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 symptomatology identical to that of 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 cerebrospinal fluid biomarkers are important in distinguishing PsD from bvFTD.

Methods: Patients with late-onset behavioral disturbances (aged 45–75 years, 73% male) were included based on their scores on the Frontal Behavioral Inventory and the Stereotypy Rating Inventory and followed for 2 years from April 2011 to June 2015. Odds ratios (ORs) were calculated with backward stepwise logistic regression analyses to investigate the association between baseline clinical and demographic variables and the 2-year follow-up diagnosis of PsD (n = 46) (*DSM-IV*) versus probable/definite bvFTD (n = 27) (International Behavioral Variant FTD Criteria Consortium criteria). We separately measured the association between additional investigations and the 2-year follow-up diagnosis. Finally, we combined the selected variables to measure the predictive value of both clinical and additional investigations in a single model.

Results: Male gender (OR = 5.9; 95% CI, 1.3–26.0), less stereotypy (OR = 0.08; 95% CI, 0.02–0.34), and more depressive symptoms (OR = 1.13; 95% CI, 1.04–1.24) explained 49% of the variance predicting PsD versus bvFTD ($\chi^2_3 = 29.4$, $P < .001$) and correctly classified 82.1% of the cases. Neuroimaging (OR = 0.02; 95% CI, 0.002–0.123) explained 55% of the variance ($\chi^2_1 = 37.5$, $P < .001$) and, in combination with clinical variables, 66.1% of the variance ($\chi^2_3 = 44.06$, $P < .001$).

Conclusions: The present study demonstrated that PsD can be distinguished from probable/definite bvFTD with a thorough clinical evaluation by a psychiatrist and neurologist along with use of validated questionnaires for depression and stereotypy; these measures are even more effective in combination with neuroimaging.

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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 neurodegenerative dementia cases.[1–3] Whereas bvFTD can be differentiated from other neurodegenerative disorders with relatively good accuracy,[4–7] 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 symptomatology identical to that of bvFTD, such as apathy, disinhibition, and stereotyped/compulsive behavior.[8,9]

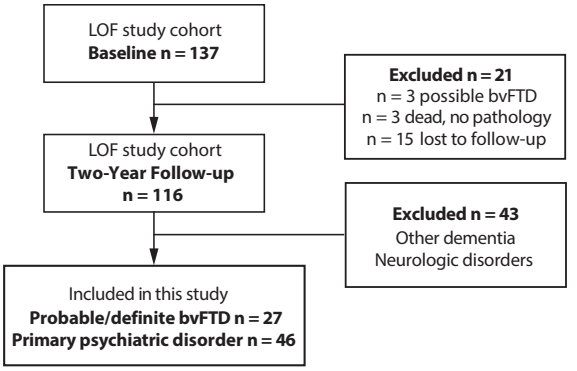
The diagnosis of bvFTD is based on the criteria of the International Behavioral Variant FTD Criteria Consortium (FTDC),[7] which include behavioral/cognitive features such as early disinhibition, apathy or inertia, loss of sympathy or empathy, stereotyped/compulsive behavior, hyperorality, and a neuropsychological profile with predominantly 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 the "behavioral disturbance is better accounted for by a psychiatric diagnosis,"[7(p2460)] and the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*)[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 to 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.[11–13] In addition, the first and crucial step for a clinical intervention trial for bvFTD or PsD is the inclusion of highly accurate diagnosis.

Clinical Points

- Male gender, less stereotypy (low Stereotypy Rating Inventory scores), more depressive symptoms (high Montgomery-Asberg Depression Rating Scale scores), and neuroimaging with absence of frontotemporal abnormalities had good abilities for predicting diagnosis of a primary psychiatric disorder rather than behavioral variant frontotemporal dementia (bvFTD) in a cohort of patients with late-onset behavior changes.
- Early recognition of primary psychiatric disorders or bvFTD and early initiation of appropriate treatment and counseling for caregivers can be gained with a thorough clinical evaluation by a psychiatrist and a neurologist in addition to use of validated questionnaires for depression and stereotypy; these measures are even more effective in combination with neuroimaging.

Figure 1. Flowchart Demonstrating Patient Selection in the Study



Abbreviations: bvFTD = behavioral variant frontotemporal dementia, LOF = Late Onset Frontal Lobe Syndrome.

In our previously 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 2 years of follow-up, 50% of patients diagnosed with bvFTD at baseline changed diagnoses, which is in contrast with a previous publication showing that more than 50% of the bvFTD cases primarily receive a psychiatric diagnosis.[11] In the current study, we included additional investigations such as neuropsychological profile, neuroimaging, and cerebrospinal fluid (CSF). To minimize the chance of misdiagnosis and so biased results, we 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 LOF study is a multicenter 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, their score on the Frontal Behavioral Inventory (FBI)[17] was ≥ 11 or the Stereotypy Rating Inventory (SRI)[18] was ≥ 10, and they were aged between 45 and 75 years.[15] 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 2-year follow-up diagnosis of possible bvFTD, as no other explanation could be found for their symptoms, cases that may be considered as bvFTD phenocopies. However, due to the open discussion on this subject, we excluded them from the final analysis. Furthermore, we excluded 3 patients who died without postmortem verification or a clear clinical diagnosis. Fifteen patients were lost to follow-up. For the current study, we selected patients with a 2-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 at baseline could distinguish between PsD and probable/definite bvFTD (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 neurologic and psychiatric examination at baseline, including a medical history, medical family history, use of medication, an informant-based history, neuropsychological assessment, and laboratory tests.[15] Furthermore, all patients underwent a magnetic resonance imaging (MRI) scan of the brain, acquired on a 3T SignaHDxt scanner (GE Medical Systems, Milwaukee, WI) using a standard dementia protocol.[16] If a normal or insufficiently explanatory MRI was found 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 to the study design and age but blinded to the patients' symptoms and medical history, evaluated the images with respect to global cortical atrophy, medial temporal lobe atrophy, and white matter hyperintensities (Fazekas scale) according to established and validated visual rating scales.[19–21] In addition, the neuroradiologist was asked to classify the MRI as consistent or not consistent with frontotemporal dementia. 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 and 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 was obtained with a lumbar puncture. It was collected in polypropylene tubes and centrifuged within an hour. The supernatant was stored in 0.5-mL aliquots at −20°C. 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 enzyme-linked immunosorbent assays (ELISAs; Fujirebio/Innogenetics, Belgium) on a routine basis.[16] A consensus diagnosis between the neurologist (Y.P., N.P., P.S.) and the psychiatrist (A.D., C.K., M.S.) was made on the basis of 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,[23–26] and the psychiatric diagnoses were based on current psychiatric criteria.[10]

After 2 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,[23–26] and the psychiatric diagnoses were based on current psychiatric criteria.[10] After 2 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.[27]

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 assess 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 5 distinct stereotypic symptoms was rated by behavior and severity with a maximum of 12 per item (range, 5–60). Higher scores on the FBI and SRI indicate more abnormal behavior or stereotypic symptoms. All clinical assessments mentioned above were performed by trained clinicians who were blind to the clinical diagnosis (F.G. and W.K.). 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 an 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 as positive and negative. Neuropsychological profile was rated positive when predominantly executive deficits with relative sparing (more than 1 *z*-score higher between domains) of memory and visuospatial function 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,[31] Letter Naming fluency,[32] and 2 subtests (Key Search and Rule Shift Cards) of the Behavioral Assessment of the Dysexecutive Syndrome.[33] For memory, the total immediate recall score of the Rey Auditory Verbal Learning Task for 15 words[34] and the visual association test[35] were used. For the visuospatial domain, 3 subtests of the Visual Object and Space Perception Battery 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, in accordance with 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 cutoff 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 *t* tests for normally distributed continuous data. Assumptions for normality were checked and if data were not normally distributed after log-transformation, a Mann-Whitney test was used (SRI was log-transformed). For categorical data, χ^2 tests were used.

We used backward stepwise logistic regression analyses (predicts the probability that an observation falls into 1 of 2 categories of a dichotomous dependent variable) to investigate the association between baseline clinical and demographic variables (based on our previous study[14]) and the 2-year follow-up diagnosis for PsD versus probable/definite bvFTD (model 1), and we separately measured the association between the additional investigations and the 2-year follow-up diagnosis (model 2). Finally, we combined the selected variables from models 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 (CIs). Selection method included backward stepwise selection with significance level of $P < .10$ 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.[38] A *P* value of < .05 was considered statistically significant except as 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 patients (5.5%) were diagnosed with definite bvFTD consisting of 2 with *C9orf72* expansion hexanucleotide repeat, 1 with progranulin mutation, and 1 with histopathologically confirmed tauopathy (Table 1). Furthermore, Table 1 illustrates that almost half of the initial bvFTD cases changed after follow-up; most changed to diagnoses of psychiatric disorders or other dementias.

Table 1. Diagnoses at Baseline and Follow-Up

	Baseline		Follow-Up[a]	
Diagnosis	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 disorder			15	
Other dementia	8	5.8	30	21.9
Neurologic diseases	23	16.8	8	5.8
Others[b]	7	5.2	5	3.6
Lost to follow-up	…	…	18	13.2
Total	137		137	

[a]Shaded area indicates patients included in the current study.
[b]Patients with subjective complaints and no psychiatric disease.
Abbreviations: bvFTD = behavioral variant frontotemporal dementia, FTD-ALS = frontotemporal dementia–amyotrophic lateral sclerosis, *GRN* mutation = progranulin mutation.

The clinical and demographic characteristics at baseline for the patients included in the current study are shown in Table 2. Patients diagnosed with a psychiatric disorder after 2 years of follow-up used more antidepressants at baseline, more often had a psychiatric history, had fewer stereotypy symptoms (lower total score on the SRI), and had 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.

Clinical/Demographic Characteristics as 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, as measured with the SRI (OR = 0.08; 95% CI, 0.02–0.34); and more depressive symptoms, as measured with the MADRS (OR = 1.13; 95% CI, 1.04–1.24). The clinical and demographic variables psychiatric history, symptom duration, MMSE, education in years, age, FAB, and FBI were not significant in predicting PsD versus probable/definite bvFTD and were excluded from the model. The combination

Table 2. Baseline Clinical and Demographic Characteristics per Diagnostic Group at Follow-Up

Characteristic	Probable/Definite bvFTD (n = 27)	Psychiatric Disorders (n = 46)	*P* Value[a]
Age, mean (SD), y	62.9 (6.7)	60.0 (6.4)	.71
Male gender, n (%)	16 (59%)	37 (80%)	.05[b]
Education, mean (SD), y	10.2 (2.6)	9.9 (2.4)	.63
Disease duration, mean (SD), y	5.37 (5.1)	3.7 (2.6)	.13
Positive psychiatric history, n (%)	5 (19%)	25 (53%)	<.01[b,*]
FBI, mean (SD)	26.3 (10.4)	25.9 (9.1)	.87
SRI, median (IQR)	15 (16)	4 (8)	<.01[c,*]
MADRS, mean (SD)	8.5 (6.1)	15.2 (10.2)	<.01*
MMSE, mean (SD)	26.08 (2.7)	26.3 (2.8)	.87
FAB, mean (SD)	14.4 (4.0)	14.8 (3.0)	.72
Neuropsychological profile with executive dysfunction, n (%)	10 (37%)	9 (20%)	.08[b]
MRI of brain with frontotemporal atrophy, n (%, missing)	19 (70%, n = 0)	3 (6.8%, n = 2)	<.01[b,*]
FDG-PET with frontotemporal hypometabolism, n (%, missing)	10 (91%, n = 16)	12 (32.4%, n = 9)	<.01[b,*]
CSF tau positive > 375 pg/mL, n (%, missing)	7 (30.4%, n = 4)	5 (15.2%, n = 13)	.17[b]
CSF amyloid-β1-42 positive < 550 pg/mL, n (%, missing)	4 (17.4%, n = 4)	10 (30.3%, n = 13)	.27[b]
CSF ptau positive > 52 pg/mL, n (%, missing)	0 (0%, n = 4)	3 (9%, n = 13)	.14[b]
Use of sedatives, n (%)	0 (0%)	3 (7%)	.17[b]
Use of antidepressants, n (%)	5 (19%)	23 (50%)	.01[b,*]
Use of antipsychotics, n (%)	0 (0%)	6 (13%)	.48[b]

[a]Independent *t* tests, unless otherwise stated.
[b]χ^2 test.
[c]Mann-Whitney test.
*$P \leq .01$.
Abbreviations: CSF = cerebrospinal fluid, FAB = Frontal Assesment Battery, FBI = Frontal Behavioral Inventory, FDG-PET = [^{18}F]-fluorodeoxyglucose positron emission tomography, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, SRI = Stereotypy Rating Inventory.

Table 3. Results of Backward Stepwise Logistic Regression Analyses for Variables Predicting Primary Psychiatric Disorders Versus Behavioral Variant Frontotemporal Dementia

	OR (95% CI)	*P* Value[a]
Model 1		
Male gender	5.91 (1.34–26.03)	.019
MADRS	1.13 (1.04–1.24)	.007
SRI (log-transformed)	0.08 (0.02–0.34)	.001
Model 2		
Neuroimaging consistent with FTD findings	0.02 (0.002–0.123)	.001
Model 3		
MADRS	1.10 (1.01–1.22)	.030
SRI (log-transformed)	0.22 (0.04–1.18)	.077
Neuroimaging consistent with FTD findings	0.02 (0.02–0.21)	.001

[a]Significant at $P \leq .10$.
Abbreviations: FTD = frontotemporal dementia, MADRS = Montgomery-Asberg Depression Rating Scale, SRI = Stereotypy Rating Inventory.

of these 3 predictors explained 49% (Nagelkerke R^2) of the variance ($\chi^2_3 = 29.4$, $P < .001$) and correctly classified 82.1% of the cases (Table 3).

Additional Investigations for 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% CI, 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 ($\chi^2_1 = 37.5$, $P < .001$) and correctly classified 80.8% of the cases.

Combination of Clinical/Demographic Characteristics and Additional Investigations as 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% CI, 0.002–0.21), less stereotypy measured with the SRI (OR = 0.08; 95% CI, 0.02–0.34), and more depressive symptoms measured with the MADRS (OR = 1.13; 95% CI, 1.04–1.24). Model 3 explained 66.1% (Nagelkerke R^2) of the variance in diagnosis of PsD versus probable/definite bvFTD ($\chi^2_3 = 44.06$, $P < .001$) 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 had good predictive 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 PsD versus probable/definite bvFTD with 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.[14] However, the clinical variables male gender, low SRI score, and high MADRS score were 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 of bvFTD compared to psychiatric disorders.[39] However, we found that stereotypic/compulsive behavior assessed with the SRI appeared to be better than other types of abnormal behavior measured with the FBI at predicting primary psychiatric disorders versus bvFTD.[40,41] This finding could be explained by the fact that in our present cohort primary psychiatric diagnosis presenting with stereotyped/compulsive behaviors 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 our cohort included predominantly mood disorders. However, it is a remarkable finding, as we also know that 33% of patients with bvFTD demonstrate depressive symptoms.[42] In addition, apathy is considered a bvFTD symptom[7]; however, it can also occur in the course of depression.[43,44] Consequently, this intertwinement of symptoms contributes to the difficulty to distinguish between bvFTD or mood disorders in daily clinical practice.[11] 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 PsD from bvFTD[30] by differentiating between symptoms of depression and apathy. More specifically, patients with behavioral changes and a higher score on the MADRS are more likely to have a diagnosis of PsD than bvFTD.

It is somewhat surprising that the total scores of the FBI and FAB, the instruments most used clinically, were found not to be able to differentiate between PsD and bvFTD. For the FAB, there are 2 likely explanations for this finding. First, executive dysfunction as measured with the FAB is not unique to bvFTD; those with PsD also have executive dysfunction in both active and remitted psychiatric states.[45] Second, the FAB has previously been found to be a poor discriminator; however, it was analyzed only between types

of dementia.[46,47] Overall, it can thus be suggested that this instrument is useful to screen only 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 association of neuroimaging. However, gender as a predictor for PsD versus probable/definite bvFTD should be taken with caution, because FTD is considered to have an equal gender incidence,[48] with some studies reporting even an overrepresentation of male gender.[3,7] Psychiatric disorders, in contrast, show varying gender distributions across disorders.[49]

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.[4,7,50] 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.[51,52]

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,[53] 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 significant contributors in predicting PsD versus probable/definite bvFTD was not surprising, because the standard biomarkers used in this study have previously been described to be nonspecific for probable/definite bvFTD or psychiatric disorders.[54] 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 the 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 behavioral 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. Also, 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 includes more psychiatric bvFTD mimics, such as schizophrenia and obsessive-compulsive disorder. Additional psychiatric symptoms, such as psychotic features, should also 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 2-year follow-up diagnosis as dependent variable, we attempted to avoid this. By dichotomizing the additional investigations as 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 behavioral 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 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 recognition of primary psychiatric disorders or bvFTD and an early start with appropriate treatment and counseling for caregivers are to be gained with these measures. 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.

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REFERENCES

1. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord*. 2004;17(4):265–268.
2. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *Br J Psychiatry*. 2002;180(2):140–143.
3. Ratnavalli E, Brayne C, Dawson K, et al. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615–1621.
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.
5. Mendez MF, Shapira JS, McMurtray A, et al. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007;64(6):830–835.
6. Piguet O, Hornberger M, Shelley BP, et al. Sensitivity of current criteria for the diagnosis

of behavioral variant frontotemporal dementia. *Neurology*. 2009;72(8):732–737.
7. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(pt 9):2456–2477.
8. Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. *J Neurol Neurosurg Psychiatry*. 2016;87(5):501–511.
9. Ducharme S, Price BH, Larvie M, et al. Clinical approach to the differential diagnosis between behavioral variant frontotemporal dementia and primary psychiatric disorders. *Am J Psychiatry*. 2015;172(9):827–837.
10. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
11. Woolley JD, Khan BK, Murthy NK, et al. 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.
12. Shinagawa S, Catindig JA, Block NR, et al. When a little knowledge can be dangerous: false-positive diagnosis of behavioral variant frontotemporal dementia among community clinicians. *Dement Geriatr Cogn Disord*. 2016;41(1–2):99–108.
13. 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.
14. 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;77(10):1391–1395.
15. Krudop WA, 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.
16. van der Flier WM, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41(1):313–327. 10.3233/JAD-132306
17. Kertesz A, Nadkarni N, Davidson W, et al. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. *J Int Neuropsychol Soc*. 2000;6(4):460–468.
18. Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res*. 2002;110(2):175–187.
19. Scheltens P, Launer LJ, Barkhof F, et al. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol*. 1995;242(9):557–560.
20. Koedam ELGE, Lehmann M, van der Flier WM, et al. Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol*. 2011;21(12):2618–2625.
21. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149(2):351–356.
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 Alzheimers Dis*. 2016;53(4):1287–1297.
23. 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. *Alzheimers Dement*. 2011;7(3):263–269.
24. McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.
25. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006–1014.
26. 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.
27. 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.
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.
29. Dubois B, Slachevsky A, Litvan I, et al. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621–1626.
30. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
31. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(3):271–276.
32. Benton AL, Hamsher K. *Multilingual Aphasia Examination*. Iowa City, IA: University of Iowa; 1976.
33. Wilson BA. *Behavioural Assessment of the Dysexecutive Syndrome*. Bury St Edmunds, UK: Thames Valley Test Company; 1996.
34. Rey A. *L'examen Clinique en Psychologie*. Paris, France: Presses Universitaires de France; 1964.
35. Lindeboom J, Schmand B, Tulner L, et al. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry*. 2002;73(2):126–133.
36. Warrington EK, James M. *The Visual Object and Space Perception Battery*. Bury St Edmunds, UK: Thames Valley Test Company; 1991.
37. Duits FH, Teunissen CE, Bouwman FH, et al. The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean? *Alzheimers Dement*. 2014;10(6):713–723.e2.
38. Midi H, Sarkar SK, Rana S. Collinearity diagnostics of binary logistic regression model. *Journal of Interdisciplinary Mathematics*. 2010;13(3):253–267.
39. Rankin KP, Santos-Modesitt W, Kramer JH, et al. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. 2008;69(1):60–73.
40. Bathgate D, Snowden JS, Varma A, et al. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand*. 2001;103(6):367–378.
41. Mendez MF, Perryman KM, Miller BL, et al. Compulsive behaviors as presenting symptoms of frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 1997;10(4):154–157.
42. Chakrabarty T, Sepehry AA, Jacova C, et al. The prevalence of depressive symptoms in frontotemporal dementia: a meta-analysis. *Dement Geriatr Cogn Disord*. 2015;39(5-6):257–271.
43. Landes AM, Sperry SD, Strauss ME, et al. Apathy in Alzheimer's disease. *J Am Geriatr Soc*. 2001;49(12):1700–1707.
44. Ishii S, Weintraub N, Mervis JR. Apathy: a common psychiatric syndrome in the elderly. *J Am Med Dir Assoc*. 2009;10(6):381–393.
45. 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.
46. Castiglioni S, Pelati O, Zuffi M, et al. The frontal assessment battery does not differentiate frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2006;22(2):125–131.
47. Boban M, Malojcić B, Mimica N, et al. The frontal assessment battery in the differential diagnosis of dementia. *J Geriatr Psychiatry Neurol*. 2012;25(4):201–207.
48. Rosso SM, Donker Kaat L, Baks T, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain*. 2003;126(pt 9):2016–2022.
49. Kessler RC, McGonagle KA, 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.
50. 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.
51. 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(pt 3):706–720.
52. Whitwell JL, Boeve BF, Weigand SD, et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. *Eur J Neurol*. 2015;22(5):745–752.
53. 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;41(1–2):16–26.
54. Schoonenboom NSM, Reesink FE, Verwey NA, et al. Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology*. 2012;78(1):47–54.

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