Cognitive Deficits in Patients With Neuropsychiatric Symptoms: A Comparative Study Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders

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ABSTRACT

Objective: To compare neuropsychological profiles in behavioral variant frontotemporal dementia (bvFTD) with its most common primary psychiatric differential diagnoses, major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia, in older patients with active symptoms.

Methods: We included patients from different cohorts with MDD (*DSM-IV-TR*: 296.20–296.23, 296.30–296.33; n = 42; mean ± SD age, 72.0 ± 8.0 years; female = 57.1%) included from 2002 to 2007, noneuthymic BD (*DSM-IV-TR*: 296.00–296.06, 296.40–296.46, 296.50–296.56, 296.60–296.66, 296.7; *DSM-IV-TR*: 296.89; *DSM-IV-TR*: 296.80; n = 41; age, 71.7 ± 8.8 years; female = 53.7%) included from 2011 to 2015, nonremitted schizophrenia (*DSM-IV-TR*: 295.10, 295.20, 295.30, 295.60, 295.90; n = 47; age, 67.5 ± 7.1 years; female = 66%) included from 2006 to 2008, or probable/definite bvFTD (n = 173; age, 62.6 ± 8.0 years; female = 39.9%) (Frontotemporal Dementia Consensus criteria) included from 2000 to 2015 and healthy controls (n = 78; age, 71.9 ± 8.0 years; female = 71.8%) included from 2005 to 2007. Neuropsychological tests concerned the domains of attention and working memory, verbal memory, verbal fluency, and executive functioning. Analyses of variance were performed with age, gender, and education level as covariates. Post hoc Bonferroni tests were used to detail group differences.

Results: Compared to the healthy controls, both the bvFTD and primary psychiatric disorder groups showed significant impairment on all cognitive domains. Executive function was more disturbed in all primary psychiatric disorders compared to bvFTD ($P < .001$). Attention and working memory were significantly better in the bvFTD and schizophrenia groups compared to the MDD and BD groups ($P < .001$). For verbal memory, the bvFTD group scored significantly higher compared to patients with schizophrenia, BD, or MDD ($P < .001$). Patients with bvFTD had significantly lower scores on verbal fluency, especially due to Animal Naming, in comparison with the BD group ($P < .001$); however, these scores were not significantly different from those of MDD or schizophrenia patients.

Conclusions: Cognitive deficits in bvFTD are less severe than in primary psychiatric disorders with active symptoms. This indicates that in the differential diagnosis of bvFTD, disturbances on tests for cognitive performance do not rule out primary psychiatric diagnoses.

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Behavioral variant frontotemporal dementia (bvFTD) is clinically characterized by fundamental changes in the regulation of social, interpersonal, and personal conduct. 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] Whereas the hallmark of Alzheimer's disease is early memory and visuospatial deficits on neuropsychological assessment,[2] bvFTD is characterized by a neuropsychological profile that consists of executive deficits with relative sparing of memory and visuospatial functions.[3] Although clinical differentiation between bvFTD and Alzheimer's disease can be difficult since anterograde amnesia is occasionally found as an initial feature in bvFTD as well,[4,5] neuropsychological profiles are helpful in discerning these types of dementia. However, it is unknown how useful neuropsychological assessment is in differentiating bvFTD from primary psychiatric disorders, since they have similar clinical presentations.

Clinical overlap between bvFTD and primary psychiatric disorders is mainly on behavioral and mood features such as disinhibition, social inappropriateness, loss of decorum, impulsivity, apathy, euphoria, and irritability. Consequently, bvFTD is often misdiagnosed as a psychiatric disorder such as major depressive disorder (MDD), bipolar disorder (BD), or schizophrenia,[6] or vice versa. In the absence of definite biomarkers, diagnosis of these psychiatric disorders is still based on clinical judgment and guidelines.[7] For bvFTD, the consensus criteria developed by an international expert consortium (Frontotemporal Dementia Consensus [FTDC])[3] are used. Since primary psychiatric disorders are treatable, the need for accurate discriminating features between bvFTD and primary psychiatric disorders is crucial. Furthermore, as stated in the FTDC criteria, a diagnosis of bvFTD is to be excluded

Clinical Points

- It is unknown how useful neuropsychological assessment is in differentiating behavioral variant frontotemporal dementia (bvFTD) from primary psychiatric disorders having similar clinical presentations.
- Clinically, the findings of this study indicate that in the differential diagnosis of bvFTD, cognitive impairment measured with neuropsychological tests does not rule out primary psychiatric diagnoses.

when "behavioral disturbance is better accounted for by a psychiatric diagnosis."[3]

In the bvFTD consensus criteria, one of the 6 clinical features for *possible* bvFTD is a neuropsychological profile that predominantly includes executive deficits.[3] Although cognitive deficits are not included in the clinical guidelines for primary psychiatric disorders, they are frequently reported in the most common psychiatric misdiagnosis for bvFTD, MDD, BD, and schizophrenia.[8–10] Affective disorders such as MDD and BD are associated with impairment in attention, psychomotor speed, memory, and executive dysfunction.[8,10] As for schizophrenia, comparable profiles are found with more severe impairment in memory and executive functions.[9]

Although primary psychiatric disorders are clinically very relevant in the differential diagnosis of bvFTD, studies comparing neuropsychological profiles across primary psychiatric disorders and bvFTD are lacking. Therefore, we set out to compare neuropsychological profiles in bvFTD with the most common psychiatric bvFTD differential diagnoses, MDD, BD, and schizophrenia,[6] in older patients with active psychiatric symptoms. In its selection of bvFTD and primary psychiatric patients with active symptoms, this study resembles clinical practice, where patients present with behavioral and mood symptoms and neuropsychological assessment is used as a diagnostic tool. Based on the findings of former comparative studies,[11–14] we hypothesize that the executive functions in bvFTD are more impaired in comparison with MDD and BD and that memory and attention are better in bvFTD than in MDD and BD. In comparison with schizophrenia, memory deficits might be less prominent or equal in bvFTD, and on executive function, both disorders might show the same impairment.

METHODS

Participants

We included subjects from 5 different cohorts that included MDD (n = 42), noneuthymic BD (n = 41), nonremitted schizophrenia (n = 47), probable/definite bvFTD (n = 173), and healthy controls (n = 78) (details described below). Patients with bvFTD were recruited from the Amsterdam Dementia Cohort,[15] and patients with primary psychiatric disorders and controls were recruited from the GGZinGeest Department of Old Age Psychiatry, Amsterdam, The Netherlands.[14,16] From these cohorts, patients were included if they were older than 45 years, had a psychiatric diagnosis with current symptoms or probable/definite bvFTD, and had undergone a neuropsychological assessment at first presentation of current episode. None of the psychiatric patients were diagnosed with dementia. The study was approved by the Medical Ethical Committee of the VU Medical Center, Amsterdam, and a written informed consent statement was obtained from all participants.

Major Depressive Disorder

Patients with MDD were included out of a group of patients who were referred to GGZinGeest for treatment with electroconvulsive therapy (ECT) between 2002 and 2007.[16] From the 72 depressed patients, 42 patients were able to complete a neuropsychological assessment before receiving ECT. They were eligible if they had been diagnosed with MDD based on the *DSM-IV* criteria[7] (*DSM-IV-TR*: 296.20–296.23, 296.30–296.33). The Montgomery-Asberg Depression Rating Scale (MADRS; range, 0–60)[17] and Center for Epidemiologic Studies Depression Scale (CES-D; range, 0–60)[18] were completed in every patient with MDD.

Bipolar Disorders

Patients with BD were selected from the outpatient clinic GGZinGeest between 2011–2015 and were assessed by experienced old age psychiatrists with the Structured Clinical Interview for *DSM-IV* Axis I Disorders[19] to confirm the bipolar diagnosis. They were eligible for the study if they were community-living and were diagnosed with bipolar I disorder (*DSM-IV-TR*: 296.00–296.06, 296.40–296.46, 296.50–296.56, 296.60–296.66, 296.7), bipolar II disorder (*DSM-IV-TR*: 296.89), or bipolar disorder not otherwise specified (*DSM-IV-TR*: 296.80).[20] Of the 41 patients with BD, 20 were in a manic state, and 21 were in a depressive state. The severity of manic and depressive symptoms was assessed by the Young Mania Rating Scale (YMRS)[20] and the CES-D.

Schizophrenia

For the schizophrenia group, data were from a study conducted between March 2006 and September 2008.[14] In this study, patients with schizophrenia spectrum disorders were screened if they were in contact with the local mental health organization and were 60 years or older. They were eligible for the study if they had been diagnosed with schizophrenia (*DSM-IV-TR*: 295.10, 295.20, 295.30, 295.60, 295.90),[7] which was determined by the Mini-International Neuropsychiatric Interview Plus (MINI-Plus).[21] The Positive and Negative Syndrome Scale (PANSS)[22] was used to assess the symptomatic state of schizophrenia patients.[14] Of 67 patients with schizophrenia, 20 were in symptomatic remission (29.9%), defined as a score of 3 or less on 8 items of the PANSS. Therefore, only the 47 nonremitted patients were included in the present study.

Behavioral Variant Frontotemporal Dementia

bvFTD patients were retrieved from the outpatient memory clinic of the Alzheimer Center of the VU University

Medical Center between 2000 and 2015. In the Amsterdam Dementia Cohort, 260 patients with bvFTD were included, and of these patients, 173 fulfilled the inclusion criteria for this study; that is, they had undergone the required neuropsychological examinations. Some patients had missing data mainly due to severe behavioral disturbances, such as disinhibition or motivational disorders; however, we included these patients. For the diagnostic procedure, patients underwent a standardized 1-day assessment, which includes a medical and neurologic assessment including the medical history and a cognitive assessment by a neurologist, informant-based history, neuropsychological assessment, and additional investigations (additional information on the assessment is provided elsewhere[15]). In a multidisciplinary consensus meeting, the diagnosis probable/definite bvFTD was made according to the consensus guidelines for bvFTD.[3]

Healthy Controls

Healthy controls were recruited in the region of Amsterdam, The Netherlands, between 2005–2007, via advertisements in local newspapers and community centers. None of the healthy controls had recent memory problems or lifetime history psychiatric disorders, which was determined through a medical assessment including medical history. The absence of manic/depressive symptoms was assessed by the YMRS and the CES-D.

Neuropsychological Assessment

Neuropsychological assessment in the primary psychiatric patient groups and healthy controls was performed in GGZinGeest, and for the bvFTD group, the assessment was performed in the Alzheimer Center of the VU University Medical Center. To assess global cognitive performance, we used the MMSE[23] in bvFTD, MDD, BD, and schizophrenia patients and healthy controls. The neuropsychological test batteries were all designed to screen the major cognitive functions including attention/working memory, verbal memory, verbal fluency, and executive functioning. The following tests were selected and were used in all cohorts: Digit Span Test from the Wechsler Adult Intelligence Scale-III (WAIS-III)[24] and Trail Making Test part A (TMT A)[25] to assess attention, working memory, and mental speed. For verbal memory, in the bvFTD group, the Rey Auditory Verbal Learning Test (RAVLT) for 15 words was used, and in the primary psychiatric disorder groups and healthy controls, the RAVLT Test 10 words test was used.[26] The Animal Naming fluency (Category Fluency)[27] and Letter Naming fluency (Letter D)[28] were used to assess verbal ability and language skills. Furthermore, executive function was assessed by the Trail Making Test part B (TMT B)[25] and an abbreviated version of the Stroop Color-Word Test (interference test).[29]

Statistical Analysis

Data analysis was performed using IBM SPSS statistics version 22.0 (IBM SPSS Statistics, Armonk, NY) for Mac. Clinical and demographical data were compared with the 1-way analysis of variance test for numerical data—assumptions for normality were checked and, if not normally distributed after log-transformation, Kruskal-Wallis test was used—and χ^2 tests were used for categorical data. TMT A, TMT B, and Stroop test were log-transformed because they were not normally distributed. All neuropsychological data were transformed into z-scores standardized to the performance of the healthy control group. TMT A, TMT B, and Stroop scores were inverted by computing $-1 \times$ score, because higher scores imply worse performance. The z-scores were then averaged to provide a single composite score for each of the 4 domains ($z > -1.5$ rated as no impairment). Differences in cognitive performance in the cognitive domains between the 5 groups were examined using analysis of covariance (ANCOVA) with age, gender, and education level included as covariates. Post hoc Bonferroni tests were used to detail group differences. Multiple imputation techniques were applied to account for missing values. In our study, 32.1% of the subjects had 1 or more missing values, with a maximum of 9 missing values. The imputation method used was multivariate imputation by chained equations (MICE). We applied the imputation method 10 times to the incomplete data set and pooled the data before using ANCOVA. Statistical significance was set at $P < .05$.

RESULTS

Demographic and Clinical Features

Age, age at onset, and gender were significantly different between the groups (Table 1). bvFTD patients were the youngest compared to the primary psychiatric disorder groups and healthy controls ($P < .001$). Earlier age at onset ($P < .001$) was found for schizophrenia and BD patients compared to the bvFTD group. In the bvFTD group, there were fewer women compared to the other groups ($P < .001$). The mean current symptom duration in the bvFTD group was 3.3 years, with a mean Clinical Dementia Rating of 0.87 (SD = 0.48) (data not shown), and for the MDD group, 1.0 year; for the BD and schizophrenia groups, these data were missing. Education level for MDD patients was lower compared to the other psychiatric disorder groups, the bvFTD group, and healthy controls. As expected, usage of antipsychotics, antidepressants, mood stabilizers, and benzodiazepines was different among the groups. Bipolar patients in a manic state (mean ± SD; 13.9 ± 8.4) had higher scores on the YMRS than those in a depressive state (mean ± SD; 2.0 ± 3.8) (data not shown). MMSE score was significantly lower in bvFTD compared to all the primary psychiatric disorders ($P < .001$).

Neuropsychological Profiles

The individual neuropsychological tests are shown in Table 2 with the z-scores for the 4 cognitive domains. Figure 1 shows the performance (z-scores) of the 4 cognitive domains in the 4 groups, where the healthy controls had a z-score near zero. In general, the neuropsychological profile of bvFTD patients showed no impairment; however, they

Table 1. Clinical and Demographic Features

	Probable/ Definite bvFTD	Schizophrenia	Bipolar Disorder	Major Depressive Disorder	Healthy Controls	P Value[a]	F/χ^2 (df)	Pairwise Comparisons
n	173	47	41	42[b]	78			
Age, mean (SD), y	62.6 (8.0)	67.5 (7.1)	71.7 (8.8)	72.0 (8.0)	71.9 (8.0)	<.001	F=28.2 (4)	HC, BD, MDD > SZ > bvFTD
Gender, female, n (%)	69 (39.9)	31 (66.0)	22 (53.7)	24 (57.1)	56 (71.8)	<.001[c]	χ^2=26.7 (4)	HC, MDD, BD, SZ > bvFTD
Education, n (%)[d]						<.001[c]	χ^2=82 (8)	HC, bvFTD, SZ, BD > MDD
Low	19 (12.3)	14 (29.8)	6 (15.0)	25 (71.4)	5 (6.4)			
Medium	82 (52.9)	21 (44.7)	17 (42.5)	3 (8.6)	37 (47.4)			
High	54 (34.8)	12 (25.5)	17 (42.5)	7 (20.0)	36 (46.2)			
Age at onset, mean (SD), y	59.2 (8.8)	39.3 (17.2)	44.0 (20.2)	…	…	<.001	F=55.1 (2)	bvFTD > SZ, BD
Current symptoms duration, mean (SD), y	3.3 (2.9)	…	…	1.0 (1.2)	…			
Antipsychotics, n (%)	7 (4.0)	37 (78.7)	25 (61)	20 (47.6)	…	<.001[c]	χ^2=135.7 (3)	SZ > BD > MDD > bvFTD
Antidepressants, n (%)	18 (10.4)	5 (10.6)	13 (31.7)	36 (85.7)	…	<.001[c]	χ^2=115.5 (3)	MDD > BD, SZ > bvFTD
Lithium, n (%)	1 (0.6)	0 (0)	18 (43.9)	10 (23.8)	…	<.001[c]	χ^2=87.1 (3)	BD > MDD > SZ, bvFTD
Benzodiazepines, n (%)	12 (6.9)	…	18 (43.9)	24 (57.1)	…	<.001[c]	χ^2=68 (2)	MDD > BD > bvFTD
Mood stabilizers, n (%)	1 (0.6)	0 (0)	9 (22.0)	…	…	<.001[c]	χ^2=18.8 (2)	BD > bvFTD, SZ
MADRS, mean (SD)	…	…	…	33.9 (10.2)	…			
CES-D, mean (SD)	…	14.3 (11.0)	19.1 (15.2)	35.5 (10.9)	8.6 (5.4)	<.001	F=56.8 (3)	MDD > SZ, BD > HC
YMRS, mean (SD)	…	10.2 (4.9)	7.9 (8.8)	…	0.1 (0.4)	<.001	F=65.2 (2)	SZ, BD > HC
PANSS, mean (SD)	…	64 (11.9)	…	…	…			
MMSE, mean (SD)	24.1 (4.5)	27.6 (2.3)	26.7 (2.9)	26.2 (3.9)	29 (1.1)	<.001[e]	χ^2=123.4 (4)	HC > SZ, BD, MDD > bvFTD

[a]Significant at P < .05. Analysis of variance, unless otherwise stated.
[b]Missing 1 case.
[c]χ^2 test.
[d]Education data were missing for some subjects as follows: n = 18 missing in probable/definite bvFTD group, n = 1 missing in bipolar disorder group, n = 10 missing in major depressive disorder group.
[e]Kruskal-Wallis test.
Abbreviations: BD = bipolar disorder, bvFTD = behavorial variant frontotemporal dementia, CES-D = Center for Epidemiologic Studies Depression Scale, HC = healthy controls, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale, SZ = schizophrenia, YMRS = Young Mania Rating Scale.
Symbol: … = missing or not applicable.

Table 2. Comparison in Cognitive Performance Between Probable/Definite bvFTD, Schizophrenia, Bipolar Disorder, and Major Depressive Disorder Patient Groups and Healthy Controls[a]

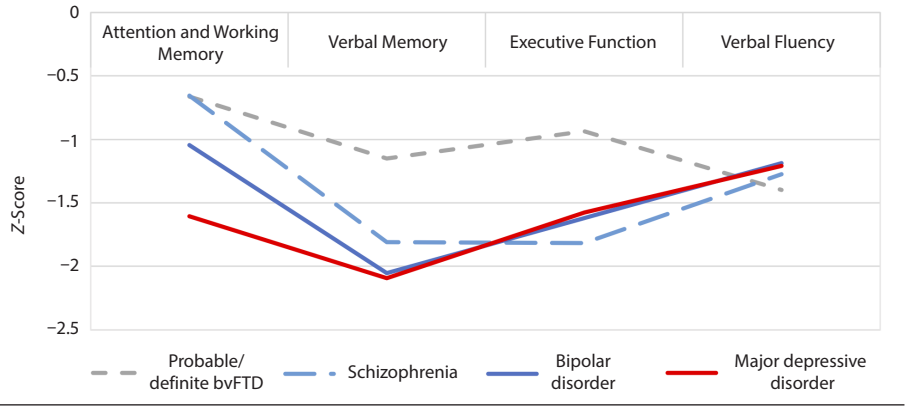
	Probable/Definite bvFTD (N = 173)		Schizophrenia (N = 47)		Bipolar Disorder (N = 41)		Major Depressive Disorder (N = 42)		Healthy Controls (N = 78)		P Value[b]	Pairwise Comparison[c]
Attention and working memory, z-scores	−0.583	n	−0.587	n	−0.975	n	−1.627	n	0.203	n	<.001	HC > SZ, bvFTD > BD > MDD
Digit span, forward	5.0 (1.1)	173	6.0 (1.0)	46	5.1 (0.9)	40	4.1 (1.4)	41	5.7 (1.0)	78		
Digit span, backward	3.8 (0.9)	165	3.9 (1.0)	46	3.4 (1.2)	40	3.0 (1.0)	41	4.7 (1.1)	78		
Trails A, sec	66.1 (49.7)	165	102.5 (76.6)	46	93.5 (58.1)	41	93.2 (65.5)	36	47 (19.6)	78		
Verbal memory, z-scores	−1.435		−1.839		−2.045		−2.099		0.001		<.001	HC > bvFTD > SZ, BD, MDD
Words learning	28.1 (10.6)	153	25.0 (7.5)	46	25.2 (7.8)	38	25.0 (7.9)	38	37.4 (5.8)	78		
Words retention	4.4 (3.5)	152	3.7 (2.3)	46	2.9 (2.3)	37	3.3 (2.3)	38	6.7 (2.0)	78		
Executive function, z-scores	−1.009		−1.833		−1.660		−1.741		0.211		<.001	HC > bvFTD > SZ, BD, MDD
Trails B, sec	136.7 (67.2)	128	257.6 (113.8)	46	290.4 (163.1)	39	166.8 (80.4)	26	109.7 (58.7)	78		
Stroop, interference, sec	63.5 (30.6)	123	86.5 (48.6)	47	68.7 (27.7)	32	77.2 (27.3)	30	45.3 (12.8)	78		
Verbal fluency, z-scores	−1.371		−1.274		−1.196		−1.298		0.000		<.001	HC > MDD, SZ, bvFTD; BD > bvFTD
Animal naming	13.3 (6.2)	162	14.4 (5.4)	47	16.3 (5.8)	37	15.2 (5.8)	39	23.2 (6.0)	78		
Letter naming (D)	7.3 (4.1)	135	7.3 (3.6)	47	7.2 (4.2)	35	7.9 (3.6)	36	12.9 (5.2)	78		

[a]Z-scores presented as mean values; raw scores presented as mean (SD).
[b]Significant at P < .05. Analysis of covariance adjusted for age, gender, and education level.
[c]Post hoc Bonferroni test.
Abbreviations: BD = bipolar disorder, bvFTD = behavioral variant frontotemporal dementia , HC = healthy controls, MDD = major depressive disorder, SZ = schizophrenia.

scored significantly lower than healthy comparison subjects on verbal fluency, verbal memory, and executive functions with relative sparing of attention. MDD patients showed impairment on verbal memory, attention, and executive functions and relative sparing of verbal fluency. Subjects with BD showed impairment on verbal memory and executive problems, with relative sparing of attention and verbal fluency. Schizophrenia patients had problems with verbal memory and executive functions, with relative sparing of verbal fluency and attention.

The differences between the 5 groups with respect to their performance on the 4 cognitive domains were examined

Figure 1. *Z*-Scores of the Individual Cognitive Domains



using ANCOVAs with age, gender, and education level included as covariates and with post hoc Bonferroni tests (Table 2). All disorder groups had significant cognitive impairment in contrast to healthy controls. bvFTD patients had the best performance on the tests that measured executive functions compared to all primary psychiatric disorder groups, especially compared with schizophrenia patients. In addition, bvFTD patients scored significantly higher on verbal memory compared to schizophrenia, MDD, and BD patients. Moreover, MDD and BD patients both had the lowest performance on the verbal memory tests. Attention and working memory were significantly better in bvFTD and schizophrenia patients compared to BD and MDD patients. bvFTD patients had the lowest scores on verbal fluency; however, they were not significantly different in relation to schizophrenia and MDD patients. Compared to BD patients, verbal fluency in bvFTD patients was significantly lower only on Animal Naming.

DISCUSSION

We set out to compare neuropsychological profiles of patients with bvFTD, MDD, BD, and schizophrenia and found that all patient groups had significantly lower scores on the cognitive test in contrast to healthy controls. Comparison between disorders showed that bvFTD patients had less severe deficits on executive functions and verbal memory tests compared to all 3 primary psychiatric disorder groups. On the other hand, bvFTD patients had more difficulties with tests of verbal fluency, more specifically on Animal Naming. However, in our study these scores were significantly different compared only with the scores of BD patients. Attention/working memory was most impaired in MDD patients compared to BD, schizophrenia, and bvFTD patients.

Contrary to our hypothesis, we found more severe impairment on executive tasks in patients with primary psychiatric disorders than in bvFTD patients. As expected, executive tasks were impaired in all patient groups; however, the more severe impairment in primary psychiatric disorders has not been found before.[12] Previous studies reported more difficulties with executive tasks in bvFTD compared to other types of dementia,[30] which can be explained by the specific neurodegeneration in the frontotemporal cortex in bvFTD.[31] For primary psychiatric disorders, the level of impairment on executive tasks can partly be explained by the severity of psychotic symptoms in schizophrenia and mood state in BD and MDD,[32,33] since these psychiatric symptoms derive from the same dysfunction of the fronto-subcortical neural circuits as executive dysfunction.[34,35] However, besides this state-dependent executive dysfunction, there is also substantial evidence that these primary psychiatric disorders in a euthymic or remitted state show stable although less severe executive impairment compared to a noneuthymic or nonremitted state,[8,14,36] suggesting a persistent dysfunction of the fronto-subcortical neural circuits. Although we did not include euthymic or remitted psychiatric disorders, our findings still imply that a higher level of impairment on executive tasks is not an argument to rule out primary psychiatric disorders in the differential diagnosis of bvFTD.

Another important finding was that patients with bvFTD showed less verbal memory deficits than primary psychiatric disorders. Our findings reproduce previous reports where memory is less impaired in bvFTD patients[37] and predominantly found to be impaired in primary psychiatric disorders such as MDD and BD.[38] Relatively spared memory deficits in bvFTD can be linked to pathological changes in bvFTD that involve mainly the orbitofrontal and dorsolateral prefrontal cortex[39] and to a lesser extent the hippocampal region, which is primarily associated with memory functions.[40] In mood disorders, there is growing evidence that there are changes in the hippocampal region, for example, caused by neuroinflammation during mood episodes, which may lead to verbal memory impairment.[41,42] Furthermore, we found less severe impairment of verbal memory in bvFTD compared to schizophrenia. In a previous study in which bvFTD was compared with inpatient and outpatient chronic schizophrenia, memory performance was less impaired in both schizophrenia groups compared to the group with bvFTD.[12] However, that study included fewer patients with an actively symptomatic state of schizophrenia. Generally, bvFTD and schizophrenia show gross similarities

in memory profiles,[12,43,44] which is in line with the evidence that dysfunction of memory in schizophrenia is mainly caused by the executive dysfunction related to the dorsolateral prefrontal and dorsal anterior cingulate cortex,[45] the same cortical areas that are disrupted in bvFTD. So, the significant dissimilarity we found between schizophrenia and bvFTD in memory might be the effect of the nonremitted state of schizophrenia patients that are included in this present study.

Verbal fluency, particularly Animal Naming, was significantly lower in bvFTD compared with BD, but not with MDD and schizophrenia. This result is supported by previous studies, indicating that bvFTD is associated with deficits in verbal abilities and language.[46] Deficits in verbal fluency have been described in both BD[47]and MDD[48]; however, these have never been directly compared with bvFTD. We found no significant difference in severity of verbal fluency between schizophrenia and bvFTD patients. This is not surprising, since the presence of verbal fluency deficits has extensively been described in schizophrenia. In a previous study, however, bvFTD patients performed more poorly on verbal fluency compared to those with schizophrenia, especially on Animal Naming.[44] Their finding can be explained by the fact that categorical fluency measures more the loss of semantic abilities, which is highly associated with bvFTD and correlates with atrophy from the inferior frontal and antero-inferior temporal cortices,[46] regions that are less involved in schizophrenia. Nevertheless, verbal fluency warrants further evaluation as a suitable test to discriminate between bvFTD and primary psychiatric disorders.

MDD showed most impairment on attention and working memory compared with BD, bvFTD, and schizophrenia. This pattern is consistent with other studies investigating cognitive impairment in MDD[38,49] and BD.[8] For bvFTD, attention/working memory is relatively spared, which is in line with our present findings. However, the fact that the MDD patients performed worse than those with schizophrenia is in contrast with a previous study comparing schizophrenia to MDD.[50] This may be explained by the fact that they studied patients with minor depression severity, while we included severely depressed patients. Overall, we found that attention impairment is more prominent in affective disorders compared to schizophrenia and bvFTD.

Global cognition measured with the MMSE was the lowest in bvFTD. This finding is probably driven by the fact that the MMSE is a diagnostic tool to screen for dementia.[23] Consequently, in the bvFTD group patients with dementia were included, whereas in the primary psychiatric disorders the patients with dementia were excluded. Due to this selection, we measured a higher MMSE score in the primary psychiatric disorders. Although we cannot rule out that some older psychiatric patients included in this study have biomarkers that are consistent with neurodegeneration, it is concluded that the cognitive impairment measured with the neuropsychological battery in the primary psychiatric disorders is part of the disorder and not due to an unexpected underlying neurodegenerative disorder.

Our findings are limited by the cross-sectional design with post hoc analyses in different cohorts. Due to this design, we created a selection bias and compared different patients with different inclusion criteria and symptom severity, which makes the interpretation and generalizability of our results difficult. Our goal, however, was not to investigate the causal basis for cognitive deficits in these disorders, but rather to emphasize the overlap in impairment of cognition between bvFTD and primary psychiatric disorders. Another limitation of this study is the effect of neuropsychiatric medication on the neuropsychological performance, which might have caused lower scores for the psychiatric patients and biased the interpretation of the results. However, because these effects vary,[51,52] we did not adjust for the use of medication. Furthermore, the neuropsychological test battery included relatively few tests, especially for executive functioning (mental flexibility and inhibition). However, 4 important domains were measured with the most commonly used neurocognitive tests in daily practice.

In summary, we found that the neuropsychological profile of bvFTD differs in severity from that of psychiatric disorders with active symptoms by showing a better performance on executive functions and verbal memory. In contrast, bvFTD was associated with worse performance on verbal fluency tests compared to BD. Clinically, our findings indicate that in the differential diagnosis of bvFTD, cognitive impairment measured with neuropsychological tests does not rule out primary psychiatric diagnoses. Further research should investigate the differences in other executive functions such as planning and social cognition and language abilities in bvFTD and active primary psychiatric disorders.

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