed an effect of worsening in the neuropsychological and behavioral performance when treated with Memantine.[36 37]

Worsening or no effect

There are several medications that are used in clinical practice, that are found to be not effective for bvFTD.

Thirty-six bvFTD and primary progressive aphasia patients were treated with Galantamine (8-24 mg/d) for 8 weeks.[33] No significant improvement was observed, concluding that Galantamine is not effective in bvFTD.

For 26 weeks seventy-six patients were treated with daily 20 mg of Memantine or placebo. No benefits of Memantine in bvFTD was found for any of the outcome measures, after 26 weeks of treatment.[36] Additionally, evidence was found that Memantine is associated with worse cognitive performance, measured by Boston test of naming (BNT) and processing speed (Digit Symbol test). In the study by Verceletto et al.,[38] a dosage of 10 mg or placebo was administered twice daily to 49 bvFTD patients. None of the outcome measures showed significant differences between the memantine (n=23) and placebo (n=26) group, except for the FBI score, which was lower in the memantine group.

NPI as outcome measure

Studies reporting NPI as outcome measure showed improvement in overall NPI score in 14 studies and no improvement in 5 studies (Table 3). Within these 14 studies, ten studies reported an significant improvement. Hereby, Trazodone showed the greatest overall NPI score reduction[31], followed by Rivastigmine[30] and Citalopram.[26]

DISCUSSION

BvFTD is a devastating disease with profound implications for the patient, family members and society.[39] While there is still no cure for bvFTD, pharmacological interventions are tested to relieve the burdening symptoms. This systematic review aimed to provide an overview of RCT, open label and case series studies into pharmacological symptom relieving options in bvFTD.

We found that 4 medications tested in RCT may have a good effect on *apathy*, including Agomelatine,[19] Dexamphetamine,[20] Oxytocin[23] and Souvenaid.[24] One open label study with Yokukansan[25] and one case series study with Memantine[21] also revealed efficacy on *apathy* in bvFTD. However, the results of these latter studies should be interpreted with caution, due to the fact that the methodological quality of these studies was considered as weak and several studies showed no effectiveness of Memantine in symptoms of bvFTD.[36 40 38] Additionally, two studies showed worsening in the neuropsychological and behavioral performance when treated with Memantine.[36 37] This leads to the conclusion that Memantine should not be recommended at this moment.

Regarding *disinhibition* we included five types of symptoms, including general disinhibition, aggression, agitation, irritability and abnormal risk taking behavior. Six medications tested in RCT were found to have a good effect on *disinhibition*, including Trazodone,[31] Dexamphetamine,[20] Methylphenidate,[28] Oxytocin,[22 23] Paroxetine,[29] Souvenaid. [24] Three medications tested in open-label studies, Citalopram,[26] Yokukansan[25] and Rivastigmine,[30] and 2 medications tested in case series, Lithium[32] and Memantine,[21] were also found to be effective. Besides medications that have a good effect on *disinhibition*, there were also medications that were found to increase the level of *disinhibition*, such as Oxytocin.[22] Oxytocin for bvFTD should prescribed with caution, as hypersexual behavior can be present as a side effect.[22]

Medications that were effective in increasing the *level of empathy or sympathy* were found in 2 RCT studies. These studies suggested that Oxytocin and Paroxetine increase the *level of empathy* and social behavior.[22 29]

The category of *hyperorality* consisted of several symptoms: hyperorality, eating problems and eating disorders. 3 RCT tested medications: Oxytocin[23], Trazodone[31] & Paroxetine[29] and 2 open-label tested medications: Yokukansan[25] and Rivastigmine[30] showed an improvement in eating behavior.

Limited research on *stereotypical behavior* is carried out until this moment. Only 2 open-label studies and one case series provided results that suggest improvement in aberrant and compulsive behavior by use of Clomipramine, Fluvoxamine and Yokukansan.[35] [34] [25] Further research is needed to provide more information about the improvement of *stereotypical behavior*.
In summary, few medications were found to be effective on various symptoms of bvFTD: Rivastigmine,[30] Trazodone,[31] [41] Yokukansan[25] and Souvenaid.[24] In these studies, according to the Cochrane risk of bias tool, the highest evidence was found in the study of Lebert et al. concerning Trazodone, with a moderate risk of bias.[31] Besides the probable effectiveness of Trazodone (explicitly on *disinhibition* and *hyperorality*) this emphasizes the scarcity of pharmacological intervention studies in bvFTD with strong methodological quality revealing symptom relieving options in bvFTD.

Based on the NPI measurement , we can conclude from the results of the studies that Trazodone has the greatest effect on the general symptoms of bvFTD, followed by Rivastigmine and Citalopram.[31] [41] [30] [26]
This systematic review provides actual insight in the medication that can be used to treat the main symptoms in bvFTD. During the three years between now and the next to last systematic review by Nardell et al., several medications were researched in randomized controlled trials on the effectiveness on bvFTD, such as Souvenaid and Agomelatine. Both Souvenaid and Agomelatine were found to be effective to several symptoms in bvFTD, including *apathy* and *disinhibition.*[14] The latest systematic review was published at the time of the final phase of this study, which apparently limits the impact of the current study.[15] At the same time, it underlines that insight in symptom relieving options in bvFTD seemed to be prominently needed, both from a scientific point of view as well as driven by clinical practice. The last systematic review[15] concluded that with the exception of 1 study about Paroxetine[42] all preliminary data suggests beneficial effects of serotonergic antidepressants (trazodone, paroxetine, citalopram and fluvoxamine) regarding psychiatric symptoms in bvFTD.[15] [42] Besides, the positive effects of dopaminergic compounds (selegiline and dextroamphetamine) were described. We used a slightly different search strategy compared to the systematic review of Buoli et al., (2017) as we searched for articles in Embase instead of Isi Web of Knowledge and Medscape,[15] in addition to MEDLINE and PsycINFO. Besides, in contrast to Buoli et al., we searched with MESH terms. Keywords and synonyms of

'Frontotemporal Dementia' [Mesh] and 'Drug Therapy' [Mesh] were searched while Buoli et al., searched with 'psychiatry', 'behavioral disturbances' and 'treatment'. Interestingly, we can corroborate the main findings of Buoli et al., and did not find contrary results.

The two most important differences with the latest systematic review in this field[15] is the difference in included studies and the exact aim of the study. Concerning included studies, in the systematic review of Buoli et al.[15] three studies were included that we did not include: a study by Kimura and Takamatsu[43] studying discontinuation of treatment with Donezepil concluding that discontinuation of this agent led to decreased NPI score, a study by Lebert and Pasquier[44] into the effect of Trazodone concluding a reduction in NPI total score and a study by Moretti et al.[45] revealing an improvement of psychiatric symptoms in three patients with bvFTD with Selegiline (the last two studies were not included in our systematic review due to the lack of an abstract). Contrary to the systematic review by Buoli et al.[15] we included 7 studies that were not included in their work: 4 open label studies,[46 37 41 25] 1 case series,[32] 1 RCT [19] and 1 controlled trial.[28] In addition to the conclusions of Buoli et al., we can conclude that also Lithium,[32] Methylphenidate,[28] Yokukansan[25] and Agomelatine[19] might have beneficial effects regarding behavioral symptoms in bvFTD.

Another important addition to the previous systematic reviews into pharmacological interventions in bvFTD is our focus at providing clinical guidance in pharmacological management based on symptom profile according to the FTDC criteria: Apathy, Disinhibition, Lack of empathy or sympathy, Hyperorality, Stereotypical behavior and Executive dysfunction. [13 14 15 16] Although descriptions of the pharmacological effect of agents sometimes included the effect of specific symptoms, previous systematic reviews have never been primarily focused at this clinically guidance.

Our findings should be understood in the context of some limitations. Studies could not always be compared accurately due the following characteristics of the studies. First, due to the fact that there are different criteria of bvFTD over the years, different studies use different criteria to diagnose bvFTD. Most of the studies use the Neary criteria or the Lund and Manchester criteria but there are also studies in which the criteria were unclear. [1 47] Second, outcome measurements of changes in symptoms of bvFTD differ between studies, although nearly all studies used NPI as

outcome measure. Lastly, most or all studies were sponsored by medical health care institutes.

Researchers worldwide are working on the progress of understanding the pathology of bvFTD and its most adequate treatment. Due to the lack of a disease modifying therapy, it is still important to develop an accurate symptomatic pharmacological therapy. Research on symptomatic pharmacological therapy is still limited until this moment and further research is necessary to advance the progress in symptomatic pharmacological therapy. This systematic review gives a solid step in this process and gives an accessible guideline with an overview of the existing treatment of the main symptoms in bvFTD. Advancement of therapeutics and disease management is to be gained.

REFERENCES

1. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140-143. doi:10.1192/bjp.180.2.140.
2. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. *BMJ*. 2013;347(August):f4827. doi:10.1136/bmj.f4827.
3. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615-1621. doi:10.1212/WNL.58.11.1615.
4. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. In: *Dementia and Geriatric Cognitive Disorders*. Vol 17. ; 2004:265-268. doi:10.1159/000077151.
5. Rosso SM, Kaat LD, Baks T, et al. Frontotemporal dementia in The Netherlands: Patient characteristics and prevalence estimates from a population-based study. *Brain*. 2003;126(9):2016-2022. doi:10.1093/brain/awg204.
6. Shinagawa, S., Nakajima, S., Plitman, E., Graff-Guerrero, A., Mimura, M., Nakayama, K., Miller BL. Non-pharmacological management for patients with Frontotemporal dementia: a systematic review. *J Alzheimer's Dis*. 2015;45(1):283-293. doi:10.3233/JAD-142109.
7. Diehl-Schmid J, Schmidt E-M, Nunnemann S, et al. Caregiver burden and needs in frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 2013;26(4):221-229. doi:10.1177/0891988713498467.
8. Boxer AL, Boeve BF. Frontotemporal Dementia Treatment: Current Symptomatic Therapies and Implications of Recent Genetic, Biochemical, and Neuroimaging Studies. *Alzheimer Dis Assoc Disord*. 2007;21(4):S79-S87. doi:10.1097/WAD.0b013e31815c345e.
9. Mackenzie, I. R., Rademakers, R., & Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Lancet Neurol*. 2010;9(10):995-1007.
10. Wilcock DM, Rojiani A, Rosenthal A, et al. Passive immunotherapy against Aβ in aged APP-transgenic mice reverses cognitive deficits and depletes parenchymal amyloid deposits in spite of increased vascular amyloid and microhemorrhage. *J Neuroinflammation*. 2004;1(1):24. doi:10.1186/1742-2094-1-24.
11. Nunnemann S, Kurz A, Leucht S, Diehl-Schmid J. Caregivers of patients with frontotemporal lobar degeneration: a review of burden, problems, needs, and interventions. *Int Psychogeriatrics*. 2012;24(9):1368-1386. doi:10.1017/S104161021200035X.
12. Chakrabarty T, Sepehry AA, Jacova C, Hsiung GYR. The prevalence of depressive symptoms in frontotemporal dementia: A meta-analysis. *Dement Geriatr Cogn Disord*. 2015;39(5-6):257-271. doi:10.1159/000369882.
13. Portugal M da G, Marinho V, Laks J. Pharmacological treatment of frontotemporal lobar degeneration: systematic review. *Rev Bras Psiquiatr*. 2011;33(1):81-90. doi:10.1590/S1516-44462011000100016.

14. Nardell M, Tampi RR. Pharmacological Treatments for Frontotemporal Dementias: A Systematic Review of Randomized Controlled Trials. *Am J Alzheimers Dis Other Demen*. 2013;29(2):123-132. doi:10.1177/1533317513507375.
15. Buoli M, Serati M, Caldiroli A, Galimberti D, Scarpini E, Altamura AC. Pharmacological Management of Psychiatric Symptoms in Frontotemporal Dementia: A Systematic Review. *J Geriatr Psychiatry Neurol*. 2017;30(3):162-169. doi:10.1177/0891988717700506.
16. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
17. Chakrabarty T, Sepehry AA, Jacova C, Hsiung G-YR. The prevalence of depressive symptoms in frontotemporal dementia: A meta-analysis. *Dement Geriatr Cogn Disord*. 2015;39(5-6). doi:10.1159/000369882.
18. Higgins JPT AD. Chapter 8. Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. *Cochrane Collab*. 2011. www.cochrane-handbook.org.
19. Callegari I, Mattei C, Benassi F, et al. Agomelatine improves apathy in frontotemporal dementia. *Neurodegener Dis*. 2016;16(5-6):352-356. doi:10.1159/000445873.
20. Huey ED, Garcia C, Wassermann EM, Tierney MC, Grafman J. Stimulant treatment of frontotemporal dementia in 8 patients. *J Clin Psychiatry*. 2008;69(12):1981-1982. doi:10.4088/JCP.v69n1219a.
21. Swanberg MM. Memantine for behavioral disturbances in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord*. 2007;21(2):164-166. doi:10.1097/WAD.0b013e318047df5d.
22. Finger EC, MacKinley J, Blair M, et al. Oxytocin for frontotemporal dementia: a randomized dose-finding study of safety and tolerability. *Neurology*. 2015;84(2):174-181. doi:10.1212/WNL.0000000000001133.
23. Jesso S, Morlog D, Ross S, et al. The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. *Brain*. 2011;134(9):2493-2501. doi:10.1093/brain/awr171.
24. Pardini, M., Serrati, C., Guida, S., Mattei, C., Abate, L., Massucco, D., ... & Emberti Gialloreti L. Souvenaid reduces behavioral deficits and improves social cognition skills in frontotemporal dementia: a proof-of-concept study. *Neurodegener Dis*. 2015;15(1):58-62.
25. Kimura T, Hayashida H, Furukawa H, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: Effect of Yokukansan on behavioral symptoms. *Psychiatry Clin Neurosci*. 2010;64(2):207-210. doi:10.1111/j.1440-1819.2010.02072.

26. Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. *Am J Geriatr Psychiatry*. 2012;20(9):789-797. doi:10.1097/JGP.0b013e31823033f3.

27. Devanand, D. P., Pelton, G., D'antonio, K., Strickler, J., Kreisl, W., Noble, J. & Huey, E. et al. Low-dose Lithium treatment for agitation in Frontotemporal dementia: A case series. *J Neurochem*. 2016.

28. Rahman S; Robbins Tw, Hodges JR, Mehta MA, Nestor PJ, Clark L SB. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology*. 2006;31(3):651-658.

29. Moretti, R., Torre, P., Antonello, R. M., Cazzato, G., & Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. *2002*. 49(1):13-19.

30. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in Frontotemporal Dementia. *Drugs & Aging*. 2004;21(14):931-937. doi:10.2165/00002512-200421140-00003.

31. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: A randomised, controlled trial with trazodone. In: *Dementia and Geriatric Cognitive Disorders*. Vol 17. ; 2004:355-359. doi:10.1159/000077171.

32. Devanand, D. P., Pelton, G. H., D'antonio, K., Strickler, J. G., Kreisl, W. C., Noble, J. & Huey ED. Low-dose Lithium Treatment for Agitation and Psychosis in Alzheimer Disease and Frontotemporal Dementia: A Case Series. *Alzheimer Dis Assoc Disord*. 2017.

33. Kertesz A, Morlog D, Light M, et al. Galantamine in frontotemporal dementia and primary progressive aphasia. *Dement Geriatr Cogn Disord*. 2008;25(2):178-185. doi:10.1159/000113034.

34. Ikeda M, Shigenobu K, Fukuhara R, et al. Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. *Dement Geriatr Cogn Disord*. 2004;17(3):117-121. doi:10.1159/000076343.

35. Furlan JC, Henri-Bhargava A, Freedman M. Clomipramine in the treatment of compulsive behavior in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord*. 2014;28(1):95-98. doi:10.1097/WAD.0b013e318265c104.

36. Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2013;12(2):149-156. doi:10.1016/S1474-4422(12)70320-4.

37. Gu, X. H., Xu, J., & Wei CS. Memantine in patients with behavioral variant frontotemporal dementia: An open-label pilot study. *Alzheimer's Dement*. 2015;11(7):751-753.

38. Vercelletto M, Boutoleau-Bretonniere C, Volteau C, et al. Memantine in behavioral variant frontotemporal dementia: negative results. *J Alzheimers Dis*. 2011;23(4):749-759. doi:10.3233/jad-2010-101632.

39. Svanberg E, Spector A, Stott J. The impact of young onset dementia on the family: a literature review. *Int Psychogeriatrics*. 2011;23(3):356-371. doi:10.1017/S1041610210001353.
40. Diehl-Schmid J, Förstl H, Perneczky R, Pohl C, Kurz A. A 6-month, open-label study of memantine in patients with frontotemporal dementia. *Int J Geriatr Psychiatry*. 2008;23(7):754-759. doi:10.1002/gps.1973.
41. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Trazodone in fronto-temporal dementia. *Res Pract Alzheimers Dis*. 2006;11:356-360.
42. Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: A double-blind randomized controlled trial. *Psychopharmacology (Berl)*. 2004;172(4):400-408. doi:10.1007/s00213-003-1686-5.
43. Kimura T, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: risk of donepezil treatment for behavioral and psychological symptoms. *Geriatr Gerontol Int*. 2013. doi:10.1111/j.1447-0594.2012.00956.
44. Lavenu I, Pasquier F, Lebert F, Petit H, Van der Linden M. Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1999;13(2):96-101.
45. Moretti R, Torre P, Antonello RM, Cazzato G BA. Effects of selegiline on fronto-temporal dementia: a neuropsychological evaluation. *Int J Geriatr Psychiatry*. 2002;17(4):391-392.
46. Boxer AL, Lipton AM, Womack K, et al. An Open-label Study of Memantine Treatment in 3 Subtypes of Frontotemporal Lobar Degeneration. *Alzheimer Dis Assoc Disord*. 2009;23(3):211-217. doi:10.1097/WAD.0b013e318197852f.
47. Englund, B. Brun, A. Gustafson, L. Passant, U. Mann, D. Neary, D., Snowden JS. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994;57(4):416-418.

Summary and general discussion

Summary and general discussion

Driven by the clinical dilemma of the large symptomatic overlap of bvFTD and psychiatric disorders, the general aim of this thesis was to define clinical hallmarks able to discern a psychiatric origin from behavioral variant frontotemporal dementia in the late onset frontal lobe syndrome. We described our research on different aspects of the clinical overlap and differentiation of bvFTD, other neurodegenerative diseases and psychiatric disorders. In this section, the results of these research projects, implications for clinical practice and future perspectives are discussed.

Section 1. Behavioral variant frontotemporal dementia and psychiatric disorders

The starting point of **section 1** was to describe main aspects of clinical similarities between bvFTD and psychiatric disorders. In **chapter 2** we investigated the frequency and character of DSM-IV psychiatric disorders in patients with probable and definite bvFTD compared to patients with possible bvFTD, other neurodegenerative diseases, and patients diagnosed with a psychiatric disorder, using MINI-International Neuropsychiatric Interview. The MINI-International Neuropsychiatric Interview was based on DSM-IV and ICD-10 criteria for a psychiatric disorder.[1] We additionally compared psychiatric prodromes between these diagnostic groups. In this research 23 patients with probable and definite bvFTD, 3 patients with possible bvFTD, 25 with a non bvFTD neurodegenerative disease and 40 patients with a clinical psychiatric diagnosis were studied. Overall frequency of formal current and past psychiatric disorders in patients with probable and definite bvFTD (21.7% current, 8.7% past) did not differ from other neurodegenerative diseases (12.0% current, 16.0% past) or possible bvFTD (66.7% current, 66.7% past), but was less than in patients with a clinical psychiatric diagnosis (57.5% current, 62.5% past) ($P<0.01$). In patients with probable and definite bvFTD unipolar mood disorders were most common. Contrary to our expectations we concluded that formally diagnosed psychiatric disorders are not overrepresented in probable bvFTD. This conclusion is remarkable in the context of previous literature reporting that 50.7% of bvFTD patients receive a prior psychiatric diagnosis, found by retrospective chart review.[2] Our longitudinal study showed that correctly applying DSMIV and ICD-10 criteria in bvFTD gives a

lower rate of formal psychiatric disorders in bvFTD (23.3%), and we suggested that psychiatric misdiagnosis in bvFTD might be reduced by strictly applying diagnostic criteria.

Further we found that in probable bvFTD patients unipolar mood disorders were the most common psychiatric disorders (13.9%). Previous literature has already shown the relative high prevalence of mood disturbances in bvFTD. A recent meta-analysis including 29 studies showed that depressive mood and its manifestations are recognized in approximately one third (33%) of patients with bvFTD.[3] Striking, the majority of these studies about the prevalence of (comorbid) depression in bvFTD were based upon reports of depressed mood only while studies into the prevalence of mood disorders based on formal criteria for depression are scarce.[3 4 5] The discrepancy between the prevalence of depressive mood in bvFTD and the prevalence of depressive and dysthymic disorder according to DSMIV and ICD-10 criteria as found in our study, highlights the symptomatic overlap of bvFTD and psychiatric disorders. More importantly, this research suggested that the use of formal criteria, not only for bvFTD but also for psychiatric disorders, might act as one of the clinical hallmarks helpful to distinguish psychiatric disorders from bvFTD in an early stage.

Chapter 3 was an overview of the prevalence of the broad spectrum of psychotic symptoms in bvFTD. This was the first study which was focused at psychosis in bvFTD beyond the well-known positive psychotic symptoms (hallucinations, delusions and suspiciousness/ paranoia). Besides positive psychotic symptoms we also studied negative psychotic symptoms (a diminution or loss of normal functions, e.g. reduced motivation or reduced emotion) and formal thought disorders (a disorganization of thought). We prospectively employed a commonly used and validated clinical scale which quantifies the broad spectrum of psychotic symptoms (Positive and Negative Symptom Scale, PANSS) in patients with probable and definite bvFTD (n=22) and patients with a primary psychiatric disorder (n=35). Despite frequent misdiagnosis with schizophrenia, we found that bvFTD patients are not mainly characterized by positive psychotic symptoms (22.7% of bvFTD patients) while negative psychotic symptoms such as social and emotional withdrawal and blunted affect (95.5%) and formal thought disorders (81.8%) were frequent. It is remarkable that the prevalence of positive psychotic symptoms in bvFTD differed in several studies.[6 7 8] The frequency of positive psychotic symptoms we found might be associated with the amount of genetic mutations in the sample size, as positive psychotic symptoms have recently

repeatedly been described in progranulin and C9ORF72 mutation carriers.[9 10 11 12] As our study contained only three patients with a genetic mutation (13.6% of bvFTD patients), the percentage of known genetic variants was lower compared to other studies (percentages of approximately 20-50% of hereditary etiologies found in other studies).[13 14] However, besides the discrepancies in frequency of positive psychotic symptoms, this first study into the broad spectrum of psychotic symptoms in bvFTD showed that negative psychotic symptoms and formal thought disorders are the main overlapping psychotic symptoms of bvFTD and psychiatric disorders. This was highlighted by the fact that our bvFTD patients tended to have a lower total score at the positive subscale of the PANSS than found in studies into schizophrenia (respectively 9.5 in our bvFTD patients versus 18.2 in schizophrenia patients) but similar scores at the negative subscale. [15] This paragraph also showed that difficulty in abstract thinking and stereotypical thinking (formal thought disorders) differentiated bvFTD from psychiatric disorders. The combined predictors "difficulty in abstract thinking", "stereotypical thinking", "anxiety", "guilt feelings," and "tension" explained 75% of variance in the diagnosis of bvFTD versus psychiatric disorders. Besides the use of formal diagnostic criteria, exploring the broad spectrum of psychotic symptoms in patients suspected of bvFTD can therefore be valuable in the differentiation of bvFTD and psychiatric disorders in clinical practice.

Section 2. Differentiating behavioral variant frontotemporal dementia from other neurodegenerative diseases and psychiatric disorders

In the **second section** we further elaborated on the clinical distinction of behavioral variant frontotemporal dementia from psychiatric disorders and other neurodegenerative diseases. Whereas deficits in social cognition have repeatedly been found in bvFTD, in **chapter 4** we studied whether social cognition distinguishes bvFTD from other neurodegenerative diseases and psychiatric disorders in patients presenting with the late onset frontal lobe syndrome. Social cognition was determined by the *Ekman 60 Faces test* and *Faux Pas test*.[16 17] We also set out to determine *executive functioning, memory, attention/concentration/mental speed* and *visuospatial functioning* in the diagnostic groups. Several previous studies already suggested that social cognition is markedly impaired in bvFTD when compared to healthy controls [18 19 20], AD patients and patients with a psychiatric disorder but the comparison was never

completed within the symptom profile of the frontal lobe syndrome. We found that besides bvFTD, also patients with other neurodegenerative diseases and psychiatric disorders presenting with frontal symptoms had impaired social cognition, but even with overlapping symptomatology, total scores at *Ekman 60 Faces test* were significantly lower in bvFTD than in other neurodegenerative diseases and psychiatric disorders. We found that *Faux Pas* did not discriminate between the diagnostic groups. It is conceivable that *Faux Pas* is a more sensitive method for measuring social cognition while *Ekman 60 Faces test* is a more specific method.[21] [22] *Ekman 60 Faces test* explained 91.2% of the variance of psychiatric disorders and other neurodegenerative diseases versus bvFTD. We therefore suggested *Ekman 60 Faces test* as a valuable test to endorse clinical differentiation of bvFTD from other neurodegenerative diseases and psychiatric disorders.

One of the most striking results of this research was the finding that despite the association of social cognition with all other cognitive domains (*executive functioning, memory, attention/concentration/tempo and visuospatial functioning*), the other cognitive domains except *visuospatial functioning* did not differentiate between diagnostic groups. The current bvFTD criteria emphasize the impairment of executive functioning in neuropsychological tests in bvFTD[23], whereas the results we found suggest that social cognition measured by *Ekman 60 Faces test* might even be more useful.

The research described in **section 2, chapter 5,** focused at the diagnostic value of clinical variables and additional investigations to distinguish between psychiatric disorders and bvFTD. We found that the variables male gender, absence of stereotypy based on a low score on the *Stereotype Rating Inventory* (SRI), and the presence of depressive symptoms with high scores on the *Montgommery Asperg Depression Rating Scale* (MADRS) had good discriminating abilities for psychiatric disorders versus bvFTD (86%). We found that normal neuroimaging only slightly increased the diagnostic value for a psychiatric disorder versus bvFTD to 88.4%. Although depression and apathy are overlapping concepts, the MADRS focuses on symptoms specific for depression and may therefore be useful especially in diagnosing depression as comorbidity in bvFTD or as an alternative diagnosis of depression. Apathy is considered a bvFTD symptom, and may be misdiagnosed as major depression, as also discussed in **chapter 3** While MADRS may point to a psychiatric diagnosis in patients suspected of bvFTD, it is conceivable that a measuring instrument only focused at apathy would be indicative for a bvFTD diagnosis but this has not been studied so far. This chapter

suggested that in patients with a late-onset frontal lobe syndrome psychiatric diagnoses can be established at a high accuracy based on clinical phenotyping and that the presence of stereotypy might be seen as another hallmark to differentiate bvFTD from psychiatric disorders.

Section 3. Disease course in late onset frontal lobe syndrome

In **section 3** we studied different aspects of disease course in the late onset frontal lobe syndrome. Patients with the benign bvFTD phenocopy syndrome were a first focus of interest, because of their remarkable disease course, as described in **chapter 6.**

As previously mentioned, in 2011, the International bvFTD Criteria Consortium established new diagnostic criteria whereby a degree of probability was assigned to the clinical diagnosis.[23] Some patients with a diagnosis of possible bvFTD develop changes on neuroimaging or will be found to have a genetic mutation and will therefore 'progress' into probable or definite bvFTD. Nevertheless, a significant number of possible patients with bvFTD do not convert clinically to probable or definite bvFTD and their neuroimaging results remain unchanged over time. In this study, we included 33 of these bvFTD phenocopy patients, while 19 patients with probable bvFTD served as a control group. We saw that according to previous research on the bvFTD phenocopy syndrome, most of our included bvFTD phenocopy cases were men and they were younger than patients with probable bvFTD.[24 25 26]

In patients with the bvFTD phenocopy syndrome the frequency of recent life events, relationship problems and cluster C personality traits was higher than in the probable bvFTD group and in most cases multiple factors played a contributory role. In accordance with previous hypotheses, mood disorders had a relatively large share in patients with benign bvFTD phenocopy syndrome (both major depressive disorder as well as bipolar disorder).[27] A bipolar disorder seemed to be more often present in patients with phenocopy than in patients with probable bvFTD. However, the relative frequency of a depression among patients with the phenocopy syndrome was not higher than among patients with probable bvFTD, but exceeded the community prevalence of depression in late life.[28] As previously discussed, previous studies suggested depressive traits in neurodegenerative bvFTD (with percentages around 33% of cases), which might explain why the phenocopy group and probable bvFTD group showed approaching frequencies of

depression.[29] [3] Relative frequencies of alcohol abuse among patients with the benign phenocopy syndrome and patients with probable bvFTD were also approaching possibly due to comorbidity in probable bvFTD, as studies reported compulsive consummatory behaviors in bvFTD including alcohol abuse. [30] It was remarkable that among patients with the benign bvFTD phenocopy syndrome, 85.2% of patients had psychiatric or psychological conditions that mainly consisted of recent life events, relationship problems and cluster C personality traits. By a focus at this aspect of disease course, treatment of reversible conditions is to be gained.

Chapter 7 was focused at the role of clinical and demographical variables in predicting progression in patients with a late onset frontal lobe syndrome. In this research progression was defined as institutionalisation, progression of frontal or temporal atrophy at Magnetic Resonance Imaging (MRI) or death after two years of follow up. Non-progression was defined as the absence of progression at MRI in addition to stable or improved *Mini Mental State Examination (MMSE)* and *Frontal Assessment Battery (FAB)* scores. As hypothesized we found that *progressors* in LOF were mainly patients with a neurodegenerative disease (82.9%), while *non-progressors* were mostly affected by psychiatric disorders (53.6%). Tools to predict progression in LOF were stereotypy and a neuropsychological profile with primarily executive deficits and relative sparing of episodic memory and visuospatial functions. Stereotypy as a predictor for progression in LOF was a new finding but joins in with previous studies into progression in bvFTD and has also been described as a hallmark in **chapter 5.**[31] It is remarkable that although more than half of the *progressors* had another disease than bvFTD in our cohort, a neuropsychological profile with mainly executive deficits, as described in Rascovsky criteria, still had value in the differentiation of *progression* versus *non-progression* in LOF.[23] A patients history and a family history with psychiatric disorders were found to be predictors for non-progression. Stereotypy and a neuropsychological profile with primarily executive deficits and relative sparing of episodic memory and visuospatial functions together with the absence of a psychiatric history or family history with psychiatric disorders were considerable capable to distinguish a *progressive* from a *non-progressive* discourse.

Section 4. Care and interventions in the late onset frontal lobe syndrome and bvFTD

After we cast light on disease course, we studied possible options for care and treatment in bvFTD and the late onset frontal lobe syndrome in **section 4**. In **chapter 8** we performed a systematic review on pharmacological treatment in patients with bvFTD.

All literature between 1970 and 2016 was searched systematically for reports on pharmacological interventions for bvFTD. A total number of 23 studies were included with 12 randomized controlled trials, 8 open-label studies and 3 case series reporting on 583 patients. We described the efficacy of pharmacological interventions by symptom profiles according to the FTDC-criteria: apathy, disinhibition, lack of empathy or sympathy, hyperorality, stereotypical behavior and executive dysfunction. This was the first systematic review based on symptom profile in bvFTD and not limited to randomized controlled trials but also including open label studies and case series. We found that, based on the *NeuroPsychiatric Inventory* (NPI), Trazodone had the greatest effect on the general symptoms of bvFTD followed by Rivastigmine and Citalopram. As one of the limitations it needs to be noted that most studies were sponsored by pharmaceutical companies.[32] [33] [34] Besides, outcome measurements of changes in symptoms of bvFTD differed between studies. This needs attention in future research. However, this systematic research was an up to date clinical guidance in symptomatic pharmacological therapy for bvFTD. Highlighted by the lack of a disease modifying therapy in bvFTD so far, symptom management for this devastating disease may be of importance.

In **chapter 9** we discussed care in bvFTD by focusing on the caregiver. We described an explorative pilot study in caregivers of early onset dementia patients with behavioral problems. As frontal symptoms affect the personal identity of a patient, several studies have shown that burden and stress are higher in caregivers of dementia patients with predominantly frontal symptoms as compared to caregiver's burden in dementia patients with mainly memory problems.[35] We performed a tailored intervention including psychoeducation, social support and behavioral cognitive therapy for caregivers of dementia patients affected by apathy, disinhibition and/or stereotypical behavior. The intervention was given during 6 months and quantitative and qualitative data were collected at baseline and after the intervention. We found an increased sense of competence in the intervention group.

Burden, perceived stress and depressive symptoms decreased, although not significantly different from the control group. The improvement in the caregiver's sense of competence in the intervention group is an interesting result that confirms some previous studies about support programs for caregivers of dementia patients who were not specifically selected on the base of dealing with behavioral problems.[36 37] It is interesting that an absence of any significant group effect on the other indicators of feelings of burden (caregiver burden, perceived stress and depressive symptoms) was a result that was also found in previous research into the effectiveness of caregiver support programs.[38] Although caregivers who participated in these programs were satisfied with the support and managed to go on caring longer than caregivers who did not receive this support, a reduction of levels of burden could hardly be proven scientifically.[36] In the study of Mioshi with an intervention program performed in caregivers of patients with bvFTD, significant results on levels of burden were measured.[39] However, due to practical constraints, the participants in that study were not randomized, and the burden scores between the intervention group and control group differed at baseline. This lack of randomisation may have limited the results of their study, but these positive effects are hopeful. Another important aim of our study was the qualitative assessment of the intervention and to summarize recommendations for future caregiver interventions. After the intervention, caregivers turned out to have high levels of satisfaction and they reported various positive benefits in daily life. The three elements of this intervention, psychoeducation, cognitive behavioral therapy and social support, were equally appreciated and are recommended in future studies. Further research, on a larger scale, should conclude on the effectiveness of this support program for caregivers of early onset dementia patients with frontal behavioral changes.

Towards an early discrimination between bvFTD and psychiatric disorders in clinical practice

The distinction between bvFTD and other neurodegenerative diseases has become easier by the use of biomarkers, but differentiating bvFTD from psychiatric disorders remains difficult. The FTDC consensus criteria have clearly improved diagnostics but clinical practice still urges for hallmarks that can distinguish bvFTD from psychiatric disorders in an early stage.[23] This is notably of importance since the current clinical criteria require that "if behavioral disturbance is better

accounted for by a psychiatric diagnosis, a diagnosis of bvFTD has to be excluded". To date, scientific research has no answer yet on how we should include or exclude bvFTD in case of a difficult differential diagnosis of bvFTD versus a psychiatric disorder.

Above all, this thesis revealed hallmarks helpful in the clinical differentiation of bvFTD and psychiatric disorders. In case of 'suspicion of bvFTD' the clinical workup should at least include an interview and medical history of the patient, a family history, a mental state examination, a neurological examination and informant-based history with preferably multiple informants. Our data suggest that besides FTDC consensus criteria, formal criteria for a psychiatric disorder can be of value. In our cohort of patients with the late onset frontal lobe syndrome, DSM criteria were able to distinguish patients with a psychiatric disorder from patients with bvFTD. However, diagnostic interviews designed to establish psychiatric diagnosis according to DSM criteria are time-consuming as it takes at least 60 minutes for each interview, and they can only be performed by well-trained clinicians.[1] These types of interview do not seem suitable for screening. A face to face examination by a psychiatrist appears to be more appropriate, especially when the psychiatrist is aware that bvFTD can mimic a psychiatric disorder but rarely meets formal criteria for a psychiatric disorder.

Regarding hallmarks for the early differentiation between bvFTD and psychiatric disorders we also saw the importance of detecting stereotypy in an early stage. Both in our research primarily focused at the discrimination between bvFTD and psychiatric disorders as well as in our research aimed at distinguishing *progressors* from *non-progressors* in the late onset frontal lobe syndrome, we saw the predictive value of stereotypy, both for bvFTD and 'progression'. Amidst a difficult differential diagnosis of bvFTD versus psychiatric disorders the presence of stereotypy seems to be an early warning sign and a high risk of impending dementia. Since the *Stereotypy Rating Inventory* includes both severity as well as frequency of stereotypical behavior, it appears to be a suitable method to gather information about the prevalence of stereotypy in daily life of patients.

To distinguish primary psychiatric disorders from bvFTD, we also found discriminating abilities in the *Montgomery Asberg Depression Rating Scale (MADRS)*, which is an applicable patient-based measuring instrument.[40] The good diagnostic value for psychiatric disorders versus bvFTD of this instrument was revealed while neuroimaging only slightly increased this value. This emphasizes

the importance to distinguish bvFTD from psychiatric disorders as far as possible already in the clinical phase.

To exclude a psychiatric disorder in an early stage, use of the *Positive and Negative Symptoms Scale (PANSS*) could be considered. [41] In three-quarter of our patients with the late onset frontal lobe syndrome, the variance of psychiatric disorders versus bvFTD could be explained by items of the *PANSS.* Above all, our implementation of the *PANSS* in patients with the late onset frontal lobe syndrome, provided insight in the high prevalence of formal thought disorders and negative psychotic symptoms in patients with bvFTD and the relatively small prevalence of positive psychotic symptoms such as hallucinations and paranoia. The pitfall of misdiagnosis with a psychotic disorder in patients with bvFTD seems to be largely caused by the presence of negative psychotic symptoms such as emotional withdrawal and reduced affect. However, performance of the PANSS is reserved for well-trained clinicians and the hazard of inter-person variability is clearly present. Besides, implementation of the PANSS amidst a difficult diagnosis of bvFTD versus psychiatric disorders is time-consuming and does not seem advisable. Instead, it underlines the need for a close collaboration between the neurologist and psychiatrist in diagnostics of bvFTD and both should stay aware that especially negative psychotic symptoms can mimic bvFTD. Besides, in case of a difficult differential diagnosis of bvFTD versus a psychotic disorder, specific items from the *PANSS*, especially formal thought disorders such as "difficulty in abstract thinking" and "stereotypical thinking" can help to differentiate as these items pointed to bvFTD.

Other hallmarks to distinguish bvFTD from psychiatric disorders and vice versa were found by studying disease course in the late onset frontal lobe syndrome. A subset of bvFTD patients appear to show a benign course and do not deteriorate at the same speed as other bvFTD patients, despite meeting clinical diagnostic criteria for possible bvFTD at presentation. Our study into these patients taught us that calling them 'phenocopy cases' does not cover the full load. In most of these patients a combination of psychiatric and psychological conditions was present among which recent life events, relationship problems and mood disorders were the most common. Being aware of these conditions, the ability to discern psychiatric conditions from bvFTD in an early stage can increase. Noteworthy, in 9% of our bvFTD phenocopy patients an intellectual disability was present which leads to the recommendation to test intelligence in case of diagnostic doubt, especially in case of a non-progressive disease course with a lack of a genetic mutation. The high

prevalence of relationship problems (30.3%) in this bvFTD phenocopy group emphasized the importance of a history from a second and sometimes even third independent informant.

By studying disease course in the late onset frontal lobe syndrome, besides stereotypy we also found executive dysfunction to be a predictor for progression. In the current criteria for bvFTD a neuropsychological profile with mainly executive deficits with relative sparing of memory and visuospatial functions is supportive for a bvFTD diagnosis. As we found this neuropsychological profile to be a predictor for progression (in terms of a neurodegenerative disease), in case of late onset behavioral changes, this neuropsychological profile might gingerly act as an early warning sign to discern frank incapacitating dementia in general from psychiatric disorders. However, this outcome needs to be take with caution as it has not been replicated so far and another recent study shows less differences in neuropsychological profile between bvFTD and psychiatric disorders. [Vijverberg et al., submitted]

Last but not least, a promising hallmark to differentiate bvFTD from psychiatric disorders seemed to be social cognition as measured with the *Ekman 60 Faces Test.* While deficits in social cognition can also be found in neurodegenerative diseases and psychiatric disorders such as autism spectrum disorders, total scores at the *Ekman 60 Faces Test* were significantly lower in bvFTD than in these other diagnostic groups. It is promising that this test appeared to have a good diagnostic accuracy in precisely the most difficult differential diagnosis. Previous research was also focused at discriminating abilities of this test but was never performed in a group of patients included on the base of symptom profile instead of diagnoses. The maximum test score indicating best performance for all six tested emotions of the *Ekman Faces Test* is 60. While none of the patients with another neurodegenerative disease or a psychiatric disorder scored below 20, several bvFTD patients did. The discriminating ability of the *Ekman 60 Faces Test* in the difficult differential diagnosis of bvFTD versus psychiatric disorders in the late onset frontal lobe syndrome suits in with previous literature and seems meaningful for clinical practice. Social cognition is recommended as a convincing hallmark for clinical practice and our study even provided arguments for incorporation of social cognition in future diagnostic guidelines for bvFTD.

Table 4 presents hallmarks useful in the early differentiation between bvFTD and psychiatric disorders.

Presenting symptoms	**Supporting probable or definite bvFTD**	**Supporting a psychiatric disorder**
Mood and apathy	· Low score at the *Montgomery Asperg Depression Rating Scale(MADRS)*	· High score at *Montgomery Asperg Depression Rating Scale(MADRS)* · High score at PANSS items *Tension, Anxiety* and *Guilt feelings*
Stereotypy	· High score at the *Stereotypical Rating Inventory*	· Low score at the *Stereotypical Rating Inventory* · Being male
Disinhibition	· Not fulfilling DSM criteria for Bipolar Disorder	· Fulfilling criteria for Bipolar Disorder
Loss of empathy	· Low score at *Ekman 60 Faces test* (preferably score <20)	· High score at *Ekman 60 Faces test* (preferably score >46)
Psychotic symptoms	· High score at PANSS items *Stereotypical thinking* and *Difficulty in abstract thinking*	· Low total score at the *Negative subscale* of PANSS
Indistinct behavior	· Not fulfilling formal *DSM criteria* for a psychiatric disorder	· Fulfilling *DSM criteria* for a psychiatric disorder
Symptom duration		
Long symptom duration without conversion from possible to probable bvFTD, lacking a genetic mutation	· Being female and absence of most of the following conditions, or being male and absence of all of the following conditions: recent life events, mood problems, cluster C personality traits, relationship problems, low intelligence	· Being male and one of the following conditions, or being female and at least 3 of the following conditions: recent life events, mood problems, cluster C personality traits, relationship problems, low intelligence

Table 4. Clinical hallmarks useful for the differentiation of bvFTD from psychiatric disorders and vice versa in patients presenting with the late onset frontal lobe syndrome

Care and symptom relief in the late onset frontal lobe syndrome

Besides hallmarks for differentiation between bvFTD and psychiatric disorders, this thesis highlighted the importance of care and symptom relief in clinical practice. In the first place, the focus at an early differentiation between bvFTD and psychiatric disorders had an important aim: psychiatric disorders are treatable and with therapy, symptom relief in patients with a psychiatric disorder is to be gained. Second, whereas the aim of our systematic review in chapter 8 was to study the effect of medication on the specific symptoms of bvFTD based on the FTDC criteria[23], guidance for symptom relief in bvFTD was given. Based on NPI scores, Trazodone followed by Rivastigmine and Citalopram was recommended to relief the general symptoms of bvFTD. [42] [43] [44] [45] Besides these medications, Memantine can be considered in case of apathy as it has been found in multiple studies to slightly relief this symptom[46] [47], while Dexamphetamin, Methylphenidate and Paroxetin can be taken into account in case of disinhibition.[48] [49] [50]Paroxetin might be prescribed to increase empathy in bvFTD patients.[50] In case of hyperorality Trazodone is suggested.[43] Recommendations regarding stereotypical behavior in bvFTD are still pending as only limited research on stereotypical behavior in bvFTD is carried out until this moment.

While there is still no cure for bvFTD and other neurodegenerative diseases, some improvement of quality of life of patients and their loved ones might be achieved by support for the caregivers. As caregivers of dementia patients with predominantly behavioral problems experience high levels of burden, support for these caregivers is indispensable. The support program we invented for these caregivers was a group wise intervention given on a regular base during 6 months. Although it was an explorative pilot study and further research on a larger scale is needed to conclude on the effectiveness of this support program, it is a hopeful result that the sense of competence of the caregivers significantly increased in the intervention group. The three components of the intervention (psychoeducation, social support and cognitive behavioral therapy) were highly rated and an implementation of these three components in future support groups seems valuable. This focus at support for caregivers might not only be favorable for the quality of life of caregivers, in accordance with previous research, it could contribute to extended possibilities for patients to live at home, with beneficial consequences for the patient as well as for society. [51] [52]

Future recommendations

A longer prospective follow-up of a cohort of patients with a late onset frontal lobe syndrome is warranted to confirm our results. In our cohort of patients with a late onset frontal lobe syndrome, we currently use a gold standard of two years follow-up but it has not been confirmed yet if this follow up duration is indeed long enough for the best diagnostic certainty that is possible during patient' life or if a longer follow up duration is needed.

We would also recommend to develop clinical instruments to investigate the course of frontal behavioral symptoms during progression of disease. This may include electronic equipment or gadgets able to measure behavioral changes over time. Clinical practice urges for measuring instruments able to measure the progression of late onset behavioral problems to surpass the subjective character of current notifications of progression as done by caregivers. In patients with the benign bvFTD phenocopy syndrome caregivers often report a progression of symptoms while impending dementia is lacking. Furthermore, predicting progression is demanded by patients and family when the diagnosis is told.

Next, we would also recommend to study whether neuropsychological profiles change over time in bvFTD as well as in psychiatric disorders. In the current consensus criteria for bvFTD, besides supporting imaging results, functional decline is needed to meet criteria for probable bvFTD. As it has not been investigated so far, it needs to be examined whether bvFTD patients indeed show progression at neuropsychological tests during time and if this discriminates them from patients with a psychiatric disorder presenting with a late onset frontal lobe syndrome.

We recommend adjustment of the criteria for bvFTD. The FTDC criteria from 2011 are more sensitive for bvFTD compared to the older criteria, but also less restrictive. In patients with late onset behavioral changes, the diagnostic certainty of bvFTD increases when frontotemporal abnormalities are found on structural neuroimaging.[53 54] However, both the clinical symptoms as well as the functional imaging findings in psychiatric patients may mimic bvFTD. These psychiatric 'bvFTD mimics' lower the specificity of the FTDC criteria and will cloud the outcomes of trials in bvFTD. It is warranted to examine whether frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT is indeed indicative of a bvFTD diagnosis in patients presenting with late onset behavioral problems, as abnormal frontal and/or temporal lobe function at neuroimaging may

also point to psychiatric disorders.[55] [56] [57] [58] Psychiatric 'bvFTD mimics' who exhibit similar FDG-PET results need to be recognized in an early stage and excluded from a bvFTD diagnosis. Careful multidisciplinary follow-up by a neurologist and a psychiatrist, especially in this group of bvFTD mimics, seems to improve the reliability of the diagnosis in the long run.

Following our own hopeful results concerning the discriminating abilities of social cognition in patients presenting with a late onset frontal lobe syndrome, it is recommended to replicate studies into social cognition in bvFTD and patients with a psychiatric disorder wherein these patients are not included on the base of their diagnosis but based on symptom profile resembling clinical practice. This would strengthen our results and is needed to eventually incorporate social cognition in future diagnostic guidelines for bvFTD.

Last but not least, genetic screening, especially for the C9orf72 repeat mutation, contributes to the diagnostic work-up. Accumulating research exists into traits of symptom duration and psychotic phenomena in patients with C9ORF72 repeat mutation, but other characteristics of this subgroup of patients have not been described so far. Clinical practice urges to study whether patients with bvFTD due to the C9ORF72 repeat expansion can be characterized by a profile of typical neuropsychiatric symptoms (during disease course or even before onset of bvFTD symptoms) which discerns them from other bvFTD patients or patients with a psychiatric disorder. Clinical practice seems to reveal that especially this subgroup of patients has a diagnostic delay due to medical referral from neurologist to psychiatrist and vice versa during the disease course. This obliges early recognition of the symptom profile or course of life of these patients which can ensure straight profit for clinical practice. As for daily clinical practice, patient care for suspected bvFTD cases is improved by a multidisciplinary approach, reuniting neurology with psychiatry.

REFERENCES

1. Sheehan D V., Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: *Journal of Clinical Psychiatry*. Vol 59. ; 1998:22-33. doi:10.1016/S0924-9338(99)80239-9.
2. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011. doi:10.4088/JCP.10m06382oli.
3. Chakrabarty T, Sepehry AA, Jacova C, Hsiung GYR. The prevalence of depressive symptoms in frontotemporal dementia: A meta-analysis. *Dement Geriatr Cogn Disord*. 2015;39(5-6):257-271. doi:10.1159/000369882.
4. Lopez OL, Gonzalez MP, Becker JT, Reynolds III CF, Sudilovsky A, DeKosky ST. Symptoms of depression and psychosis in Alzheimer's disease and frontotemporal dementia. Exploration of underlying mechanisms. *Neuropsychiatry, Neuropsychol Behav Neurol*. 1996;9(3).
5. Gregory CA, Hodges JR. Frontotemporal dementia: Use of consensus criteria and prevalence of psychiatric features. *Neuropsychiatry, Neuropsychol Behav Neurol*. 1996;9(3):145-153. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=1996208799.
6. Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. *Br J Psychiatry*. 2009;194(4):298-305. doi:10.1192/bjp.bp.108.057034.
7. Mendez MF, Perryman KM. Neuropsychiatric Features of Frontotemporal Dementia: Evaluation of Consensus Criteria and Review. *J Neuropsychiatry Clin NeurosciThe J Neuropsychiatry Clin Neurosci*. 2002;144(14):424-429. doi:10.1176/jnp.14.4.424.
8. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: Prevalence and review. *Dement Geriatr Cogn Disord*. 2008;25(3):206-211. doi:10.1159/000113418.
9. Galimberti D, Fenoglio C, Serpente M, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: Late-onset psychotic clinical presentation. *Biol Psychiatry*. 2013;74(5):384-391. doi:10.1016/j.biopsych.2013.01.031.
10. Shinagawa S, Naasan G, Karydas a. M, et al. Clinicopathological Study of Patients With C9ORF72-Associated Frontotemporal Dementia Presenting With Delusions. *J Geriatr Psychiatry Neurol*. 2014;28(2):99-107. doi:10.1177/0891988714554710.

11. Urwin H, Josephs KA, Rohrer JD, et al. FUS pathology defines the majority of tau-and TDP-43-negative frontotemporal lobar degeneration. *Acta Neuropathol*. 2010;120(1):33-41. doi:10.1007/s00401-010-0698-6.
12. Kertesz A, Cyn Ang L, Jesso S, et al. Psychosis and Hallucinations in FTD with C9ORF72 mutation: A detailed clinical cohort. *Cogn Behav Neurol*. 2013;26(3):146-154. doi:10.1097/WNN.0000000000000008.
13. Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009;73(18):1451-1456. doi:10.1212/WNL.0b013e3181bf997a.
14. Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol*. 2011;24(6):542-549. doi:Doi 10.1097/Wco.0b013e32834cd442.
15. Harvey PD WE. *Positive and Negative Symptoms in Psychosis: Description, Research, and Future Directions.* Routledge; 2013.
16. Young a W, Perrett DI, Calder a J, Sprengelmeyer R, Ekman P. *Facial Expressions of Emotion: Stimuli and Tests (FEEST)*. Vol 126.; 2002. doi:10.1016/S0010-0277(97)00003-6.

17. Stone VE. Faux Pas Recognition Test Faux Pas Recognition Test (Adult Version). *J Cogn Neurosci Brain*. 2002;10(125):640-656.
18. Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. *Arch Clin Neuropsychol*. 2007;22(4):459-464. doi:10.1016/j.acn.2007.01.024.
19. Funkiewiez A, Bertoux M, de Souza LC, Lévy R, Dubois B. The SEA (Social Cognition and Emotional Assessment): A clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology*. 2012;26(1):81-90. doi:10.1037/a0025318.
20. Bertoux M, Delavest M, de Souza LC, et al. Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry*. 2012;83(4):411-416.
21. Baron-cohen S, Riordan MO, Stone V, Jones R, Plaisted K. A new test of social sensitivity : Detection of faux pas in normal children and children with Asperger syndrome : *J Autism Dev Disord*. 1999;29:407-418.
22. O'Toole MS, Pedersen AD, Hougaard E, Rosenberg NK. Neuropsychological test performance in social anxiety disorder. *Nord J Psychiatry*. 2015;69(6):444-452. doi:10.3109/08039488.2014.997288.
23. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179.
24. Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at

presentation? *J Neurol Neurosurg Psychiatry*. 2009;80(6):591-593. doi:10.1136/jnnp.2008.163873.
25. Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in Frontotemporal Dementia. *Group*. 2006;63(11):1627-1631. doi:10.1001/archneur.63.11.1627.
26. Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: Application of an MRI visual rating scale. *Dement Geriatr Cogn Disord*. 2007;23(5):334-342. doi:10.1159/000100973.
27. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: Diagnosis, clinical staging, and management. *Lancet Neurol*. 2011;10(2):162-172. doi:10.1016/S1474-4422(10)70299-4.
28. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174(4):307-311. doi:10.1192/bjp.174.4.307.
29. Waldö ML, Santillo AF, Gustafson L, Englund E, Passant U. Somatic complaints in frontotemporal dementia. *Am J Neurodegener Dis*. 2014;3(2):84-92.
30. Perry DC, Sturm VE, Seeley WW, Miller BL, Kramer JH, Rosen HJ. Anatomical correlates of reward-seeking behaviours in behavioural variant frontotemporal dementia. *Brain*. 2014;137(6):1621-1626. doi:10.1093/brain/awu075.
31. Dols A, van Liempt S, Gossink F, et al. Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome. *J Clin Psychiatry*. 2016; doi:10.4088/JCP.15m09844.
32. Finger EC, MacKinley J, Blair M, et al. Oxytocin for frontotemporal dementia: a randomized dose-finding study of safety and tolerability. *Neurology*. 2015;84(2):174-181. doi:10.1212/WNL.0000000000001133.
33. Furlan JC, Henri-Bhargava A, Freedman M. Clomipramine in the treatment of compulsive behavior in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord*. 2014;28(1):95-98. doi:10.1097/WAD.0b013e318265c104.
34. Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res*. 2002;110(2):175-187. doi:10.1016/S0165-1781(02)00094-X.
35. Diehl-Schmid J, Schmidt E-M, Nunnemann S, et al. Caregiver burden and needs in frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 2013;26(4):221-229. doi:10.1177/0891988713498467.
36. RM D. *Amsterdamse Ontmoetingscentra; Een Nieuwe Vorm van Ondersteuning Voor Dementerende Mensen En Hun Verzorgers [Amsterdam Meeting Centres: A New Type of Support for People with Dementia and Their Carers]*. Amsterdam; 1996.
37. Dröes R-M, Meiland FJM, Schmitz MJ, van Tilburg W. Effect of the Meeting Centres Support Program on informal carers of people with dementia: results from a multi-centre study. *Aging Ment Health*. 2006;10(2):112-124. doi:10.1080/13607860500310682.

38. Dröes R-M, Breebaart E, Meiland FJM, Van Tilburg W, Mellenbergh GJ. Effect of Meeting Centres Support Program on feelings of competence of family carers and delay of institutionalization of people with dementia. *Aging Ment Health*. 2004;8(3):201-211. doi:10.1080/13607860410001669732.

39. Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR. Improving burden and coping skills in frontotemporal dementia caregivers: a pilot study. *Alzheimer Dis Assoc Disord*. 2013;27(1):84-86. doi:10.1097/WAD.0b013e31824a7f5b.

40. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382-389. doi:10.1192/bjp.134.4.382.

41. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276. doi:10.1093/schbul/13.2.261.

42. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in Frontotemporal Dementia. *Drugs {&} Aging*. 2004;21(14):931-937. doi:10.2165/00002512-200421140-00003.

43. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: A randomised, controlled trial with trazodone. In: *Dementia and Geriatric Cognitive Disorders*. Vol 17. ; 2004:355-359. doi:10.1159/000077171.

44. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Trazodone in fronto-temporal dementia. *Res Pract Alzheimers Dis*. 2006;11:356-360.

45. Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. *Am J Geriatr Psychiatry*. 2012;20(9):789-797. doi:10.1097/JGP.0b013e31823033f3.

46. Boxer AL, Lipton AM, Womack K, et al. An Open Label Study of Memantine Treatment in Three Subtypes of Frontotemporal Lobar Degeneration. *Alzheimer Disord Assoc Disord*. 2010;23(3):211-217. doi:10.1097/WAD.0b013e318197852f.An.

47. Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2013;12(2):149-156. doi:10.1016/S1474-4422(12)70320-4.

48. Huey ED, Garcia C, Wassermann EM, Tierney MC, Grafman J. Stimulant treatment of frontotemporal dementia in 8 patients. *J Clin Psychiatry*. 2008;69(12):1981-1982. doi:10.4088/JCP.v69n1219a.

49. Rahman S; Robbins Tw, Hodges JR, Mehta MA, Nestor PJ, Clark L SB. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology*. 2006;31(3):651-658.

50. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: Paroxetine as a possible treatment of behavior symptoms: A randomized, controlled, open 14-month study. *Eur Neurol*. 2003;49(1):13-19. doi:10.1159/000067021.

51. Gottlieb BH, Johnson J. Respite programs for caregivers of persons with dementia: A review with practice implications. *Aging Ment Health*. 2000;4(2):119-129. doi:10.1080/13607860050008637.
52. Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. *J Am Geriatr Soc*. 2003;51(5):657-664. doi:10.1034/j.1600-0579.2003.00210.x.
53. Harris JM, Gall C, Thompson JC, et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology*. 2013;80(20):1881-1887. doi:10.1212/WNL.0b013e318292a342.
54. Vijverberg EGB, Dols A, Krudop WA, et al. Diagnostic accuracy of the frontotemporal dementia consensus criteria in the late-onset frontal lobe syndrome. *Dement Geriatr Cogn Disord*. 2016;41(3-4):210-219. doi:10.1159/000444849.
55. Gorno-Tempini ML, Hillis a E, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1-10. doi:10.1212/WNL.0b013e31821103e6.
56. Steketee RME, Meijboom R, Bron EE, et al. Structural and functional brain abnormalities place phenocopy frontotemporal dementia (FTD) in the FTD spectrum. *NeuroImage Clin*. 2016;11:595-605. doi:10.1016/j.nicl.2016.03.019.
57. Crossley NA, Scott J, Ellison-Wright I, Mechelli A. Neuroimaging distinction between neurological and psychiatric disorders. *Br J Psychiatry*. 2015;207(5). doi:10.1192/bjp.bp.114.154393.
58. Davidson LL, Heinrichs RW. Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: A meta-analysis. *Psychiatry Res - Neuroimaging*. 2003;122(2):69-87. doi:10.1016/S0925-4927(02)00118-X.

Nederlandse samenvatting

Voorwoord

Verbinding tussen klinische praktijk en wetenschap

Patiënt A, een 55-jarige man, banketbakker, getrouwd en vader van twee puberende kinderen, werd in 2011 opgenomen op een afdeling neuro- en ouderenpsychiatrie vanwege twijfel aan de reeds in 2008 bij hem gestelde diagnose gedragsvariant Frontotemporale dementie. De voorgeschiedenis van patiënt tot 2008 was zowel in psychiatrisch als somatisch opzicht blanco. Zijn psychiatrische en neurologische familieanamnese was negatief.

In 2008 werd patiënt opgenomen in een algemeen ziekenhuis wegens cognitieve problemen en gedragsveranderingen waar bij neuropsychologisch onderzoek executieve functiestoornissen werden vastgesteld; beginnende bvFTD werd als mogelijke diagnose geopperd. Voor een tweede mening kwam patiënt enkele maanden later bij een geheugenpoli van een universitair ziekenhuis. Zijn echtgenote voerde veelal het woord en vermeldde dat patiënt sinds ruim een jaar toenemend dwangmatig en ontremd gedrag vertoonde, rigide en inflexibel was en dat zijn dagelijkse zelfzorg en hygiëne was verminderd. Hij maakte een apathische en emotioneel vervlakte indruk en er leek weinig lijdensdruk. Patiënt liet het onderzoek gelaten over zich heen komen en gaf weinig blijk van inzicht in zijn situatie. Bij het neuropsychologisch onderzoek bleken opnieuw executieve stoornissen. Een MRI-cerebrum in 2008 toonde geen duidelijke afwijkingen en op FDG-PET opnames werd bipariëtaal hypometabolisme waargenomen. Vanwege het overtuigende klinisch beeld, de hetero anamnese en de ondersteunende uitslag van het neuropsychologisch onderzoek werd de waarschijnlijkheidsdiagnose bvFTD gesteld. Patiënt werd afgekeurd voor zijn werkzaamheden als banketbakker en bracht vervolgens zijn tijd veelal thuis bij zijn gezin door. De familie van patiënt legde zich bij de gestelde diagnose neer en de dochter van patiënt bracht via een tijdschrift naar buiten een relatief jonge demente vader te hebben.

Patiënt kwam onbedoeld pas in 2011 voor een vervolgafspraak op de geheugenpoli van hetzelfde universitair medisch centrum alwaar hij opnieuw een affectief vlakke indruk maakte. Op basis van anamnese en heteroanamnese bleek er geen progressie te zijn van zijn gedragssymptomen. Er werden opnieuw een MRI-cerebrum en FDGPET verricht die een ongewijzigde uitslag lieten zien ten opzichte van 2008. Wegens het ontbreken van aanwijzingen voor een progressief beloop in zowel

klinisch opzicht als bij aanvullend onderzoek ontstond twijfel aan de gestelde diagnose bvFTD. Patiënt werd daarop doorverwezen naar een afdeling neuro- en ouderenpsychiatrie voor een klinisch diagnostische opname.
Tijdens anamnese bij opname op de afdeling vertelde patiënt dat hij toenemend problemen had ervaren in zijn gezin sinds hij meer tijd thuis doorbracht. Er bleken regelmatig wrijvingen te zijn. Ook had patiënt vaker behoefte aan seksueel contact dan zijn echtgenote
waarbij hij aangaf zich wel te kunnen beheersen. Patiënt vond dat hij de afgelopen jaren niet veranderd was en hij schreef de conflicten toe aan interacties tussen hem en de andere gezinsleden.
Tijdens zijn arbeidzame leven had hij naar eigen zeggen geen problemen ervaren behoudens geringe overzichtsproblemen tijdens nachtdiensten als hij meerdere bestellingen tegelijk had. Naast zijn gezin had patiënt weinig vriendschappelijke contacten opgebouwd. Bij psychiatrisch onderzoek imponeerde zijn intelligentie lager dan gemiddeld en viel breedsprakigheid op. De Mini Mental State Examination (MMSE) bedroeg 28 uit 30, met een verminderde recall en oriëntatie in plaats, en zijn score op de Frontal Assessment Battery was eveneens hoog : 17 uit 18. Bij het uitleggen van de betekenissen van spreekwoorden bleek dat patiënt slechts een beperkt aantal spreekwoorden kende maar wel tot abstraheren in staat was.
Gedurende de opname werden uitgebreide heteroanamneses verricht met zowel echtgenote, dochter als een vroegere collega van patiënt. Zijn echtgenote gaf opnieuw aan dat er sinds 4 jaar toenemend sprake was van gedragsveranderingen bij patiënt met inflexibiliteit, slordigheid, agressie, verminderde zelfzorg en seksuele ontremming. Zijn dochter vertelde dat er sinds ongeveer 4 jaar problemen waren met vader door geheugenlacunes en hinderlijk beschermend gedrag jegens haar. Volgens haar was er geen sprake van ontremming, dwangmatig of stereotype gedrag, apathie of interesseverlies. In de heteroanamnese verstrekt door een voormalig collega van patiënt werd naar voren gebracht dat patiënt tijdens nachtdiensten soms moeite had om overzicht te houden maar dat er geen gedragsveranderingen waren opgevallen, ook niet in de periode direct voorafgaand aan de gestelde diagnose in 2008.
Uit de biografie kwam naar voren dat patiënt het op het werk en in zijn privésituatie in complexe situaties vaak moeilijk heeft gevonden om voor zichzelf op te komen. In het contact met anderen nam hij vaak een afhankelijke positie in en handelde hij conflict vermijdend. De diagnose bvFTD had hij in 2008 geaccepteerd

ondanks uitblijvende herkenning van het beeld en sindsdien had hij geen stappen ondernomen om kenbaar te maken dat hij het eigenlijk niet eens was met deze diagnose.
Er volgde ergotherapeutisch onderzoek (Assessment of Motor en Process Skills (AMPS)) waarbij hij de meest moeilijke taken probleemloos kon uitvoeren. Een neuropsychologisch onderzoek gedurende opname toonde een laag intelligentieniveau in combinatie met moeite met het verdelen van de aandacht. In vergelijking met eerder onderzoek werd geen achteruitgang geobjectiveerd. De gevonden afwijkingen bij neuropsychologisch onderzoek leken het meest passend bij het beperkte uitgangsniveau.
Klinische observaties brachten verder naar voren dat patiënt regelmatig bevestiging zocht voor zijn lijdensdruk in de gezinssituatie. Er werd geen ontremming, mentale inflexibiliteit, dwangmatig gedrag, decorumverlies, executieve functiestoornissen, affectvervlakking of stereotype gedragingen waargenomen. Ook van botheid, egoïsme of apathie bleek geen sprake. Daarentegen leek er in diagnostisch opzicht sprake van een man met een beneden gemiddelde intelligentie met afhankelijke en vermijdende trekken in de persoonlijkheid met relatieproblemen. Concluderend werden er geen aanwijzingen gevonden die de diagnose frontotemporale dementie konden ondersteunen en deze diagnose werd aldus verworpen. Patiënt gaf aan hierdoor gerustgesteld te zijn, echtgenote vond dit aanvankelijk moeilijk maar beiden konden hierin uiteindelijk acceptatie vinden.

INLEIDING

De gedragsvariant van Frontotemporale dementie

De patiënt uit het voorwoord had volgens zijn echtgenote een frontaal syndroom: apathie, ontremming en dwangmatig gedrag. Op het moment dat bij hem de diagnose gedragsvariant frontotemporale dementie (bvFTD) gesteld werd voldeed hij aan de op dat moment geldende criteria voor deze progressieve hersenziekte. Om de diagnose frontotemporale dementie te stellen werden in 1994 de eerste criteria opgesteld door de Lund en Manchester groepen. Conform de klinische criteria werd Frontotemporale Lobaire Degeneratie (FTLD) gebruikt als een paraplu term voor progressieve niet-vloeiende afasie (PNFA), semantische dementie (SD) en de gedragsvariant van frontotemporale dementie (bvFTD). In 1998 werden de criteria voor bvFTD bijgewerkt tot de volgende diagnostische kerncriteria: *sluipend begin en geleidelijke progressie, achteruitgang in sociaal*

functioneren, stoornissen in regulatie van gedrag, emotionele vervlakking en verlies van inzicht (Neary et al., 1998). Deze criteria uit 1998 hebben veel toepassing gekregen en werden tot recent gebruikt. Er bleken echter meerdere (praktische) bezwaren aan het gebruik van deze criteria waaronder het gebruik van te abstracte omschrijvingen. In 2011 werden de laatste criteria vastgesteld voor de diagnose bvFTD met de volgende kerncriteria: *apathie, ontremming, dwangmatig/stereotype gedrag, verlies van sympathie of empathie, hyperoraliteit en veranderingen in het voedingspatroon, en bij het neuropsychologisch onderzoek: executieve stoornis met relatieve sparing van geheugen- en visuospatiele functies* (Rascovsky et al., 2011). Een belangrijk kenmerk van de criteria uit 2011 is het onderscheid tussen *mogelijke bvFTD* en *waarschijnlijke bvFTD.* Om aan een diagnose van *mogelijke* FTD te voldoen moet er aan ten minste 3 criteria worden voldaan. Uitsluitend indien er sprake is van functionele achteruitgang en van ondersteuning van beeldvormend onderzoek kan er sprake zijn van een diagnose *waarschijnlijke bvFTD.* De diagnose *definitieve bvFTD* is van toepassing indien er pathologisch bewijs is bij post-mortem onderzoek of indien er een pathogenetische mutatie wordt aangetoond.
De patiënt genoemd in het voorwoord zou conform de op dit moment geldende criteria niet zijn gediagnosticeerd met *waarschijnlijke* of *definitieve* bvFTD wegens het ontbreken van ondersteuning van beeldvormend onderzoek, het ontbreken van functionele achteruitgang bij de tweede en derde hetero- anamnese en vanwege de aanwezigheid van een psychiatrische verklaring. De symptomen die kenmerkend zijn voor bvFTD overlappen met de klinische presentatie van psychiatrische aandoeningen. Het is echter nog vaak lastig om in de klinische praktijk bvFTD te onderscheiden van psychiatrische aandoeningen.

Het laat ontstaan frontaal syndroom

Het laat ontstaan frontaal syndroom (LOF) verwijst naar een klinisch syndroom geassocieerd met op latere leeftijd (>45 jaar) ontstane functionele of structurele veranderingen in de frontale cortex hetgeen leid tot apathie, ontremming of dwangmatig gedrag. Verschillende ziekten, waaronder neurodegeneratieve aandoeningen en psychiatrische stoornissen, kunnen ten grondslag liggen aan een frontaal syndroom. Dankzij recente ontwikkelingen op het gebied van biomarker onderzoek zoals onderzoek van hersenvocht is het makkelijker geworden om in de klinische praktijk onderscheid te maken tussen bvFTD en andere neurodegeneratieve aandoeningen zoals de ziekte van Alzheimer. Het is in de

klinische praktijk echter vaak nog heel lastig om bvFTD en psychiatrische aandoeningen van elkaar te onderscheiden. Wereldwijd krijgt tot op heden ongeveer de helft van de patiënten met bvFTD initieel onterecht een psychiatrische diagnose.

Psychiatrische diagnoses onderliggend aan het laat ontstaan frontaal syndroom

Door betrokkenheid van dezelfde frontosubcorticale circuits als bij bvFTD kan een uitgebreid aantal psychiatrische aandoeningen resulteren in eenzelfde frontaal syndroom. Emotionele vervlakking, apathie, spraakarmoede, stereotypie en ontremming kunnen voorkomen bij bvFTD maar zijn ook veelvoorkomende symptomen van psychiatrische aandoeningen zoals depressie, bipolaire stoornis en schizofrenie. Het is echter belangrijk om in een vroeg stadium de juiste diagnose te stellen met name omdat neurodegeneratieve aandoeningen progressief zijn terwijl er in het geval van psychiatrische aandoeningen veelal nog behandelingsmogelijkheden zijn.

Doelstellingen van dit proefschrift

Het eerste doel van dit proefschrift is om klinische handvaten te beschrijven waarmee bij patiënten die zich presenteren met LOF onderscheid gemaakt kan worden tussen bvFTD, andere neurodegeneratieve aandoeningen en psychiatrische aandoeningen. De symptomatische overlap en het onderscheid tussen bvFTD, psychiatrische stoornissen en andere neurodegeneratieve aandoeningen wordt longitudinaal onderzocht. Het tweede doel is om voorspellers te vinden voor progressie bij LOF. Het derde doel is gericht op interventies: het beschrijven van zowel effectieve medicamenteuze symptoom bestrijding bij patiënten met bvFTD als non-farmacologische ondersteuning voor mantelzorgers van dementie patiënten met een laat ontstaan frontaal syndroom.

De laat ontstaan frontaal syndroom studie

De laat ontstaan frontaal syndroom studie (LOF studie) werd opgezet met als doel om het brede spectrum aan ethologiën onderliggend aan LOF te onderzoeken en om bvFTD te onderscheiden van de meest brede relevante differentiaal diagnose. De patiënten werden bij deze studie niet geïncludeerd op basis van hun onderliggende aandoening maar op basis van symptomen waardoor het de dagelijkse klinische praktijk goed representeert.

Patiënten werden in de LOF studie geïncludeerd indien er sprake was van een Laat Ontstaan Frontaal syndroom gedefinieerd als zijnde de aanwezigheid van apathie, ontremming of dwangmatig gedrag ontstaan na het 45e levensjaar. Patiënten werden geïncludeerd via het Alzheimercentrum VUmc of GGZinGeest te Amsterdam, Nederland, tussen April 2011 en Juni 2013. Op baseline en na 1 en 2 jaar follow up vond uitgebreide diagnostiek plaats door zowel neuroloog als psychiater waarbij ook onderzoek van hersenvocht en herhaald beeldvormend en neuropsychologisch onderzoek plaatsvond. Indien MRI van de hersenen niet conclusief was werd aanvullend ter diagnostiek PET onderzoek van de hersenen verricht.

SAMENVATTING VAN DE RESULTATEN

Deel 1. De gedragsvariant van frontotemporale dementie en psychiatrische stoornissen

In deel 1 van dit proefschrift hebben we ons gewijd aan het beschrijven van de belangrijkste klinische overeenkomsten tussen bvFTD en psychiatrische stoornissen. In hoofdstuk 2 onderzochten we hoe vaak patiënten met *waarschijnlijke* en *definitieve* bvFTD voldoen aan formele criteria voor een psychiatrische stoornis in vergelijking met patiënten met andere neurodegeneratieve aandoeningen en patiënten met een primair psychiatrische diagnose. Tevens onderzochten we hierbij de aard van de psychiatrische stoornis waaraan voldaan werd en psychiatrische prodromen in de verschillende diagnostische groepen. Er werd gebruik gemaakt van het MINI Internationaal Neuropsychiatrisch Interview (MINI) om te onderzoeken of voldaan werd aan formele criteria voor een psychiatrische aandoening. De belangrijkste bevinding van dit onderzoek was dat patiënten met *waarschijnlijke* en *definitieve* bvFTD niet significant vaker voldoen aan de criteria voor een psychiatrische aandoening dan patiënten met een andere neurodegeneratieve aandoening maar wel significant minder vaak dan patiënten met een primair psychiatrische diagnose. Dit is een opvallende bevinding omdat eerder onderzoek heeft laten zien dat patiënten met bvFTD in de praktijk vaker verward worden met patiënten met een psychiatrische stoornis dan patiënten met andere neurodegeneratieve aandoeningen. Hoewel de gelijkenis dus groot kan zijn, laat hoofdstuk 2 van dit proefschrift zien dat het in de praktijk zinvol kan zijn om formele criteria voor een psychiatrische stoornis te

gebruiken omdat bvFTD patiënten daar minder vaak aan voldoen men op het eerste gezicht zou kunnen verwachten. BvFTD patiënten vertonen vaak 'vreemd gedrag' maar voldoen dan niet direct aan formele criteria voor een psychiatrische aandoening. Indien zij wel voldoen aan de formele criteria voor een psychiatrische aandoening komen stemmingsstoornissen het meest voor. We vonden tevens dat depressie en dysthymie het meest voorkomt als psychiatrisch prodroom bij bvFTD. Dit sluit aan bij eerdere studies waarin hypotheses werden beschreven aangaande depressie als prodroom voor bvFTD en studies waarin depressie voorkomt als familiaire risicofactor voor bvFTD.
In de studie beschreven in hoofdstuk 3 onderzochten we het brede spectrum van psychotische symptomen bij bvFTD met behulp van de Positieve en Negatieve Symptoom Schaal (PANSS). Het betrof de eerste studie bij patiënten met bvFTD waarbij niet alleen positieve psychotische symptomen meegenomen werden, zoals wanen, hallucinaties en paranoïdie, maar ook formele denkstoornissen en negatieve psychotische symptomen zoals affectvervlakking en initiatiefvermindering. We vergeleken de aanwezigheid van psychotische symptomen bij bvFTD patiënten en patiënten met een primair psychiatrische stoornis waarbij tevens sprake was van een frontaal syndroom. We ontdekten dat niet de positieve psychotische symptomen het meest voorkwamen bij bvFTD patiënten (22.7% van de bvFTD patiënten) maar negatieve psychotische symptomen (95.5%) en formele denkstoornissen (81.8%). De symptomen *stereotype denken* en *moeite met abstraheren* onderscheidde bvFTD van psychiatrische stoornissen, terwijl *angst*, *schuldgevoelens* en *spanning* (generieke subschaal van de PANSS) significant vaker werden gezien bij een primair psychiatrische diagnose. De combinatie van deze symptomen verklaarde 75% van de variantie tussen bvFTD en een psychiatrische stoornis.

Deel 2. Het onderscheiden van bvFTD van andere neurodegeneratieve aandoeningen en psychiatrische stoornissen

In deel 2 zijn we ons verder gaan verdiepen in het klinisch onderscheid tussen bvFTD, andere neurodegeneratieve aandoeningen en psychiatrische stoornissen. In hoofdstuk 4 hebben we onderzocht of stoornissen in *sociale cognitie* patiënten met bvFTD onderscheidt van patiënten met een andere neurodegeneratieve aandoening of patiënten met een primair psychiatrische stoornis. Sociale cognitie werd gemeten met behulp van *Ekman faces test* en *Faux pas test.* De *Ekman faces test* is een test waarbij het de bedoeling is om de voornaamste emotie te herkennen bij een

foto van een menselijk gezicht. Bij de *Faux pas test* gaat het om het herkennen van een sociaal ongepaste situatie. De belangrijkste bevinding van deze studie was dat bij zowel patiënten met een primair psychiatrische stoornis als bij bvFTD patiënten en patiënten met een andere neurodegeneratieve aandoening sprake was van een beperkte sociale cognitie maar dat ondanks overlappende symptomatologie (het frontaal syndroom), bvFTD zich duidelijk onderscheidde door een significant lagere score op de *Ekman Faces Test.* De *Faux pas test* was niet onderscheidend in de diagnostische groepen. Sociale cognitie bleek daarnaast geassocieerd met alle andere bekende cognitieve domeinen (geheugen, aandacht, tempo, visuospatiële functies en executief functioneren). In de huidige klinische praktijk wordt er bij verdenking op bvFTD bij het neuropsychologisch onderzoek specifiek gelet op executieve stoornissen terwijl onze studie argumenten biedt om de sociale cognitie te beoordelen.

In hoofdstuk 5 hebben we ons gericht op de diagnostische waarde van klinische variabelen en aanvullend onderzoek in het onderscheid tussen bvFTD en psychiatrische stoornissen. We ontdekten dat *mannelijk geslacht, een lage score op de SRI* en de aanwezigheid van *depressieve symptomen* (bepaald met behulp van de Montgomery Asberg Depression Rating Scale-MADRS) goed in staat bleek om onderscheid te maken tussen bvFTD en psychiatrische stoornissen met een diagnostische waarde van 86%. Deze diagnostische accuratesse werd door beeldvormend onderzoek maar in beperkte mate verhoogd tot 88.4%. Dit onderzoek vormt hiermee aanwijzingen dat bij patiënten met een laat ontstaan frontaal klinische variabelen een relatief goede voorspellende waarde hebben in het onderscheid tussen psychiatrische stoornissen en bvFTD.

Deel 3. Ziekte beloop bij het laat ontstaan frontaal syndroom

In deel 3 hebben we verschillende aspecten van ziektebeloop bij patiënten met een laat ontstaan frontaal syndroom beschreven. In hoofdstuk 6 hebben we patiënten met het zogenaamde *fenocopy syndroom* van frontotemporale dementie bestudeerd. Een van de meest opvallende kenmerken van de nieuwe consensus criteria voor bvFTD, zoals vastgesteld in 2011, is het onderscheid tussen *mogelijke* en *waarschijnlijke* bvFTD. Een deel van de patiënten met *mogelijke* bvFTD vertoont over het verloop van tijd wel klinische achteruitgang en afwijkingen op beeldvormend onderzoek waardoor bij hen de diagnose verandert van *mogelijke* bvFTD in *waarschijnlijke* bvFTD. Er is echter ook een groep patiënten die tijdens verdere (jarenlange) follow-up geen klinische achteruitgang vertoont en ook geen

afwijkingen op beeldvormend onderzoek laat zien terwijl zij klinisch wel duidelijke klinische bvFTD kenmerken blijven vertonen. Indien deze patiënten ook geen genetische mutatie blijken te hebben wordt bij hen gesproken over het *fenocopy syndroom* van bvFTD. Lange tijd was het onduidelijk wat het onderliggend lijden is bij het *bvFTD phenocopy syndroom*. In hoofdstuk 6 hebben we 33 patiënten met het *fenocopy syndroom* grondig onderzocht en vergeleken met een controlegroep van 22 patiënten met *waarschijnlijke* bvFTD. Hieruit bleek dat bij 85.2% van de patiënten met het bvFTD *fenocopy syndroom* psychiatrische en psychologische condities aanwezig waren die tot dit syndroom hebben geleid waarbij het veelal ging om een combinatie van factoren. Cluster C persoonlijkheidsproblematiek, recente ingrijpende levensgebeurtenissen (zoals overlijden van een dierbare of verlies van werk) en relatieproblemen waren de meest voorkomende factoren. Door een focus op ziekte beloop, kwamen door deze studie factoren aan het licht waarbij, in tegenstelling tot bij patiënten met *waarschijnlijke* of *definitieve bvFTD,* behandeling wel degelijk zinvol is omdat de symptomen daarmee kunnen verminderen of in remissie kunnen treden.

In hoofdstuk 7 hebben we ons gericht op het voorspellen van progressie bij het laat ontstaan frontaal syndroom middels klinische en demografische variabelen. Bij dit onderzoek werd *progressie* gedefinieerd als institutionalisatie, overlijden of progressie van frontale of temporale atrofie op *Magnetic Resonance Imaging (MRI)* na 2 jaar follow-up. *Non-progressie* was gedefinieerd als de afwezigheid van progressie van atrofie op de MRI in combinatie met stabiele of verbeterde scores op de *Mini Mental State Examination (MMSE)* en *Frontal Assessment Battery (FAB).* Conform de in de wetenschappelijke literatuur heersende hypothese bleek het merendeel van de patiënten die *progressie* toonde na 2 jaar follow-up een neurodegeneratieve aandoening te hebben (82.9%). Opvallend genoeg voldeed slechts 53.6% van de patiënten *zonder progressie* aan de hypothese dat het ging om een psychiatrische aandoening. Naast psychiatrische aandoeningen bleek in deze groep van patiënten *zonder progressie* ook een deel een neurodegeneratieve aandoening te hebben (26.7%) en had het overige deel andere ‘diagnoses’ zoals relatieproblemen (10.7%), subjectieve geheugenklachten (10.7%) en *mogelijke* bvFTD (7.1%). Voorspellers voor progressie waren het vrouwelijk geslacht, stereotypie en een neuropsychologisch profiel met voornamelijk executieve stoornissen en relatieve sparing van episodisch geheugen en visuospatiële functies. Een voorgeschiedenis en familie anamnese belast met psychiatrische stoornissen was voorspellend voor *non-progressie.*

Deel 4. Zorg en interventies bij bvFTD en andere neurodegeneratieve aandoeningen zich presenterend met het laat ontstaan frontaal syndroom

In deze sectie van het proefschrift hebben we ons gewijd aan ondersteunende interventies voor zowel patiënten als mantelzorgers die te maken krijgen met bvFTD of andere neurodegeneratieve aandoeningen waarbij gedragsveranderingen in het kader van een *laat ontstaan frontaal syndroom* centraal staan. In hoofdstuk 8 wordt een systematische review over farmacologische interventies bij patiënten met bvFTD weergegeven. Alle literatuur tussen 1970 en 2016 werd systematisch bestudeerd en uiteindelijk werden 23 studies geïncludeerd waarbij randomized controlled trials het grootste aandeel hadden. Het unieke aan deze systematische review was de klinische invalshoek waarbij de farmacologische interventies beschreven werden aan de hand van het effect op de gedragssymptomen conform de bvFTD criteria uit 2011. Gebaseerd op metingen middels de *Neuropsychiatric Inventory (NPI)* had Trazodon de grootste effecten op de gedragssymptomen bij bvFTD, gevolgd door Rivastigmine en Citalopram.

In hoofdstuk 9 hebben we ons gericht op ondersteunende interventies voor mantelzorgers van dementie patiënten met een frontaal syndroom. Eerder onderzoek heeft herhaaldelijk aangetoond dat de lijdensdruk bij deze mantelzorgers extreem hoog is met vaak ook aanwezigheid van depressieve symptomen bij deze mantelzorgers. We ontwikkelden een groepsgewijze interventie bestaande uit psycho-educatie, sociale steun en cognitieve gedragstherapie die gedurende een half jaar aan mantelzorgers werd gegeven. Mantelzorgers werden blind gerandomiseerd voor ofwel deelname aan de interventie groep ofwel de controlegroep. Mantelzorgers uit de controlegroep kregen ‘de gebruikelijke zorg’ bestaande uit reguliere bezoeken van patiënt en de mantelzorger aan de medisch specialist. Kwalitatieve en kwantitatieve data werd verzameld voorafgaand en na de interventie. In de interventiegroep werd een toename gevonden van een gevoel van competentie in vergelijking met de controlegroep. Hoewel niet significant verschillend van de controlegroep werd in de interventiegroep ook een afname gezien van lijdensdruk, ervaren stress en depressieve symptomen.

CONCLUSIE

Op weg naar een vroeg onderscheid tussen bvFTD en psychiatrische stoornissen

Gedreven door de uitdagingen van de klinische praktijk, was een eerste doel van dit proefschrift om handvaten te bieden die kunnen helpen bij het klinisch onderscheid tussen bvFTD en psychiatrische stoornissen. In geval van verdenking op bvFTD adviseren we om in het diagnostisch proces in ieder geval de anamnese, lichamelijk en neurologisch onderzoek, de medische voorgeschiedenis, familie anamnese, neuropsychiatrisch onderzoek en een hetero-anamnese bij voorkeur bij meerdere informanten af te nemen. Onze data suggereert dat naast het gebruik van de consensus criteria uit 2011 ook het gebruik van formele criteria voor een psychiatrische stoornis (DSM criteria) zinvol kan zijn. Het screenen van alle patiënten middels de Mini Internationaal Neuropsychiatrisch Interview lijkt te arbeidsintensief te zijn (elk interview duurt een uur) en is daarmee ook niet van toegevoegde waarde. Als een betrokken psychiater echter ook klinisch een sterke verdenking heeft op een psychiatrische stoornis lijkt het toepassen van formele criteria voor een psychiatrische stoornis wel duidelijk van toegevoegde waarde. Ons onderzoek heeft laten zien dat ook het observeren en uitvragen van stereotype gedrag van toegevoegde waarde is omdat het aanwijzingen vormt voor zowel bvFTD als 'progressie'. De *Stereotypy Rating Inventory (SRI)* lijkt hiervoor een geschikt meetinstrument omdat het in de vragen aan de mantelzorger zowel de ernst als de frequentie van het stereotype gedrag meeneemt. Ook de *MADRS* is een zinvol instrument voor het klinisch onderscheid tussen bvFTD en psychiatrische stoornissen. De MADRS bleek van toegevoegde diagnostische waarde terwijl beeldvormend onderzoek van beperkt belang was voor de diagnostiek. Dit benadrukt het belang om bvFTD en psychiatrische stoornissen zoveel mogelijk reeds op basis van het klinisch beeld te onderscheiden.

In het onderscheid tussen bvFTD en psychiatrische stoornissen kan ook gebruik van de *PANSS* overwogen worden. In ons cohort van patiënten met een laat ontstaan frontaal syndroom kon driekwart van de variantie van psychiatrische stoornissen versus bvFTD verklaard worden door de *PANSS*. Echter het gebruik van de PANSS is arbeidsintensief, is voorbehouden aan daartoe getrainde clinici en het risico op interpersoonlijke variabiliteit is hoog.. In de klinische praktijk is een nauwe samenwerking tussen neuroloog en psychiater daarom meer aan te raden waarbij men zich bewust is van de duidelijke overlap in symptomatologie

waaronder ook in het brede palet van psychotische symptomen. Het gebruik van de PANSS heeft ons laten zien dat misdiagnose met een psychotische stoornis bij bvFTD veelal wordt veroorzaakt door overlappende negatieve symptomen.

Andere handvaten bruikbaar voor het onderscheid tussen bvFTD en psychiatrische stoornissen zagen we tijdens het bestuderen van het ziekte beloop bij het laat ontstaan frontaal syndroom.. Ons onderzoek heeft laten zien dat er veelal een combinatie van meerdere psychiatrische en psychologische condities ten grondslag ligt aan het *bvFTD phenocopy syndroom.* Het betreft veelal een combinatie van psychiatrische en psychologische condities waarbij recente traumatische levensgebeurtenissen, cluster C persoonlijkheidsproblematiek, relatieproblemen en stemmingsproblemen de meest voorkomende oorzakelijke factoren bleken. Bij 9% van de patiënten met een *bvFTD phenocopy syndroom* was er sprake van een beneden gemiddelde intelligentie. Hiermee wordt aanbevolen om specifiek bij patiënten bij wie gedacht wordt aan bvFTD maar die geen progressie vertonen, geen afwijkingen hebben op beeldvormend onderzoek en geen genetische mutatie blijken te hebben in ieder geval ook de intelligentie te testen, de genoemde psychologische en psychiatrische factoren te overwegen en in ieder geval ook meer dan een hetero-anamnese af te nemen.
Een laatste maar niet minder belangrijk handvat voor het klinisch onderscheid tussen bvFTD en psychiatrische stoornissen kwam naar voren in ons onderzoek naar sociale cognitie bij patiënten met het laat ontstaan frontaal syndroom. Sociale cognitie werd middels de *Ekman 60 Faces test* en de *Faux pas test* gemeten bij patiënten met bvFTD, andere neurodegeneratieve aandoeningen en patiënten met een psychiatrische aandoening. Bij de *Ekman 60 faces test* staat het herkennen van emoties bij middels foto's getoonde gezichten centraal, terwijl het bij de *Faux pas test* gaat om het herkennen van een sociaal ongepaste situatie. BvFTD patiënten hadden een significant lagere score op de *Ekman 60 faces test* en deze test bleek met een goede diagnostische waarde onderscheid te kunnen maken tussen psychiatrische stoornissen, andere neurodegeneratieve aandoeningen en bvFTD. Dit is een veelbelovend resultaat en sluit aan bij hypotheses uit eerdere publicaties. Hiermee raden we dan ook met overtuiging aan om de sociale cognitie te bepalen met in ieder geval de *Ekman 60 faces test* bij patiënten bij wie een verdenking bestaat op bvFTD.

Zorg en symptoomverlichting bij het laat ontstaan frontaal syndroom

Dit proefschrift heeft niet alleen de aandacht gevestigd op handvaten om in de klinische praktijk onderscheid te maken tussen bvFTD en psychiatrische stoornissen maar het belang van symptoomverlichting en zorg voor patiënten en mantelzorgers werd ook benadrukt. In onze studie gericht op symptoomverlichting voor bvFTD patiënten zagen we dat Trazodon, Rivastigmine en Citalopram een gunstig effect kunnen hebben op de gedragssymptomen. Gezien het momenteel nog ontbreken van een oorzakelijke behandeling voor bvFTD patiënten en het gegeven dat met name de naasten van patiënten met bvFTD veel lijdendruk ondervinden van deze progressieve aandoening, is de zorg voor en rondom deze aandoening in belangrijke mate gericht op de mantelzorgers. Gebaseerd op de resultaten van de exploratieve interventie studie die we zelf hebben opgezet, raden we specifieke ondersteuning voor mantelzorgers van dementie patiënten met een frontaal syndroom aan. Een supportgroep waarbij de aspecten psycho educatie, sociale steun en cognitieve gedragstherapie aandacht krijgen lijken zeker zinvol lijdensdruk te verlichten en het gevoel van competentie bij mantelzorgers te versterken.

Aanbevelingen voor de toekomst

Een langere follow up duur van patiënten met een *laat ontstaan frontaal syndroom* is nodig om onze bevindingen te bevestigen. We hebben bij ons onderzoek een follow up duur van 2 jaar gebruikt maar onderzoek heeft tot op heden nog niet uitgewezen of deze gouden standaard voldoende is voor de hoogst haalbare diagnostische zekerheid die *ante mortem* mogelijk is. We bevelen daarnaast klinische instrumenten aan die het beloop van frontale symptomen objectief kunnen meten. In de klinische praktijk zijn we tot op heden nog afhankelijk van mantelzorgers die de frontale symptomen rapporteren waarbij duidelijk is dat er veel verschillen zijn tussen de mantelzorgers ten aanzien van de weergave van deze symptomen. Zo is er bij patiënten met het *bvFTD phenocopy syndroom* geen progressie van ziekte zichtbaar terwijl mantelzorgers een toename van symptomen rapporteren. Het kunnen objectiveren van het beloop van frontale symptomalogie is niet alleen gewenst in het kader van vervolg van wetenschappelijk onderzoek maar ook met het oog op zorg voor patiënten en naasten zodat na het bespreken van de diagnose ook de eventuele progressie van symptomen besproken kan worden.

We bevelen verder onderzoek aan naar eventuele achteruitgang van bevindingen bij neuropsychologisch onderzoek bij patienten met een *frontaal syndroom*. De

huidige criteria stellen dat er bij patienten met bvFTD ten minste sprake moet zijn van klinische achteruitgang om te kunnen spreken van *waarschijnlijke bvFTD.* De vraag is echter of er bij patienten met een psychiatrische aandoening, zich presenterend met een *frontaal syndroom* niet ook sprake kan zijn van achteruitgang, bijvoorbeeld bij neuropsychologisch onderzoek, en hoe zich dit verhoudt tot bvFTD patienten en patienten met andere neurodegeneratieve aandoeningen.

Een aanpassing van de huidige criteria voor bvFTD wordt voorts aanbevolen ten behoeve van een betere diagnostische accuraatheid bij patienten met een *laat ontstaan frontaal syndroom*. Ten eerste wordt toevoeging van beoordeling van sociale cognitieve bij deze patienten aanbevolen. Ten tweede zijn er voldoende aanwijzingen om genetische screening, specifiek ten aanzien van C9orf72 mutatie, mee te nemen in diagnostisch onderzoek, met name vanwege het langzaam progressieve beloop en de soms atypische presentatie met voornamelijk psychiatrische symptomen bij bvFTD voortkomend uit deze mutatie. Daarnaast laten zowel de klinische symptomen als functioneel beeldvormend onderzoek, zoals PET en SPECT onderzoek, overlappende resultaten zien bij bvFTD patienten en patienten met een psychiatrische stoornis. Psychiatrische bvFTD ‘mimics’ moeten in een zo vroeg mogelijk stadium herkend worden en niet onnodig de diagnose bvFTD krijgen. Zorgvuldige diagnostische follow-up, door zowel een neuroloog als psychiater is geïndiceerd, specifiek bij deze groep van bvFTD ‘mimics’, om de betrouwbaarheid van diagnoses op de lange termijn te waarborgen.

Appendix

REFERENCES

A
Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. Lancet. 2009;374(9688):491-499.

Access BA, Gleichgerrcht E, Torralva TT, Manes F. A neuropsychological battery to detect speci c executive and social cognitive impairments in early frontotemporal dementia ´. Brain. 2009.

Albert MS, Cohen C, Koff E. Perception of affect in patients with dementia of the Alzheimer type. Arch Neurol. 1991;48(8):791-795.

Allen-Walker L, Beaton AA. Empathy and perception of emotion in eyes from the FEEST/Ekman and Friesen faces. Pers Individ Dif. 2014;72:150-154.

Alloy LB, Urošević S, Abramson LY, et al. Progression along the bipolar spectrum: a longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. J Abnorm Psychol. 2012;121(1):16-27.

American Psychiatric Association. DSM-IV.; 2000.

Ames D, Chiu E, Lindesay J, Shulman KI. Guide to the Psychiatry of Old Age.; 2010.

Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. J Clin Exp Neuropsychol. 2000;22(4):518-528.

B
Bakker C, Vugt ME De, Vernooij-dassen M, et al. Needs in Early Onset Dementia : A Qualitative Case From the NeedYD Study. Am J Alzheimer 's Dis Other Dementias. 2010;25:634-640.

Balogh N, Égerházi A, Berecz R, Csukly G. Investigating the state-like and trait-like characters of social cognition in schizophrenia: A short term follow-up study. Schizophr Res. 2014;159(2-3):499-505.

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015.

Baron-cohen S, Riordan MO, Stone V, Jones R, Plaisted K. A new test of social sensitivity : Detection of faux pas in normal children and children with Asperger syndrome : J Autism Dev Disord. 1999;29:407-418.

Basso MR, Carona FD, Lowery N, Axelrod BN. Practice effects on the WAIS-III across 3- and 6-month intervals. Clin Neuropsychol. 2002;16(1):57-63.

Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. Acta Neurol Scand. 2001;103(6):367-378.

Beck J, Rohrer JD, Campbell T, et al. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain. 2008;131(3):706-720.

Beck Judith S. Cognitive Therapy: Basics and beyond.; 1995. doi:10.1016/0005-7916(96)89143-9.
Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: A New Short Version and Screening Version. Gerontologist. 2001;41(5):652-657.

Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. Br J Psychiatry. 1999;174(4):307-311.

Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. BrJPsychiatry. 1999;174:307-311.

Benton A, Hamsher K. Multilingual Aphasia Examinationle.; 1983.

Bertoux M, Delavest M, de Souza LC, et al. Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. J Neurol Neurosurg Psychiatry. 2012;83(4):411-416.

Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. Int Psychogeriatrics. 2004;16(3):295-315.

Blennerhassett R, Lillo P, Halliday GM, Hodges JR, Kril JJ. Distribution of pathology in frontal variant Alzheimer's disease. J Alzheimer's Dis. 2014;39(1):63-70.

Boban M. b, Malojčić B. b, Mimica N. c, Vuković S., Zrilić I. The frontal assessment battery in the differential diagnosis of dementia. J Geriatr Psychiatry Neurol. 2012;25(4):201-207.

Boxer AL, Boeve BF. Frontotemporal Dementia Treatment: Current Symptomatic Therapies and Implications of Recent Genetic, Biochemical, and Neuroimaging Studies. Alzheimer Dis Assoc Disord. 2007;21(4):S79-S87.

Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2013;12(2):149-156. doi:10.1016/S1474-4422(12)70320-4.

Boxer AL, Lipton AM, Womack K, et al. An Open Label Study of Memantine Treatment in Three Subtypes of Frontotemporal Lobar Degeneration. Alzheimer Disord Assoc Disord. 2010;23(3):211-217.

Brodaty H, Green A, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc. 2003;51(5):657-664.

Brodaty H, Roberts K PK. Quasi-experimental evaluation of an educational model for dementia caregivers. Int J Geriatr Psychiatry. 1994;9(195):204.

Brodaty H, Roberts K, Peters K. Quasi experimental evaluation of an educational model for dementia caregivers. Int J Geriatr Psychiatry. 1994;9(3):195-204.

Buoli M, Serati M, Caldiroli A, Galimberti D, Scarpini E, Altamura AC. Pharmacological Management of Psychiatric Symptoms in Frontotemporal Dementia: A Systematic Review. J Geriatr Psychiatry Neurol. 2017;30(3):162-169.

C

Caceres BA, Frank MO, Jun J, Martelly MT, Sadarangani T, de Sales PC. Family caregivers of patients with frontotemporal dementia: An integrative review. Int J Nurs Stud. 2015;55:14. doi:10.1016/j.ijnurstu.2015.10.016.

Cagnin A, Gnoato F, Jelcic N, et al. Clinical and cognitive correlates of visual hallucinations in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2012:1-6.

Callegari I, Mattei C, Benassi F, et al. Agomelatine improves apathy in frontotemporal dementia. Neurodegener Dis. 2016;16(5-6):352-356.

Castiglioni S, Pelati O, Zuffi M, Somalvico F, Marino L, Tentorio T et al. The Frontal Assessment Battery Does Not Differentiate Frontotemporal Dementia from Alzheimer's Disease. Dement Geriatr Cogn Disord. 2006.

Chakrabarty T, Sepehry AA, Jacova C, Hsiung G-YR. The prevalence of depressive symptoms in frontotemporal dementia: A meta-analysis. Dement Geriatr Cogn Disord. 2015;39(5-6).

Chang BL. Cognitive-behavioral intervention for homebound caregivers of persons with dementia. Nurs Res. 1999;48(3):173-182.

Charmaz K. Constructing Grounded Theory: A Practical Guide through Qualitative Analysis. Constr Grounded Theory A Pract Guid Through Qual Anal. 2006:SAGE Publications Ltd.

Cohen S, Williamson G. Perceived stress in a probability sample of the United States. Soc Psychol Heal. 1988;13:31-67.

Cora J. Kerssens, Welmoed A. Krudop, Niels D. Prins, Bart N. M. van Berckel, Annemieke Rozemuller, William W. Seeley, Philip Scheltens MLS& YALP. Schizophrenia as a mimic of behavioral variant frontotemporal dementia. Neurocase. 2016.

Creswell JW. Research Design: Qualitative, Quantitative, and Mixed Methods Approaches.; 2013.

Crews FT, Boettiger CA. Impulsivity, frontal lobes and risk for addiction. Pharmacol Biochem Behav. 2009;93(3):237-247.

Crossley NA, Scott J, Ellison-Wright I, Mechelli A. Neuroimaging distinction between neurological and psychiatric disorders. Br J Psychiatry. 2015;207(5).
Cuijpers P, Hosman CM, Munnichs JM. Change mechanisms of support groups for caregivers of dementia patients. Int Psychogeriatr. 1996;8(4):575-587.

D

Da Ponte G, Paiva A LM et al. Mania like symptoms in frontotemporal dementia. Eur Psychiatry. 2010;25(563).

Davidson LL, Heinrichs RW. Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: A meta-analysis. Psychiatry Res - Neuroimaging. 2003;122(2):69-87.

Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in Frontotemporal Dementia Identifying a Benign Behavioral Variant by Magnetic Resonance Imaging. Arch Neurol. 2006;63:1627-1631.

de Vugt ME, Stevens F, Aalten P, Lousberg R, Jaspers N, Winkels I, Jolles J VF. Behavioural disturbances in dementia patients and quality of the marital relationship. Int J Geriatr Psychiatry. 2003;18(2):149-154.

Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: A double-blind randomized controlled trial. Psychopharmacology (Berl). 2004;172(4):400-408.

Devanand, D. P., Pelton, G. H., D'antonio, K., Strickler, J. G., Kreisl, W. C., Noble, J. & Huey ED. Low-dose Lithium Treatment for Agitation and Psychosis in Alzheimer Disease and Frontotemporal Dementia: A Case Series. Alzheimer Dis Assoc Disord. 2017.

Devanand, D. P., Pelton, G., D'antonio, K., Strickler, J., Kreisl, W., Noble, J. & Huey, E. et al. Low-dose Lithium treatment for agitation in Frontotemporal dementia: A case series. J Neurochem. 2016.

Devenney E, Bartley L, Hoon C, et al. Progression in Behavioral Variant Frontotemporal Dementia: A Longitudinal Study. JAMA Neurol. 2015;72(12):1501-1509.

Devenney, E., Forrest, S. L., Xuereb, J., Kril, J. J., & Hodges JR. The bvFTD phenocopy syndrome: a clinicopathological report. J Neurol Neurosurg Psychiatry. 2016.
Diehl-Schmid J, Förstl H, Perneczky R, Pohl C, Kurz A. A 6-month, open-label study of memantine in patients with frontotemporal dementia. Int J Geriatr Psychiatry. 2008;23(7):754-759.

Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. Arch Clin Neuropsychol. 2007;22(4):459-464.

Diehl-Schmid J, Schmidt E-M, Nunnemann S, et al. Caregiver Burden and Needs in Frontotemporal Dementia. J Geriatr Psychiatry Neurol. 2013;26(4):221-229.

Dols A, van Liempt S, Gossink F, et al. Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome. J Clin Psychiatry.

Dröes R.M, Meiland FJM, Schmitz MJ, van Tilburg W. Effect of the Meeting Centres Support Program on informal carers of people with dementia: results from a multi-centre study. Aging Ment Health. 2006;10(2):112-124.

Dröes R.M. Amsterdamse Ontmoetingscentra; Een Nieuwe Vorm van Ondersteuning Voor Dementerende Mensen En Hun Verzorgers [Amsterdam Meeting Centres: A New Type of Support for People with Dementia and Their Carers]. Amsterdam; 1996.

Dröes R-M, Breebaart E, Meiland FJM, Van Tilburg W, Mellenbergh GJ. Effect of Meeting Centres Support Program on feelings of competence of family carers and delay of institutionalization of people with dementia. Aging Ment Health. 2004;8(3):201-211.

Dubois B, Slachevsky a, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000;55(11):1621-1626. doi:10.1212/WNL.57.3.565.

Ducharme S, Dickerson BC, Larvie M, Price BH, et al. Differentiating frontotemporal dementia from catatonia: a complex neuropsychiatric challenge. J Neuropsychiatry Clin Neurosci. 2015;27(2):e174-e176.

Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical Approach to the Differential Diagnosis Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders.
Duits FH, Teunissen CE, Bouwman FH, et al. The cerebrospinal fluid "alzheimer profile": Easily said, but what does it mean? Alzheimer's Dement. 2014;10(6):713-723.

E
Englund, B. Brun, A. Gustafson, L. Passant, U. Mann, D. Neary, D., Snowden JS. Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1994;57(4):416-418.
Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. J Neuropsychiatry Clin Neurosci. 2011;23(1):74-82.

Estévez-González A, Kulisevsky J, Boltes A, Otermín P, García-Sánchez C. Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: Comparison with mild cognitive impairment and normal aging. Int J Geriatr Psychiatry. 2003;18(11):1021-1028.

Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: A review of the literature. J Am Acad Nurse Pract. 2008;20(8):423-428.

F
Fazekas F, Chawluk JB, Alavi A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Neuroradiol. 1987;8(3):421-426.

Figuerido JL, Gutierrez M, Gonzalez Pinto A, et al. [Predictors of rehospitalization in schizophrenia]. Predict rehospitalizacion en la esquizofrenia. 1997;25(4):217-224.

Finger EC, MacKinley J, Blair M, et al. Oxytocin for frontotemporal dementia: a randomized dose-finding study of safety and tolerability. Neurology. 2015;84(2):174-181.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198.

Funkiewiez A, Bertoux M, de Souza LC, Lévy R, Dubois B. The SEA (Social Cognition and Emotional Assessment): A clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. Neuropsychology. 2012;26(1):81-90.

Furlan JC, Henri-Bhargava A, Freedman M. Clomipramine in the treatment of compulsive behavior in frontotemporal dementia: a case series. Alzheimer Dis Assoc Disord. 2014;28(1):95-98.

G
Gaebel W, Zielasek J. Focus on psychosis. Dialogues Clin Neurosci. 2015;17(1):9-18.

Galea M, Woodward M. Mini-mental state examination (MMSE). Aust J Physiother. 2005;51(3):198. doi:10.1017/CBO9781107415324.004.

Galimberti D, Fenoglio C, Serpente M, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: Late-onset psychotic clinical presentation. Biol Psychiatry. 2013;74(5):384-391.

Gigi A, Pirrotta R, Kelley-Puskas M, Lazignac C, Damsa C. [Behavior disturbances in emergency psychiatry or fronto-temporal dementia diagnosis? A challenge for psychiatrists]. [French] Troubles du comportement aux urgences, ou demence fronto-temporale? Un defi pour les psychiatres. Encephale. 2006;32(5 Pt 1):775-780.

Gilbert P. The relationship of shame, social anxiety and depression: the role of the evaluation of social rank. Clin Psychol Psychother. 2000;7(3):174-189.

Goodrich-Hunsaker NJ, Hopkins RO. Word memory test performance in amnesic patients with hippocampal damage. Neuropsychology. 2009;23(4):529-534.

Gorno-Tempini ML, Hillis a E, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1-10.

Gottlieb BH, Johnson J. Respite programs for caregivers of persons with dementia: A review with practice implications. Aging Ment Health. 2000;4(2):119-129.
Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci. 2015;16(10):620-631.

Gregoire J, Van Der Linden M. Effect of age on forward and backward span tasks. J Int Neuropsychol Soc. 2004;10(4):475-481.

Gregory C, Lough S, Stone V, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. Brain. 2002;125(4):752-764.

Gregory CA, Hodges JR. Frontotemporal dementia: Use of consensus criteria and prevalence of psychiatric features. Neuropsychiatry, Neuropsychol Behav Neurol. 1996;9(3):145-153.

Gregory CA. Frontal variant of frontotemporal dementia: a cross-sectional and longitudinal study of neuropsychiatric features. Psychol Med. 1999;29(5):S0033291799008934.

Gu, X. H., Xu, J., & Wei CS. Memantine in patients with behavioral variant frontotemporal dementia: An open-label pilot study. Alzheimer's Dement. 2015;11(7):751-753.

H

Hallam BJ, Silverberg ND, LaMarre AK, Mackenzie IRA, Feldman HH. Clinical Presentation of Prodromal Frontotemporal Dementia. Am J Alzheimers Dis Other Demen. 2008;22(6):456-467.

Haller S, Xekardaki A, Delaloye C, et al. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. J Psychiatry Neurosci. 2011;36(6):391-401.

Hargrave R, Maddock RJ, Stone V. Impaired recognition of facial expressions of emotion in Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2002;14(1):64-71.

Harper L, Barkhof F, Fox NC, Schott JM. Using visual rating to diagnose dementia: a critical evaluation of MRI atrophy scales. J Neurol Neurosurg Psychiatry. 2015;86(11):1225-1233.

Harris JM, Gall C, Thompson JC, et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. Neurology. 2013;80(20):1881-1887.

Harvey PD WE. Positive and Negative Symptoms in Psychosis: Description, Research, and Future Directions. Routledge

Harvey PD, Penn D. Social cognition: the key factor predicting social outcome in people with schizophrenia? Psychiatry (Edgmont). 2010;7(2):41-44.

Hattink B, Meiland F, Van Der Roest H, et al. Web-based STAR E-learning course increases empathy and understanding in dementia caregivers: Results from a randomized controlled trial in the netherlands and the United Kingdom. J Med Internet Res. 2015;17(10).

Herrmann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. Am J Geriatr Psychiatry. 2012;20(9):789-797.

Higgins JPT AD. Chapter 8. Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Cochrane Collab. 2011.

Holshausen K, Harvey PD, Elvevåg B, Foltz PW, Bowie CR. Latent semantic variables are associated with formal thought disorder and adaptive behavior in older inpatients with schizophrenia. Cortex. 2014;55(1):88-96.

Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. Neurology. 2008;71(19):1481-1488.

Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? J Neurol Neurosurg Psychiatry. 2009;80(6):591-593.

Huey ED, Garcia C, Wassermann EM, Tierney MC, Grafman J. Stimulant treatment of frontotemporal dementia in 8 patients. J Clin Psychiatry. 2008;69(12):1981-1982.

I

Ibanez A, Manes F. Contextual social cognition and the behavioral variant of frontotemporal dementia. Neurology. 2012;78(17):1354-1362.

Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2002;73(4):371-376.

Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. In: Dementia and Geriatric Cognitive Disorders. Vol 17. ; 2004:265-268.

Ikeda M, Shigenobu K, Fukuhara R, et al. Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. Dement Geriatr Cogn Disord. 2004;17(3):117-121.

Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? Neurology. 1986;36(3):340-345.

Ishii S, Weintraub N, Mervis JR. Apathy: A Common Psychiatric Syndrome in the Elderly. J Am Med Dir Assoc. 2009;10(6):381-393.

J

Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9(1):119-128.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-216.

Jesso S, Morlog D, Ross S, et al. The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. Brain. 2011;134(9):2493-2501.

Johns EK, Phillips N a, Belleville S, et al. Executive functions in frontotemporal dementia and Lewy body dementia. Neuropsychology. 2009;23(6):765-777.

K
Kay SR, Fiszbein A OL. The Positive and Negative Syndrome Scale for schizophrenia. Schizophr Bull. 1987;13(2):261-276.
Kerstein AH, Schroeder RW, Baade LE, Lincoln J, Khan AY. Frontotemporal dementia mimicking bipolar disorder. J Psychiatr Pract. 2013;19(6):498-500.

Kertesz A, Cyn Ang L, Jesso S, et al. Psychosis and Hallucinations in FTD with C9ORF72 mutation: A detailed clinical cohort. Cogn Behav Neurol. 2013;26(3):146-154.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain. 2005;128(9):1996-2005.

Kertesz A, Morlog D, Light M, et al. Galantamine in frontotemporal dementia and primary progressive aphasia. Dement Geriatr Cogn Disord. 2008;25(2):178-185.

Kertesz A, Nadkarni N, Davidson W, Thomas a W. The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc. 2000;6(4):460-468.

Keshavan MS, Rabinowitz J, Desmedt G, Harvey PD, Schooler N. Correlates of insight in first episode psychosis. Schizophr Res. 2004;70(2-3):187-194.

Kessler RC, McGonagle K a, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51(1):8-19.

Khan BK, Woolley JD CS et al. Schizophrenia or neurodegenerative disease prodrome? Outcome of a first psychotic episode in a 35-year old woman. Psychosomatics. 2012;53(280).

Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. J Neurol Neurosurg Psychiatry. 2012;83(4):358-364.

Kimura T, Hayashida H, Furukawa H, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: Effect of Yokukansan on behavioral symptoms. Psychiatry Clin Neurosci. 2010;64(2):207-210.

Kimura T, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: risk of donepezil treatment for behavioral and psychological symptoms. Geriatr Gerontol Int. 2013.
Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: Application of an MRI visual rating scale. Dement Geriatr Cogn Disord. 2007;23(5):334-342.

Kipps CM, Hodges JR, Fryer TD, Nestor PJ. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. Brain. 2009;132(Pt 9):2566-2578.

Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome." Curr Opin Neurol. 2010;23(6):628-632.

Knopman DS, Boeve BF, Parisi JE, et al. Antemortem diagnosis of frontotemporal lobar degeneration. Ann Neurol. 2005;57(4):480-488.

Koedam ELGE, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YAL, Fox N et al. Visual assessment of posterior atrophy development of a MRI rating scale. Eur Radiol. 2011.

Kosmidis MH, Aretouli E, Bozikas VP, Giannakou M, Ioannidis P. Studying social cognition in patients with schizophrenia and patients with frontotemporal dementia: theory of mind and the perception of sarcasm. Behav Neurol. 2008;19(1-2):65-69.

Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. Am J Geriatr Psychiatry. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.

Krudop W a, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. Am J Geriatr Psychiatry. 2014;22(7):735-740. doi:10.1016/j.jagp.2013.02.002.

Krudop WA, Bosman S, Geurts JJG, et al. Clinico-pathological correlations of the frontal lobe syndrome: Results of a large brain bank study. Dement Geriatr Cogn Disord. 2015.

Krudop WA, Dols A, Kerssens CJ, et al. Impact of Imaging and Cerebrospinal Fluid Biomarkers on Behavioral Variant Frontotemporal Dementia Diagnosis within a Late-Onset Frontal Lobe Syndrome Cohort. Dement Geriatr Cogn Disord. 2016.

Krudop WA, Kerssens CJ, Dols A, et al. Identifying bvFTD within the wide spectrum of late onset frontal lobe syndrome: A clinical approach. Am J Geriatr Psychiatry. 2015.

Krudop WA, Pijnenburg YAL. Historical evolution of the frontal lobe syndrome. Psychopathology. 2015.

Kumfor F HJ. Social Cognition in Frontotemporal Dementia Proceedings: Special Lecture Neuropsychology Association of Japan 40th annual meeting. Japanese J Neuropsychol. 2017;33.

Kumfor F, Irish M, Leyton C, et al. Tracking the progression of social cognition in neurodegenerative disorders. J Neurol Neurosurg Psychiatry. 2014;85(10):1076-1083.

L
Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry.

Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. J Am Geriatr Soc. 2001;49(12):1700-1707.

Lavenu I, Pasquier F, Lebert F, Petit H, Van der Linden M. Perception of emotion in frontotemporal dementia and Alzheimer disease. Alzheimer Dis Assoc Disord. 1999;13(2):96-101.

Le Ber I, Guedj E GA et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain. 2006.

Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: A randomised, controlled trial with trazodone. In: Dementia and Geriatric Cognitive Disorders. Vol 17. ; 2004:355-359.

Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Trazodone in fronto-temporal dementia. Res Pract Alzheimers Dis. 2006;11:356-360.

Li J-Q, Tan L, Wang H-F, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. J Neurol Neurosurg Psychiatry. 2016;(6):1-9.

Lima-Silva TB, Bahia VS, Carvalho VA, et al. Neuropsychiatric symptoms, caregiver burden and distress in behavioral-variant frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord. 2015;40(5-6):268-275.

Lindeboom J. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry. 2002;73(2):126-133.

Lopez OL, Gonzalez MP, Becker JT, Reynolds III CF, Sudilovsky A, DeKosky ST. Symptoms of depression and psychosis in Alzheimer's disease and frontotemporal dementia. Exploration of underlying mechanisms. Neuropsychiatry, Neuropsychol Behav Neurol. 1996;9(3).

Lough S, Gregory C, Hodges JR. Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. Neurocase case Stud Neuropsychol neuropsychiatry, Behav Neurol. 2001;7(2):123-130.

Lough S, Hodges JR. Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. J Psychosom Res. 2002;53(2):639-646.

Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia. 2006;44(6):950-958.

Luteijn F V der PH. Handleiding Groninger Intelligentie Test (GIT). Lisse: Sweitz&Zeitlinger; 1983.

Luzzi S, Fabi K, Pesallaccia M, Cafazzo V, Silvestrini M PL. To clap or not to clap? Applause sign in apathetic and disinhibited/stereotypical behavioural variants of FTD. J Neurol Neurosurg Psychiatry. 2014.

M
Mackenzie, I. R., Rademakers, R., & Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. Lancet Neurol. 2010;9(10):995-1007.

Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease : A longitudinal analysis. Neurology. 2015;84(6):617-622.

Maudsley G. Mixing it but not mixed-up: Mixed methods research in medical education (a critical narrative review). Med Teach. 2011;33(2):e92-e104.
Mckeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65:1863-1872.

Mckeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65:1863-1872.

McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol. 2001;58(11):1803-1809.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7(3):263-269.

McKinnon C, OÇonnor CM, Savage S, Hodges JR ME. Qualitative results of a structured group program for carers of peopple with fronotemporal dementia. Alzheimer Dis Assoc Disord. 2013;27(1):84-86.

M
Meesters PD, Schouws S, Stek M, et al. Cognitive impairment in late life schizophrenia and bipolar i disorder. Int J Geriatr Psychiatry. 2013;28(1):82-90. doi:10.1002/gps.3793.
Meiland FJM, Kat MG, van Tilburg W, Jonker C, Dröes R-M. The emotional impact of psychiatric symptoms in dementia on partner caregivers: do caregiver, patient, and situation characteristics make a difference? Alzheimer Dis Assoc Disord. 2005;19(4):195-201.

Mendez MF, Lauterbach EC, Sampson SM. An Evidence-Based Review of the Psychopathology of Frontotemporal Dementia: A Report of the ANPA Committee on Research. J Neuropsychiatry Clin Neurosci. 2008;20(2):130-149.

Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2006;77(1):4-7.

Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. Compulsive behaviors as presenting symptoms of frontotemporal dementia. J Geriatr Psychiatry Neurol. 1997;10:154-157.
Mendez MF, Perryman KM. Neuropsychiatric Features of Frontotemporal Dementia: Evaluation of Consensus Criteria and Review. J Neuropsychiatry Clin NeurosciThe J Neuropsychiatry Clin Neurosci. 2002;144(14):424-429.

Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. Arch Neurol. 2007;64(6):830-835.

Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: Prevalence and review. Dement Geriatr Cogn Disord. 2008;25(3):206-211.

Midi H, Sarkar SK, Rana S. Collinearity diagnostics of binary logistic regression model. J Interdiscip Math. 2010;13(3):253-267.

Milak MS, Aniskin DB ED et al. The negative syndrome as a dimension: factor analyses of PANSS in major depressive disorder and organic brain disease compared with negative syndrome structures found in the schizophrenia literature. Cogn Behav Neurol. 2007;20:113-120.

Milan G, Lamenza F, Iavarone A, et al. Frontal Behavioural Inventory in the differential diagnosis of dementia. Acta Neurol Scand. 2008;117(4):260-265.

Miller WC, Anton HA, Townson AF. Measurement properties of the CESD scale among individuals with spinal cord injury. Spinal Cord. 2008;46(4):287-292.

Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR. Improving burden and coping skills in frontotemporal dementia caregivers: a pilot study. Alzheimer Dis Assoc Disord. 2013;27(1):84-86.

Moniz-Cook E, Vernooij-Dassen M, Woods R, et al. A European consensus on outcome measures for psychosocial intervention research in dementia care. Aging Ment Health. 2008;12(1):14-29.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134(4):382-389.

Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in Frontotemporal Dementia. Drugs & Aging. 2004;21(14):931-937.
Moretti R, Torre P, Antonello RM, Cazzato G BA. Effects of selegiline on fronto-temporal dementia: a neuropsychological evaluation. Int J Geriatr Psychiatry. 2002;17(4):391-392.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: Paroxetine as a possible treatment of behavior symptoms: A randomized, controlled, open 14-month study. Eur Neurol. 2003;49(1):13-19.

Moretti, R., Torre, P., Antonello, R. M., Cazzato, G., & Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. 2002. 49(1):13-19.

Mourik JC, Rosso SM, Niermeijer MF, Duivenvoorden HJ, Van Swieten JC, Tibben A. Frontotemporal dementia: Behavioral symptoms and caregiver distress. Dement Geriatr Cogn Disord. 2004;18(3-4):299-306.

Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol Psychiatry. 2012;18(5):595-606. doi:10.1038/mp.2012.33.

N
Nardell M, Tampi RR. Pharmacological Treatments for Frontotemporal Dementias: A Systematic Review of Randomized Controlled Trials. Am J Alzheimers Dis Other Demen. 2013;29(2):123-132.

Narme P, Mouras H, Roussel M, Devendeville A, Godefroy O. Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimer's disease. J Clin Exp Neuropsychol. 2013;35(7):728-744.

Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51(6):1546-1554.

Nunnemann S, Kurz A, Leucht S, Diehl-Schmid J. Caregivers of patients with frontotemporal lobar degeneration: a review of burden, problems, needs, and interventions. Int Psychogeriatrics. 2012;24(9):1368-1386.

O
O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ. 2010;341(aug07_3):c4587.
O'Toole MS, Pedersen AD, Hougaard E, Rosenberg NK. Neuropsychological test performance in social anxiety disorder. Nord J Psychiatry. 2015;69(6):444-452.

Ossenkoppele R, Pijnenburg YAL, Perry DC, et al. The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. Brain. 2015;138(9):2732-2749.

P
Pardini, M., Serrati, C., Guida, S., Mattei, C., Abate, L., Massucco, D., ... & Emberti Gialloreti L. Souvenaid reduces behavioral deficits and improves social cognition skills in frontotemporal dementia: a proof-of-concept study. Neurodegener Dis. 2015;15(1):58-62.

Pasquier F, Deramecourt V, Lebert F. [From Pick's disease to frontotemporal dementia]. Bull Acad Natl Med. 2012;196(2):431-433.

Pasquier F, Lebert F, Lavenu I, Guillaume B. The clinical picture of frontotemporal dementia: diagnosis and follow-up. Dement Geriatr Cogn Disord. 1999;10 Suppl 1(suppl 1):10-14.

Pasquier F. New behavioural variant FTD criteria and clinical practice. In: Revue Neurologique. Vol 169. ; 2013:799-805.

Passant U, Elfgren C, Englund E, Gustafson L. Psychiatric symptoms and their psychosocial consequences in frontotemporal dementia. Alzheimer Dis Assoc Disord. 2005;19 Suppl 1(3950):S15-S18.

Peeters, JM, De Lange J, Van Asch I, Spreeuwenberg P, Veerbeek M, Pot AM F AL. Landelijke evaluatie van casemanagement dementia [National evaluation of case management dementia, the Netherlands]. NIVEL, Utr. 2012.

Perry DC, Sturm VE, Seeley WW, Miller BL, Kramer JH, Rosen HJ. Anatomical correlates of reward-seeking behaviours in behavioural variant frontotemporal dementia. Brain. 2014;137(6):1621-1626.

Piguet O, Halliday GM, Reid WGJ, et al. Clinical phenotypes in autopsy-confirmed pick disease. Neurology. 2011;76(3):253-259.

Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. Lancet Neurol. 2010;10(2):162-172.

Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. Neurology. 2009;72(8):732-737.

Pijnenburg YAL, Mulder JL, Van Swieten JC, et al. Diagnostic accuracy of consensus diagnostic criteria for frontotemporal dementia in a memory clinic population. Dement Geriatr Cogn Disord. 2008;25(2):157-164.

Pinquart M, Sörensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr. 2006;18(4):577-595.

Poletti M, Lucetti C, Logi C, et al. Cognitive correlates of negative symptoms in behavioral variant frontotemporal dementia: implications for the frontal lobe syndrome. Neurol Sci. 2013;34(11):1893-1896.

Portugal M da G, Marinho V, Laks J. Pharmacological treatment of frontotemporal lobar degeneration: systematic review. Rev Bras Psiquiatr. 2011;33(1):81-90.

Possin KL, Laluz VR, Alcantar OZ, Miller BL, Kramer JH. Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. Neuropsychologia. 2011;49(1):43-48. doi:10.1016/j.neuropsychologia.2010.10.026.

R
Rabinovici G, Miller B. Frontotemporal Lobar Degeneration: Epidemiology, Pathophysiology, Diagnosis and Management. Vol 24.; 2010.

Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1977;1(3):385-401. doi:10.1177/014662167700100306.

Rahman S; Robbins Tw, Hodges JR, Mehta MA, Nestor PJ, Clark L SB. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. Neuropsychopharmacology. 2006;31(3):651-658.

Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. J Clin Psychiatry. 2008;69(1):60-73.

Rascovsky K, Grossman M. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. Int Rev Psychiatry. 2014;25(2):145-158.

Rascovsky K, Hodges JR, Kipps CM, et al. Diagnostic Criteria for the Behavioral Variant of Frontotemporal Dementia (bvFTD): Current Limitations and Future Directions. Alzheimer Dis Assoc Disord. 2007;21(4):S14-S18.

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(9):2456-2477.

Rascovsky K, Salmon DP, Ho GJ, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. Neurology. 2002;58(12):1801-1808.

Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology. 2002;58(11):1615-1621.

Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271-276.

Rey A. L'examen Clinique En Psychologie.; 1958.

Riedijk SR, De Vugt ME, Duivenvoorden HJ, et al. Caregiver burden, health-related quality of life and coping in dementia caregivers: A comparison of frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;22(5-6):405-412.

Rienstra A, Spaan PEJ, Schmand B. Reference data for the word memory test. Arch Clin Neuropsychol. 2009;24(3):255-262. doi:10.1093/arclin/acp035.

Ringman JM, Liang LJ, Zhou Y, et al. Early behavioural changes in familial Alzheimer's disease in the Dominantly Inherited Alzheimer Network. Brain. 2015;138(4):1036-1045.
RM D. Amsterdamse Ontmoetingscentra; Een Nieuwe Vorm van Ondersteuning Voor Dementerende Mensen En Hun Verzorgers [Amsterdam Meeting Centres: A New Type of Support for People with Dementia and Their Carers]. Amsterdam; 1996.

Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73(18):1451-1456.

Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. Curr Opin Neurol. 2011;24(6):542-549.

Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-260.

Ropacki SA, Jeste D V. Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. Am J Psychiatry. 2005;162(11):2022-2030.

Rosso SM, Kaat LD, Baks T, et al. Frontotemporal dementia in The Netherlands: Patient characteristics and prevalence estimates from a population-based study. Brain. 2003;126(9):2016-2022. doi:10.1093/brain/awg204.

Roth RM, Flashman LA, Saykin AJ, McAllister TW, Vidaver R. Apathy in Schizophrenia: Reduced Frontal Lobe Volume and Neuropsychological Deficits. Am J Psychiatry. 2004;161(1):157-159.

Rowland JE, Hamilton MK, Vella N, Lino BJ, Mitchell PB, Green MJ. Adaptive associations between social cognition and emotion regulation are absent in schizophrenia and bipolar disorder. Front Psychol. 2013;3(JAN).

S
Samamé C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: Systematic review and meta-analytic approach. Acta Psychiatr Scand. 2012;125(4):266-280.

Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE, Hawkins JM. Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry. 1999;156(1):139-141.
Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. JNeurol. 1995;242(0340-5354 (Print)):557-560.

Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967-972.

Schene AH VWB. De Betrokkenen Evaluatie Schaal (BES) [The Dutch Version of the Involvement Evaluation Questionnaire (IEQ). Amsterdam; 1991.

Schmand B, Groenink SC, Van Den Dungen M. Letterfluency: psychometrische eigenschappen en Nederlandse normen. Tijdschr Gerontol Geriat. 2008;39:64-76.

Schoonenboom NSM, Reesink FE, Verwey NA, Kester MI, Teunissen CE, van de Ven PM et al. Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. Neurology. 2012.

Seeley WW, Crawford R, Rascovsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol. 2008;65(2):249-255.

Seeley WW, Crawford R, Rascovsky K, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol. 2008;65(2):249-255. doi:10.1001/archneurol.2007.38.

Sepehry A, Chakrabarty T JC. Prevalence of depressive mood in frontotemporal dementia (FTD): a meta-analyses of studies from 2000 to present. Alzheimer's &Dementia J Alzheimer's Assoc. 2013;9(4):607.

Sepehry A, Chakrabarty T JC. Prevalence of depressive mood in frontotemporal dementia (FTD): a meta-analyses of studies from 2000 to present. Alzheimer's &Dementia J Alzheimer's Assoc. 2013;9(4):607.

Sheehan D V., Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: Journal of Clinical Psychiatry. Vol 59. ; 1998:22-33.
Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res. 2002;110(2):175-187.

Shinagawa S, Catindig J, Block N, Miller B, Rankin K. When a little knowledge can be dangerous: False positive diagnosis of bvFTD among community clinicians. Am J Neurodegener Dis. 2014;3:374.

Shinagawa S, Catindig J, Block N, Miller B, Rankin K. When a little knowledge can be dangerous: False positive diagnosis of bvFTD among community clinicians. Am J Neurodegener Dis. 2014;3:374.

Shinagawa S, Naasan G, Karydas a. M, et al. Clinicopathological Study of Patients With C9ORF72-Associated Frontotemporal Dementia Presenting With Delusions. J Geriatr Psychiatry Neurol. 2014;28(2):99-107.

Shinagawa, S., Nakajima, S., Plitman, E., Graff-Guerrero, A., Mimura, M., Nakayama, K., Miller BL. Non-pharmacological management for patients with Frontotemporal dementia: a systematic review. J Alzheimer's Dis. 2015;45(1):283-293.

Shulman KI. Clock Drawing: Is It the Ideal Cognitive Screening Test? Int J Geriatr Psychiatry. 2000;15(March):548-561.

Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. Br J Psychiatry. 2002;180(2):140-143.

Snowden JS. Frontotemporal dementia. Br J Psychiatry. 2002;180(2):140-143.

Solje E, Aaltokallio H, Koivumaa-Honkanen H, et al. The phenotype of the C9ORF72 expansion carriers according to revised criteria for bvFTD. PLoS One. 2015.

Steketee RME, Meijboom R, Bron EE, et al. Structural and functional brain abnormalities place phenocopy frontotemporal dementia (FTD) in the FTD spectrum. NeuroImage Clin. 2016;11:595-605.

Stone J, Griffiths TD RS. Non-Pick's frontotemporal dementia imitating schizophrenia in a 22-year-old man. J Neurol. 2003;250:369-370.
Stone VE. Faux Pas Recognition Test Faux Pas Recognition Test (Adult Version). J Cogn Neurosci Brain. 2002;10(125):640-656.

Svanberg E, Spector A, Stott J. The impact of young onset dementia on the family: a literature review. Int Psychogeriatrics. 2011;23(3):356-371.

Swanberg MM. Memantine for behavioral disturbances in frontotemporal dementia: a case series. Alzheimer Dis Assoc Disord. 2007;21(2):164-166.

Swartz JR, Miller BL, Lesser IM, et al. Behavioral phenomenology in Alzheimer's disease, frontotemporal dementia, and late-life depression: a retrospective analysis. J Geriatr Psychiatry Neurol. 1997;10(2):67-74.

T
Taragano FE, Allegri RF, Krupitzki H, et al. Mild behavioral impairment and risk of dementia: A prospective cohort study of 358 patients. J Clin Psychiatry. 2009;70(4):584-592.

Thalheimer W, Cook S. How to calculate effect sizes from published research: A simplified methodology. Work Res. 2002;(August):1-9.

Tifratene K, Robert P, Metelkina A, Pradier C, Dartigues JF. Progression of mild cognitive impairment to dementia due to AD in clinical settings. Neurology. 2015;85(4):331-338.

Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19(2):203-214.

Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain. 2009;132(5):1299-1309.

Toseland RWE, Haigler DHE, Monahan DJE. Education and support programs for caregivers: Research, practice, policy. Educ Support programs caregivers Res Pract policy. 2011:85-105.

U
Uljarevic M, Hamilton A. Recognition of emotions in autism: A formal meta-analysis. J Autism Dev Disord. 2013;43(7):1517-1526.

Urwin H, Josephs KA, Rohrer JD, et al. FUS pathology defines the majority of tau-and TDP-43-negative frontotemporal lobar degeneration. Acta Neuropathol. 2010;120(1):33-41.

V
Vaish A, Grossmann T, Woodward A. Not all emotions are created equal: The negativity bias in social-emotional development. Psychol Bull. 2008;134(3):383-403.

Van Der Flier WM, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: The Amsterdam dementia cohort. J Alzheimer's Dis. 2014;41(1):313-327.

Van Vliet D, De Vugt ME, Bakker C, Koopmans RTCM, Verhey FRJ. Impact of early onset dementia on caregivers: A review. Int J Geriatr Psychiatry. 2010;25(11):1091-1100.

Van Wijngaarden B SA. Caregiving consequences in The Netherlands and other european countries: the development and use of the family. Fam Interv Ment Illn Int Perspect. 2002.
Vandenberghe R. Sense and sensitivity of novel criteria for frontotemporal dementia. Brain. 2011;134(9):2450-2453.

Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. Br J Psychiatry. 2009;194(4):298-305.

Vercelletto M, Boutoleau-Bretonniere C, Volteau C, et al. Memantine in behavioral variant frontotemporal dementia: negative results. J Alzheimers Dis. 2011;23(4):749-759.

Vernooij-Dassen JFJ, Felling JA, Brummelkamp E, Dauzenberg GH, van Geertrudis AM, Grol R. Assessment of caregiver's competence in dealing with the burden of caregiving for a dementia patient: A Short Sense of Competence Questionnaire (SSCQ) suitable for clinical practice. J Am Geriatr Soc. 1999;47(2):256.

Vernooij-Dassen MJFJ, Persoon JMG, Felling AJA. Predictors of sense of competense in caregivers of demented persons. Soc Sci Med. 1996;43(1):41-49.
Vijverberg EGB, Dols A, Krudop WA, et al. Diagnostic accuracy of the frontotemporal dementia consensus criteria in the late-onset frontal lobe syndrome. Dement Geriatr Cogn Disord. 2016;41(3-4):210-219.

W
Wald C, Fahy M, Walker Z, Livingston G. What to tell dementia caregivers - The rule of threes. Int J Geriatr Psychiatry. 2003;18(4):313-317.

Waldö ML, Gustafson L, Passant U, Englund E. Psychotic symptoms in frontotemporal dementia: a diagnostic dilemma? Int Psychogeriatrics. 2015;27(4):531-539.

Waldö ML, Santillo AF, Gustafson L, Englund E, Passant U. Somatic complaints in frontotemporal dementia. Am J Neurodegener Dis. 2014;3(2):84-92.

Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ. 2013;347(August):f4827.

Warrington EK, James M. The Visual Object and Space Perception Battery.; 1991.
Watson D, Clark LA, Carey G. Positive and negative affectivity and their relation to anxiety and depressive disorders. J Abnorm Psychol. 1988;97(3):346-353.

Wechsler D. WAIS-III Administration and Scoring Manual.; 1997.
Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal Dementias: A Review. Ann Gen Psychiatry. 2007;6(1):15.

Whitwell JL, Boeve BF, Weigand SD, Senjem ML, Gunter JL, Baker MC et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. Eur J Neurol. 2015.

Wilcock DM, Rojiani A, Rosenthal A, et al. Passive immunotherapy against Aβ in aged APP-transgenic mice reverses cognitive deficits and depletes parenchymal amyloid deposits in spite of increased vascular amyloid and microhemorrhage. J Neuroinflammation. 2004;1(1):24. doi:10.1186/1742-2094-1-24.

Wilson, B. Alderman, N., Burgess, P., Emslie, H., Evans J. Behavioural Assessment of the Dysexecutive Syndrome (BADS). J Occup Psychol Employ Disabil. 2003;5(2):33-37.

Woodward M, Jacova C, Black SE, et al. Differentiating the frontal variant of Alzheimer's disease. Int J Geriatr Psychiatry. 2010;25(7):732-738. doi:10.1002/gps.2415.

Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. J Clin Psychiatry. 2011.

World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Int Classif. 1992;10:1-267.
Young a W, Perrett DI, Calder a J, Sprengelmeyer R, Ekman P. Facial Expressions of Emotion: Stimuli and Tests (FEEST). Vol 126.; 2002.

Y
Young A W, Perrett DI, Calder a J, Sprengelmeyer R, Ekman P. Facial Expressions of Emotion: Stimuli and Tests (FEEST). Vol 126.; 2002.

Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in late-life depression: Common, persistent, and disabling. Am J Geriatr Psychiatry. 2015;23(5):488-494.

Z
Zalla T, Sav AM, Stopin A, Ahade S, Leboyer M. Faux pas detection and intentional action in asperger syndrome. A replication on a French sample. J Autism Dev Disord. 2009;39(2):373-382.

Zarit SH, Anthony CR BM. Interventions with caregivers of dementia patients: comparison of two approaches. Psychol Aging. 1987;2(3):225-232.

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ABOUT THE AUTHOR

Flora Toribia Gossink was born in Huancayo, Peru, on June 11th 1981. She is a daughter of two dutch parents who lived and worked in Latin America for more than five years. After graduating elementary school and high school in Groningen, the Netherlands, she studied Humanistic Studies in Utrecht, the Netherlands, and obtained her bachelor degree in 2004. In 2004, she started Medical School at the VU University in Amsterdam. As part of her doctorate she worked on a research project at the Ministry of Public Health in Mexico City. She fulfilled extra internships in internal medicine at the Hospital Clinical Universitario in Santiago de Compostela, Spain, and an extra internship in neurology at the Academic Hospital Paramaribo, Surinam. She accomplished medical school with a last internship neurology at the VU University Medical Centre. In 2010 she obtained her medical doctor degree and started to work as a resident at the department of neuropsychiatry and elderly psychiatry of the *Valeriuskliniek* in Amsterdam. Inspired by a complex patient in the *Valeriuskliniek* she wrote a case report which turned out to be the start of the current PhD research project.

After working as a resident in the *Valeriuskliniek* she worked as a resident at an outpatient psychiatric clinic for children. In 2012 she started her specialist training to become a psychiatrist and combined this with the writing of the current dissertation. She is currently completing the last year of her specialist education. Flora lives at the Zuidas Amsterdam with Elwin Johan.

LIST OF PUBLICATIONS

Gossink F, Schouws S, Krudop W, Scheltens P, Stek M, Pijnenburg Y, Dols A. Social Cognition Differentiates Behavioral Variant Frontotemporal Dementia From Other Neurodegenerative Diseases and Psychiatric Disorders. The American Journal of Geriatric Psychiatry. 2018 March.

Vijverberg EG, **Gossink F**, Krudop W, Sikkes S, Kerssens C, Prins N, Stek M, Scheltens P, Pijnenburg Y, Dols A. The Diagnostic Challenge of the Late-Onset Frontal Lobe Syndrome: Clinical Predictors for Primary Psychiatric Disorders Versus Behavioral Variant Frontotemporal Dementia. The Journal of clinical psychiatry. 2017 Oct.

Gossink FT, Vijverberg EG, Krudop W, Scheltens P, Stek ML, Pijnenburg YA, Dols A. Psychosis in behavioral variant frontotemporal dementia. Neuropsychiatric disease and treatment. 2017;13:1099.

Vijverberg EG, Dols A, Krudop WA, Milan MD, Kerssens CJ, **Gossink F**, Prins ND, Stek ML, Scheltens P, Teunissen CE, Pijnenburg YA. Cerebrospinal fluid biomarker examination as a tool to discriminate behavioral variant frontotemporal dementia from primary psychiatric disorders. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017 Jan 1;7:99-106.

Dols A, Van Liempt S, **Gossink F**, Krudop WA, Sikkes S, Pijnenburg YA, Stek ML. Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome. The Journal of clinical psychiatry. 2016 Oct;77(10):1391-5.

Vijverberg EG, Wattjes MP, Dols A, Krudop WA, Möller C, Peters A, Kerssens CJ**, Gossink F**, Prins ND, Stek ML, Scheltens P. Diagnostic accuracy of MRI and additional [18F] FDG-PET for behavioral variant frontotemporal dementia in patients with late onset behavioral changes. Journal of Alzheimer's Disease. 2016 Jan 1;53(4):1287-97.

Vijverberg EG, Dols A, Krudop WA, Peters A, Kerssens CJ, van Berckel BN, Wattjes MP, Barkhof F, **Gossink F**, Prins ND, Stek ML. Diagnostic accuracy of

the frontotemporal dementia consensus criteria in the late-onset frontal lobe syndrome. Dementia and geriatric cognitive disorders. 2016;41(3-4):210-9.

Gossink FT, Dols A, Krudop WA, Sikkes SA, Kerssens CJ, Prins ND, Scheltens P, Stek ML, Pijnenburg YA. Formal Psychiatric Disorders are not Overrepresented in Behavioral Variant Frontotemporal Dementia. Journal of Alzheimer's Disease. 2016 Jan 1;51(4):1249-56.

Gossink FT, Dols A, Kerssens CJ, Krudop WA, Kerklaan BJ, Scheltens P, Stek ML, Pijnenburg YA. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2015 Jan 24:jnnp-2014.

Gossink F, Dols A, Kerssens CJ, Scheltens P, Stek ML, Pijnenburg YA. The behavioural variant of frontotemporal dementia: A challenging diagnosis. Nederlands tijdschrift voor geneeskunde. 2013;157(42):A6370

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