PCN Psychiatry and Clinical Neurosciences

REGULAR ARTICLE

Neuropsychiatric symptoms cluster and fluctuate over time in behavioral variant frontotemporal dementia

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Aim: Cognitive and behavioral phenomena define behavioral variant frontotemporal dementia (bvFTD), but neuropsychiatric symptoms (NPS) outside the core criteria are common throughout the illness. Identifying how NPS cluster in bvFTD may guide development of future therapies.

Methods: Participants ($n = 354$) with sporadic and genetic bvFTD were enrolled in the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Consortium. Dementia stage was defined as early (CDR® plus NACC FTLD ≤1) or advanced (CDR® plus NACC FTLD ≥1). Baseline and annual follow-up visit data were analyzed to compare NPS across stages of bvFTD. Psychiatric states were captured using the Neuropsychiatric Inventory-Questionnaire and Clinician Judgment of Symptoms. Polychoric cluster analysis was used to describe NPS clusters.

Results: NPS were highly prevalent (≥90%) in early and late bvFTD. Four NPS clusters were identified based on magnitude of factor loadings: affective, disinhibited, compulsive, and psychosis. Neuropsychiatric symptoms fluctuated across visits. In the affective cluster, depression showed the least visit-to-visit stability. In the disinhibited cluster, elation showed the least stability. Symptoms in the psychosis and compulsive clusters (hallucinations, delusions, obsessions/compulsions, and hyperorality) were largely stable, persisting from visit-to-visit in more than 50% of cases. Symptoms in the affective and disinhibited cluster were associated with the highest caregiver burden, while symptoms in the obsessive cluster were associated with the most functional impairment.

Conclusion: NPS in bvFTD are frequent and cluster into four discrete groups. The fluctuating nature of some NPS in bvFTD suggests that they may not be reliable markers of disease progression or stage.

Keywords: *behavioral symptoms, behavioral variant frontotemporal dementia, frontotemporal lobar degeneration, FTLD, neuropsychiatry.*

http://onlinelibrary.wiley.com/doi/10.1111/pcn.13810/full

The behavioral variant of frontotemporal dementia (bvFTD) is a clinically and pathologically heterogeneous syndrome defined by specific cognitive and behavioral phenomena.[1] However, neuropsychiatric symptoms (NPS) outside the core diagnostic criteria, like depression, elation, hallucinations, and delusions, are common at every stage of the disease. The common bvFTD-related NPS can overlap with those seen in primary psychiatric disorders (PPD), often obscuring diagnostic clarity.[2–4] Understanding how NPS emerge and cluster in bvFTD could improve the accuracy of early diagnosis and inform treatment strategies.

There is preliminary evidence of psychiatric symptom clusters in bvFTD, but the validity and stability of these clusters across diverse patient cohorts has not been established.[5,6] Identifying reliable NPS clusters in bvFTD may provide insights into the patterns of NPS presentation in bvFTD as well as in related neurodegenerative disorders like Alzheimer disease (AD) and dementia with

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Lewy bodies (DLB), where psychiatric symptoms are similarly prevalent.[7] Better understanding of NPS clusters in bvFTD could also inform treatment strategies, improving quality of life and function for patients living at all stages of bvFTD. Furthermore, understanding how psychiatric symptoms relate to disease stage may provide useful information regarding the utility of NPS for bvFTD staging and monitoring. Identifying early symptoms and biomarkers of bvFTD is essential for optimizing recruitment for clinical trials of emerging disease-modifying therapies.[8,9] If NPS correlate with bvFTD stage, they will provide helpful staging information; however, if they fluctuate in bvFTD as they do in PPD or in AD, they are not likely to be reliable markers of disease progression.[10]

Given this background, our primary aim was to identify NPS clusters in bvFTD based on symptom correlations across bvFTD-defining behavioral symptoms and those NPS outside the core criteria. Using cluster analysis techniques, we tested the hypothesis that NPS clusters in bvFTD overlap with constructs commonly observed in PPD. A complementary aim of this study was to evaluate the stability, functional impact, and caregiver burden associated with specific NPS over time. We tested the hypothesis that specific NPS fluctuate at different rates in bvFTD and may not reliably associate with neurodegeneration.

Methods

Participants

Participants were enrolled in the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study. The ALLFTD study is a prospective cohort study, and the detailed protocol can be found in earlier papers.[11,12] A secondary analysis of ALLFTD data was performed. Participants with a primary clinical diagnosis of bvFTD meeting formal criteria for probable bvFTD at one or more study visits were included in the analyses; those not meeting criteria for probable bvFTD or having a primary diagnosis other than bvFTD were excluded.[1] Pathological confirmation of bvFTD diagnosis was not available. Disease severity was defined based on Clinical Dementia Rating (CDR®) plus NACC FTLD Behavior & Language Domains global score (CDR® plus NACC FTLD).[13,14] Participants with CDR® plus NACC FTLD scores of ≤1 at visit 1 were classified as early-stage, and those with CDR® plus NACC FTLD scores of 2 or 3 as advanced-stage.

Clinical assessment

Questionnaire (NPI-Q) captured the following neuropsychiatric symptoms: depression, anxiety, hallucinations, delusions, agitation, apathy, disinhibition, irritability, and elation. We used these NPS as they correspond most closely with symptoms in common PPD including major depressive disorder, bipolar disorder, and schizophrenia. The NPI-Q is a validated informant-rated scale to assess NPS in dementia syndromes, including bvFTD.[15–19] NPS were analyzed as dichotomous variables based on their presence or absence on the NPI-Q. The hyperorality and ritualistic/compulsive behavior variables were drawn from Uniform Data Set (UDS) version 3 Form B9F–Clinical PPA and bvFTD Features, part of the FTLD Module.[20] Hyperorality and ritualistic/compulsive behavior variables were recorded as present if marked as "definitely present" and absent otherwise. Cognitive and functional ability were assessed using the Montreal Cognitive Assessment (MoCA) and the CDR® plus NACC FTLD sum of boxes score.[21,22] We examined caregiver burden using the Zarit Burden Interview, a 22-item instrument validated for capturing caregiver burden in FTD spectrum disorders.[23] Functional ability was assessed using the Functional Activities Questionnaire (FAQ).

Statistical methods

Differences in participant characteristics and clinical outcomes were compared using two-sided *t*-tests for continuous variables and Pearson χ^2 tests for categorical variables. A sensitivity analysis including only those NPI-Q scores that were moderate or severe was conducted. A sensitivity analysis including cases of "questionable" hyperorality and ritualistic/compulsive behavior was also conducted.

We performed an exploratory factor analysis of NPS to determine whether specific symptoms could be psychometrically grouped into distinct factors. We included bvFTD-defining behavioral symptoms and NPS outside the core criteria to account for the heterogeneity of behavioral and psychiatric presentations in bvFTD. To determine the appropriate number of factors, a polychoric correlation matrix of all 11 NPS (hallucinations, delusions, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, hyperorality, and ritualistic/compulsive behavior) was evaluated in a parallel analysis for principal components. To evaluate the robustness of the principal components analysis (PCA), we generated 1000 bootstrap samples from the original dataset and performed a PCA on each sample to examine for variability in the principal components. Polychoric correlations, rather than Pearson correlations, were used because the NPS measures included missing values and were not normally distributed (i.e., non-parametric).[24] Parallel analysis consists of randomly generating a number of simulated data sets (conventionally 1000) with dimensions, means, and standard deviations identical to those in the observed data but without intrinsic relationships between variables as the data are randomly generated.[25] The simulated datasets undergo PCA, and the means of each eigenvalue are calculated. The ideal number of factors is chosen such that eigenvalues in the observed data are greater than the respective mean eigenvalues from the simulated data sets.[26] We inspected a scree plot and confirmed that the number of factors identified using the parallel analysis matched those identified on the scree plot. A scree plot consists of a graphical representation of eigenvalues with the appropriate number of factors typically occurring at a point where the decrease in eigenvalue with additional factors levels off. If the parallel analysis was ambiguous (i.e., the observed eigenvalue was only slightly higher (<0.05) than the simulated eigenvalue) and the scree plot favored a smaller number of factors, we selected the smaller number of factors.

Once the appropriate number of factors was selected, a factor analysis was performed. Factor loadings were rotated using the promax rotation, allowing for correlations among the factors. Specific NPS were excluded if they had high unique variance (uniqueness >0.6) as high unique variance indicates that a significant amount of the variance is complementary to that of the other variables. Excluding variables with high unique variance from the final model improves the model's overall fit and factor structure and helps minimize the influence that variables not strongly linked to the latent constructs have on the model.[27]

A final model was fit using the optimal number of factors with the final set of NPS. The factor loadings were rotated using the promax rotation. These analyses were performed for the entire participant population across all visits, as well as cross-sectionally using baseline visit data in early-stage and advanced-stage participant groups, respectively. Individual NPS with loadings close to +1.00 or −1.00 were interpreted as loading strongly onto a factor, while those nearest zero were considered as loading weakly onto a factor. Given the exploratory nature of factor analysis, no statistical threshold was set to determine the adequacy of factor loading. However, loadings of 0.3 or higher are generally considered to be salient, and we interpreted loadings of 0.5 or higher as constituting a meaningful (moderately high) association between a variable and a factor.[28]

The stability of NPS overtime was assessed by calculating the proportion of NPS that either resolved or persisted from one study visit to the subsequent visit. Visits occurred at approximately annual intervals although there was variability across participants (mean of 463 days between visits). Disease progression was considered present if a participant's CDR® plus NACC FTLD increased by 1 or more points over the course of the study. Symptom persistence was also modeled over time using a mixed-effects

regression analysis with symptom persistence as the dependent variable and individual NPS as predictor variables.

The statistical significance level, α, was set at 0.05. STATA SE 17 (StataCorp LP, College Station, TX) was used for all analyses.

Protocol approval and patient consent

The ALLFTD study was approved by the Trial Innovation Network at Johns Hopkins University (IRB00227492), and local ethics committees at each of the sites approved the study. All participants or their legally authorized representatives provided written and informed consent to take part in the study. All procedures involving human subjects were done following the ethical standards of the Committee on Human Experimentation of the institution and in accord with the Helsinki Declaration of 1975.

Results

Demographics

Demographic data are shown in Table 1. Of 1316 participants with baseline data, 354 participants had a primary clinical diagnosis of bvFTD. Of the 354 participants with a baseline visit, there were 109 participants with one follow-up visit, 45 participants with two, 24 participants with three, 12 participants with four, and five participants with five follow-up visits. The mean number of visits in the study was 2.2 with a standard deviation of 1.5 visits. There were 145 participants classified as early-stage (22 with a CDR® plus NACC FTLD of 0.5) and 209 classified as advanced stage at the baseline visit. As expected, mean MoCA scores were lower in the advanced-stage participants (15.3 vs. 21.6, $P < 0.001$) and CDR® FTLD-SoB scores were higher (12.1 vs. 44.9, $P < 0.001$). Genetic status was defined for 78% of participants: 14% had a *C9orf72* mutation, 7% a GRN mutation, 8% a MAPT mutation, 49% were sporadic bvFTD cases, and 22% had unknown genetic status. There was a higher proportion of *C9orf72* mutation carriers in the advanced-stage group than the early-stage group (18.2% vs. 7.6%, $P = 0.01$). There were no other differences in age, sex, education, or gene status between the early-stage and advanced-stage groups.

Baseline neuropsychiatric symptoms

The frequency of NPS at baseline is displayed in Table 2. Neuropsychiatric symptoms were common in early and advanced-stage participants. Apathy, irritability, and disinhibition were the most common NPS at baseline—occurring in 74%, 63%, and 64% of participants, respectively. Within the early-stage group, apathy occurred in 38% of MAPT mutation carriers compared to 77% of GRN mutation carriers and 83% of those with sporadic bvFTD. Obsessions/compulsions occurred in 8% of early-stage MAPT mutation carriers compared to 52% of those with sporadic bvFTD. Within the advanced-stage group, disinhibition occurred in 33% of MAPT mutation carriers compared to 81% of C9orf72 mutation carriers and 75% of those with sporadic bvFTD. Hyperorality occurred in 73% of those with advanced stage sporadic bvFTD compared to 50% of C9orf72 mutation carriers and 47% of MAPT mutation carriers.

Hyperorality and obsessions/compulsions were more common in advanced-stage participants compared to early-stage participants (63% [95% CI 56%–70%] vs. 50% [95% CI 42%–58%], *P*-value 0.02 and 70% [95% CI 64%–76%] vs. 46% [95% CI 37%–54%], $P < 0.001$) respectively. Depression was more common in early-stage participants compared to advanced-stage participants (49.3% [95% CI 41%–58%] vs. 29.0% [95% CI 23%–35%], $P < 0.001$). A higher proportion of participants with GRN mutations progressed (change in CDR® plus NACC FTLD ≥1) during the study than those with C9orf72 mutations (75% [95% CI 54%–96%] vs. 29% [95% CI 13%–45%], *P*-value 0.003), and sporadic bvFTD (75% [95% CI 54%–96%] vs. 36% [95% CI 18%–53%], *P*-value 0.01). At the baseline visit, the majority (>70%) of participants experienced three or more NPS concurrently (Table 3).

Exploratory factor analysis

The results of the exploratory factor analysis are displayed in Tables 4–6. The parallel analysis of the 11 NPS items supported a model with 4 factors for early-stage, advanced-stage, and all participants combined. Details regarding eigenvalues and scree plot results for each factor analysis are displayed in the Supplementary Materials.

For the early-stage group (Table 4), the final model included: Factor 1–*Affective* (depression, anxiety, agitation, irritability); Factor 2–*Disinhibited Type A* (elation, disinhibition); Factor 3–*Compulsive* (obsessive/ritualistic behaviors, hyperorality); and Factor 4–*Psychosis* (hallucinations, delusions).

For the advanced-stage group (Table 5), the final model included: Factor 1–*Affective* (depression, anxiety, agitation, irritability); Factor 2–*Disinhibited Type B* (disinhibition, apathy); Factor 3–*Compulsive* (obsessive/ritualistic behaviors, hyperorality); and Factor 4 – *Psychosis* (hallucinations, delusions).

When all participants were assessed together across all visits (Table 6), the final model included: Factor 1–*Affective* (depression, anxiety, agitation, irritability); Factor 2–*Disinhibited Type A* (disinhibition, elation); Factor 3–*Compulsive* (obsessive/ritualistic behaviors, hyperorality); and Factor 4–*Psychosis* (hallucinations, delusions).

The sensitivity analysis limiting NPS to only moderate or severe symptoms resulted in small changes to the derived clusters. In the

Table 1. Baseline demographic characteristics and mutation status for bvFTD patients

	All participants $n = 354$	Early stage (CDR® FTLD ≤1) $n = 145$	Advanced stage (CDR® FTLD >1) $n = 209$	*P*-value
		Mean (SD)	Mean (SD)	
Age (years)	61.9 (9.2)	61.9 (7.8)	61.8 (10.0)	0.95
Sex (% men)	56.2	60.7	53.1	0.16
Education level (years)	15.8 (2.6)	16.0 (2.6)	15.6 (2.6)	0.11
MoCA	18.0 (7.0)	21.6 (5.2)	15.3 (7.0)	<0.001
CDR® FTLD-SOB score (mean)	9.2 (525.1)	4.9 (292.0)	1212.1 (44.4)	<0.001
C9orf72 (*n*, %)	49 (13.8)	11 (7.6)	38 (18.2)	0.01
GRN (*n*, %)	23 (6.5)	13 (9.0)	10 (4.8)	0.05
MAPT (*n*, %)	31 (8.8)	16 (11.0)	15 (7.2)	0.07
Sporadic (*n*, %)	174 (49.2)	67 (46.2)	107 (51.2)	0.24

bvFTD, behavioral variant frontotemporal dementia; CDR®, clinical dementia rating; MoCA, Montreal cognitive assessment.

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Table 2. Percent frequency of individual neuropsychiatric symptoms at baseline visit

	Early stage (CDR® FTLD ≤1)						Advanced stage (CDR® FTLD >1)					
NPS	All ($n = 145$)	Sporadic ($n = 67$)	GRN ($n = 13$)	MAPT ($n = 16$)	C9 ($n = 11$)	*P*-value	All ($n = 209$)	Sporadic ($n = 107$)	GRN ($n = 10$)	MAPT ($n = 15$)	C9 ($n = 38$)	*P*-value
Hallucinations	5.8	1.9	7.7	7.7	11.1	0.49	7.9	3.3	11.1	15.4	9.1	0.26
Delusions	18.1	17.2	7.7	25.0	20.0	0.67	18.4	16.4	20.0	15.4	19.0	0.98
Agitation	48.2	58.5	38.5	37.5	20.0	0.07	54.0	58.7	50.0	53.9	54.1	0.92
Depression	49.3	53.1	53.9	31.3	40.0	0.41	29.0	31.1	30.0	0.0	27.8	0.13
Anxiety	48.9	48.4	38.5	37.5	40.0	0.80	47.5	49.0	70.0	33.3	40.5	0.28
Apathy	73.6	82.8	76.9	37.5	70.0	0.003	79.7	79.1	90.0	50.0	78.4	0.10
Elation	27.9	28.2	38.5	37.5	20.0	0.75	24.4	22.9	30.0	0.0	33.3	0.12
Disinhibition	64.3	71.9	61.5	62.5	60.0	0.49	71.9	75.0	50.0	33.3	80.6	0.005
Irritability	62.6	70.3	46.2	62.5	40.0	0.15	56.2	58.1	60.0	38.5	62.2	0.51
Hyperorality	50.0	56.7	30.0	25.0	33.3	0.08	63.0	72.6	70.0	46.7	50.0	0.03
Obsessions/ compulsions	45.6	52.2	20.0	8.3	22.2	0.008	70.2	75.5	40.0	73.3	73.7	0.12

χ^2 comparison by gene category within disease stage.
CDR®, clinical dementia rating; MoCA, Montreal cognitive assessment; NPS, neuropsychiatric symptoms.

Table 3. Percent frequency of individual NPS at baseline visit by CDR® FTLD score

	CDR® FTLD					
NPS	0 ($n = 6$)	0.5 ($n = 22$)	1 ($n = 117$)	2 ($n = 176$)	3 ($n = 33$)	*P*-value
Hallucinations	20.0	4.5	5.3	8.0	7.4	0.72
Delusions	33.3	9.1	19.1	18.7	16.7	0.69
Agitation	16.7	36.4	52.2	54.7	50.0	0.23
Depression	33.3	45.5	50.9	30.6	20.0	0.002
Anxiety	33.3	36.4	52.3	43.0	75.0	0.02
Apathy	16.7	68.2	77.7	79.2	82.8	0.006
Elation	16.7	22.7	29.5	24.3	25.0	0.85
Disinhibition	16.7	54.6	68.8	75.3	51.7	0.002
Irritability	33.3	59.1	64.9	57.2	50.0	0.35
Hyperorality	–	31.6	53.0	59.4	81.8	0.002
Obsessions/Compulsions	–	5.3	52.1	68.6	78.8	<0.001
Total no of NPS						
0	50.0	0.0	1.7	3.4	0.0	<0.001
1–2	16.7	27.3	15.4	12.5	12.1	
3+	33.3	72.7	82.9	84.1	87.9	

t-values for continuous variables, χ^2 for binary variables.
NPS, neuropsychiatric symptoms.

model limited to baseline visit data of early-stage participants, the derived factors remained the same aside from irritability loading more strongly with the disinhibited cluster. In the model limited to baseline data of advanced-stage participants, the derived factors were identical. In the model with all participants included across all visits, a three-factor model without a disinhibited cluster best fit the data (elation, disinhibition, and apathy were excluded due to elevated uniqueness).

The sensitivity analysis including questionable cases of obsessive/ritualistic behaviors and hyperorality also resulted in small changes to the derived clusters. In the model limited to baseline visit data of early-stage participants, the derived clusters were unchanged. In the model limited to baseline data of advanced-stage participants, elation and obsessions were dropped due to elevated uniqueness, resulting in four clusters including psychosis (hallucinations, delusions), affective (depression, agitation, irritability), hyperoral (hyperorality, anxiety), and disinhibited (disinhibition, apathy). In the model with all participants included across all visits, a three-factor model best fit the data (elation, anxiety, and apathy excluded due to elevated uniqueness).

Persistence of NPS

The persistence of specific NPS across visits is displayed in Table 7. At the first follow-up visit, NPS generally persisted in greater than 60% of cases with fewer than 30% of cases resolving. Elation persisted in only 55% of cases and resolved in 42% at the first follow-up. At the second follow-up visit, depression, persisted in only 39%

Table 4. Four-factor NPS cluster model in early-stage FTD

NPS	Factor 1 (Affective)	Factor 2 (Disinhibited)	Factor 3 (Compulsive)	Factor 4 (Psychosis)
Agitation	**0.84**	0.38	0.22	−0.02
Depression	**0.73**	−0.02	−0.20	0.04
Anxiety	**0.67**	0.21	−0.00	0.01
Irritability	**0.74**	0.56	−0.04	0.26
Elation	0.15	**0.92**	0.16	0.26
Disinhibition	0.61	**0.89**	0.19	0.28
Hyperorality	0.06	0.22	**0.76**	0.20
Obsessions/Compulsions	−0.04	0.10	**0.82**	0.04
Hallucinations	0.06	0.30	0.13	**0.99**
Delusions	0.06	0.30	0.13	**0.99**

Factor loadings are based on a promax rotated solution. Boldface type indicates the primary (i.e., highest) factor loading for each item. NPS loadings close to +1.00 or −1.00 are interpreted as loading strongly onto a factor, while those nearest zero are considered as loading weakly onto a factor.
FTD, frontotemporal dementia; NPS, neuropsychiatric symptoms.

Table 5. Four-factor NPS cluster model in advanced-stage FTD

NPS	Factor 1 (Affective)	Factor 2 (Disinhibited)	Factor 3 (Compulsive)	Factor 4 (Psychosis)
Agitation	**0.78**	0.36	−0.01	0.40
Depression	**0.66**	0.23	−0.23	0.12
Anxiety	**0.48**	−0.17	0.44	0.17
Irritability	**0.77**	0.17	0.20	0.29
Apathy	0.25	**0.74**	0.31	0.009
Disinhibition	0.32	**0.70**	0.02	0.19
Hyperorality	−0.02	0.25	**0.73**	−0.04
Obsessions/compulsions	0.04	0.05	**0.56**	−0.28
Hallucinations	0.35	0.10	−0.10	**1.0**
Delusions	0.35	0.10	−0.10	**1.0**

Factor loadings are based on a promax rotated solution. Boldface type indicates the primary (i.e., highest) factor loading for each item. NPS loadings close to +1.00 or − 1.00 are interpreted as loading strongly onto a factor, while those nearest zero are considered as loading weakly onto a factor.
FTD, frontotemporal dementia; NPS, neuropsychiatric symptoms.

Table 6. Four-factor NPS cluster model across all visits and disease severity

NPS	Factor 1 (Affective)	Factor 2 (Disinhibited)	Factor 3 (Compulsive)	Factor 4 (Psychosis)
Agitation	**0.75**	0.41	0.11	0.18
Depression	**0.62**	−0.02	−0.14	0.22
Anxiety	**0.62**	0.10	0.20	0.30
Irritability	**0.77**	0.37	0.06	0.30
Elation	0.25	**0.66**	0.29	0.16
Disinhibition	0.45	**0.65**	0.21	0.15
Hyperorality	0.02	0.34	**0.67**	0.07
Obsessions/compulsions	−0.02	0.20	**0.70**	−0.07
Hallucinations	0.34	0.12	0.01	**0.99**
Delusions	0.34	0.12	0.01	**0.99**

Factor loadings are based on a promax rotated solution. Boldface type indicates the primary (i.e., highest) factor loading for each item. NPS loadings close to +1.00 or − 1.00 are interpreted as loading strongly onto a factor, while those nearest zero are considered as loading weakly onto a factor.
NPS, neuropsychiatric symptoms.

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of cases with all other NPS persisting in greater than 50% of cases. Follow-up was sparse after three visits, however, at the third follow-up anxiety persisted in only 36% of cases and resolved in 64%, while depression persisted in only 29% of cases and resolved in 71%. Other NPS persisted in greater than 50% of cases at the third follow-up visit. Table S1 displays the results of a mixed-effects regression on NPS persistence. Depression and elation were both significantly associated with a decreased likelihood of symptom persistence from visit to visit. No other NPS showed significant associations with symptom persistence.

Caregiver burden and functional impact of NPS

The affective cluster and disinhibited cluster were associated with higher levels of caregiver burden (Table 8). Participants with agitation had a mean Zarit Burden Inventory (ZBI) score of 40.1 (95% CI 38.0–42.2) compared to those without agitation (35.0 [95% CI 33.0–37.1], $P < 0.001$). Within the disinhibited cluster, those with elation (40.9 [95% CI 37.7–44.1] vs. 36.7 [95% CI 35.0–38.3], P-value 0.02) and disinhibition (40.6 [95% CI 38.9–42.3] vs. 31.5 [95% CI 28.9–34.1], $P < 0.001$) had higher ZBI scores than those without elation or disinhibition.

Apathy was also associated with higher levels of caregiver burden (39.3 [95% CI 37.6–40.9] vs. 33.5 [95% CI 30.3–36.7], $P < 0.001$).

Symptoms in the obsessive cluster (hyperorality, obsessions/compulsions) as well as apathy were associated with worse functional impairment (Table 8). Functional Activity Questionnaire (FAQ) scores for those with hyperorality were 21.2 [95% CI 20.2–22.3] vs. 16.3 [95% CI 14.9–17.7] in those without hyperorality ($P < 0.001$). Those

Table 7. Persistence of symptoms across study visits in bvFTD

	Follow-up visits														
	1 ($n = 109$)			2 ($n = 45$)			3 ($n = 24$)			4 ($n = 12$)			5 ($n = 5$)		
NPS	New	Resolved‡ *n* (%)	Persistent† *n* (%)	New	Resolved *n* (%)	Persistent *n* (%)	New	Resolved *n* (%)	Persistent *n* (%)	New	Resolved *n* (%)	Persistent *n* (%)	New	Resolved *n* (%)	Persistent *n* (%)
Hallucinations	4	1 (13)	5 (63)	1	2 (40)	3 (60)	0	0 (0)	2 (100)	0	0 (0)	1 (33)	0	0 (0)	1 (100)
Delusions	10	5 (29)	11 (65)	3	4 (44)	5 (56)	0	1 (33)	2 (67)	0	0 (0)	2 (67)	0	0 (0)	1 (100)
Agitation	19	13 (26)	35 (70)	7	9 (39)	14 (61)	3	3 (30)	7 (70)	2	1 (25)	3 (75)	0	0 (0)	2 (100)
Depression	12	10 (30)	20 (61)	4	5 (28)	7 (39)	1	5 (71)	2 (29)	2	0 (0)	0 (0)	0	0 (0)	1 (100)
Anxiety	15	14 (27)	35 (69)	5	4 (25)	12 (75)	3	7 (64)	4 (36)	0	1 (25)	3 (75)	0	1 (50)	1 (50)
Apathy	18	13 (17)	59 (78)	8	9 (33)	17 (63)	4	3 (21)	11 (79)	0	1 (13)	3 (38)	0	1 (33)	1 (33)
Elation	10	13 (42)	17 (55)	8	2 (15)	10 (77)	1	3 (50)	3 (50)	0	1 (100)	0 (0)	0	–	–
Disinhibition	12	13 (18)	57 (78)	8	9 (31)	18 (62)	5	3 (27)	8 (73)	3	0 (0)	2 (67)	0	1 (33)	2 (67)
Irritability	16	10 (18)	41 (75)	6	5 (24)	16 (76)	2	6 (50)	6 (50)	0	1 (25)	3 (75)	0	1 (50)	1 (50)
Hyperorality	18	11 (21)	40 (75)	5	6 (32)	11 (58)	5	2 (29)	5 (71)	3	0 (0)	2 (100)	0	–	–
Obsessions/ compulsions	10	6 (11)	41 (76)	4	4 (29)	8 (57)	5	1 (25)	2 (50)	2	0 (0)	1 (100)	0	0 (0)	1 (100)

†Persistence is defined as a symptom continuing between two consecutive visits.
‡Resolution defined as a symptom no longer being present at a subsequent visit.
bvFTD, behavioral variant frontotemporal dementia; NPS, neuropsychiatric symptoms.

Table 8. Impact of NPS on caregiver burden and functional abilities in bvFTD

	ZBI mean (SD)			FAQ mean (SD)		
	–	+	*P*-value	–	+	*P*-value
Hallucinations	37.3 (16.2)	36.7 (17.4)	0.85	18.2 (9.2)	21.9 (7.6)	0.04
Delusions	37.3 (16.2)	39.3 (15.3)	0.31	18.2 (9.2)	20.6 (7.7)	0.05
Agitation	35.0 (15.8)	40.1 (16.0)	<0.001	18.2 (9.9)	19.0 (8.1)	0.36
Depression	37.0 (16.6)	38.6 (15.1)	0.31	19.3 (9.2)	17.0 (8.4)	0.02
Anxiety	36.0 (15.8)	39.9 (15.9)	0.01	18.2 (9.6)	19.1 (8.2)	0.37
Apathy	33.5 (17.8)	39.3 (15.1)	<0.001	15.1 (10.3)	19.6 (8.3)	<0.001
Elation	36.7 (15.7)	40.9 (16.8)	0.02	18.7 (9.6)	18.5 (7.4)	0.85
Disinhibition	31.5 (16.1)	40.6 (15.1)	<0.001	17.8 (11.0)	18.9 (8.0)	0.26
Irritability	34.5 (16.1)	40.3 (15.5)	<0.001	18.4 (9.8)	18.8 (8.3)	0.73
Hyperorality	36.5 (15.6)	39.5 (16.3)	0.05	16.3 (8.7)	21.2 (8.0)	<0.001
Obsessions/compulsions	36.5 (15.4)	39.8 (16.2)	0.03	16.7 (9.1)	21.1 (7.7)	<0.001

t-values for continuous variables, χ^2 for binary variables.
bvFTD, behavioral variant frontotemporal dementia; FAQ, functional activities questionnaire; NPS, neuropsychiatric symptoms; ZBI, Zarit Burden Inventory.

with obsessions/compulsions had FAQ scores of 21.1 [95% CI 20.1–22.2] vs. 16.7 [95% CI 15.2–18.1] in those without obsessions/compulsions ($P < 0.001$). Those with apathy had FAQ scores of 19.6 [95% CI 18.6–20.5] compared to 15.1 [95% CI 12.9–17.4] in those without apathy ($P < 0.001$).

Discussion

Overview

This study examined NPS in genetic and sporadic bvFTD, finding that NPS are common, cluster into distinct phenotypes, and have variable temporal stability. While NPS are common in many forms of neurodegenerative illness including AD, where prevalence of specific NPS often exceeds 40%, we show that in bvFTD multiple NPS are nearly universal with over 70% of participants experiencing three or more symptoms at baseline and over 90% experiencing at least one NPS at baseline.[29] As expected, distinct NPS clusters were identified in early and advanced stages of bvFTD: Affective (depression, anxiety, irritability, agitation); Disinhibited (elation, disinhibition, apathy); Compulsive (hyperorality, obsessive/compulsive behavior); Psychosis (hallucinations and delusions). As anticipated, NPS were shown to fluctuate over time, with elation and depression showing the most variability across visits.

Neuropsychiatric symptom clusters

A primary goal of this study was to identify distinct clusters of NPS in bvFTD. The four NPS clusters that emerged in both early and advanced-stage disease overlap phenotypically with some features of primary psychiatric disorders (PPD). Future studies aimed at identifying functional and structural neural correlates of these NPS clusters could be useful in efforts to understand the neurobiological substrates, and to develop targeted therapies.

Affective symptom cluster

The affective symptom cluster identified in this study consisted of a combination of depression, anxiety, agitation, and irritability. Of these symptoms, anxiety, irritability, and agitation were among those most associated with elevated caregiver burden, suggesting that this cluster has a particularly significant impact on patient and caregiver quality of life. Current management of affective symptoms in bvFTD is challenging. Affective symptoms in bvFTD can be alleviated by treatment with selective serotonin reuptake inhibitors (SSRI), but responses are often incomplete. Alterations in 5-HT activity resulting from neuronal loss, tau deposition in the raphe nucleus and loss of 5-HT receptors in the midbrain, frontal, and temporal lobes have been associated with the development of affective symptoms in bvFTD.[30–32] Investigational therapies like non-invasive electrical brain stimulation and multi-modal serotonergic neuromodulators could be more effective than current treatments for affective symptoms in bvFTD, significantly improving patient and caregiver quality of life.

Disinhibited symptom cluster

The disinhibited symptom cluster identified in this study consisted of elation and disinhibition in early-stage participants and apathy and disinhibition in advanced-stage participants. The early-stage cluster has some symptom overlap with bipolar disorder, where dysfunction in the dorsal cognitive circuit and fronto-limbic circuit has been implicated in symptoms of hypomania and mania.[33] Interestingly, lithium—the gold standard for maintenance therapy in bipolar disorder—has been used with some success for the management of behavioral symptoms in bvFTD.[34] Future studies are needed to determine which bvFTD patients exhibiting elation and disinhibition are the best candidates for therapies like lithium.

The observation that MAPT mutation carriers were less likely to exhibit disinhibition compared to C9orf72 mutation carriers or sporadic bvFTD is also interesting and suggests that in addition to neural network dysfunctions, neuropathological states may influence NPS profiles in different ways. For instance, TDP-43 predominant neuropathology may be more likely to lead to disinhibition compared to tau-predominant pathologies. Further work is needed to correlate bvFTD-related NPS with both neural network dysfunction and neuropathological background.

Compulsive symptom cluster

The compulsive symptom cluster identified in this study consisted of hyperorality and ritualistic/obsessive-compulsive behavior. These symptoms were associated with high levels of functional disability, suggesting a high correlation with skills relevant to day-to-day functioning. Hyperorality and ritualistic/obsessive-compulsive behavior have been found to co-occur in previous studies of bvFTD and are associated with striatal gray matter volume loss.[35–37] These symptoms overlap with those seen in obsessive-compulsive disorder (OCD) and binge eating disorder (BED). Obsessive symptoms are challenging to treat in both bvFTD and OCD, often with limited benefit from psychotropic medicines. However, targeted non-invasive brain stimulation techniques, stimulating the dorsolateral prefrontal cortex (dlPFC) as a means to modulate cortico-striato-thalamo-cortical circuits, have been used successfully in treating refractory symptoms of OCD and BED and may have significant potential in bvFTD.[38–40] The observation that MAPT mutation carriers were less likely to exhibit hyperorality or obsessions/compulsions compared to sporadic bvFTD is interesting and raises questions about how neuropathology influences NPS phenotypes.

While our sensitivity analysis including questionable cases of ritualistic/obsessive-compulsive behavior and hyperorality resulted in small changes to the structure of symptom clusters, given the goal of assessing symptoms that are clearly present as opposed to threshold or questionable cases, we felt the final analysis should include only those participants with symptoms marked as "definitively present."

Psychosis symptom cluster

The psychosis symptom cluster in this study consisted of hallucinations and delusions. While relatively rare, these symptoms do occur in bvFTD, particularly in those with TDP-43 pathology.[41] Treatment of psychosis in bvFTD can be challenging as parkinsonism is not uncommon. Antipsychotics can be effective but, response rates are imperfect, and utility is limited by the potential for parkinsonism and other adverse effects. As previously described, extensive areas of reduced 5-HT activity are characteristic of bvFTD. Pimavanserin, an antipsychotic with inverse agonist and antagonist properties at the 5-HT2A receptor, may have a future role in treating psychosis in bvFTD by modulating relevant circuit dysfunction, representing another example where identifying neural correlates of NPS clusters may facilitate the development of more effective, targeted therapies for NPS in bvFTD.[42]

Apathy

Notably, apathy—a core behavioral symptom of bvFTD—was excluded from several of the exploratory factor analysis models due to high unique variance. It is important to note that the exclusion of apathy from the identified clusters should not be interpreted as a minimization of the clinical importance of apathy in bvFTD. Rather, this finding implies that apathy reflects a stable and distinct bvFTD-defining NPS that warrants study in its own right. Future work would need to clarify the relationship between apathy and other NPS in bvFTD to identify therapy for this challenging clinical state.

Neuropsychiatric symptom fluctuations

A complementary aim of this study was to evaluate the stability of specific NPS over time. A major priority in advancing care for patients with bvFTD is finding ways to optimize clinical trial participation for emerging disease-modifying therapies. Identifying patients at the earliest sign of symptoms, prior to significant neurodegeneration, could maximize the potential to favorably alter the disease course. Most trials rely on measures like the CDR® plus

NACC FTLD to assess disease severity for the purpose of trial enrollment. Scales like the CDR® plus NACC FTLD have many strengths but do not fully describe the heterogeneity of the earliest stages of bvFTD. In other words, psychiatric phenomena may be relevant to preclinical bvFTD constructs.

Whether psychiatric symptoms outside the core diagnostic criteria should be included in bvFTD severity rating scales is an important and open question. Ideal elements for a disease severity rating scale are symptoms that reflect neurodegeneration and are sensitive to the temporal progression. In this study, we observed that some NPS, particularly those that are already included in the core bvFTD diagnostic criteria (disinhibition, apathy, compulsions, hyperorality) are relatively stable, persisting across visits. However, other NPS outside the core diagnostic criteria—including depression and elation—are less stable. Psychotic symptoms appear to be relatively stable. Given these findings, some psychiatric symptoms outside the core behavioral criteria may not reflect neurodegeneration reliably and therefore, would not be considered indexes of disease severity. Further longitudinal work is needed to definitively establish the role of psychiatric symptoms in the staging and monitoring of bvFTD progression.

While our study benefits from a large well-characterized population with expert diagnoses of bvFTD, several limitations merit consideration. Our study relies on clinical as opposed to pathological diagnosis, and so the possibility of diagnostic error, i.e., that a proportion have other neurodegenerative diseases (AD, DLB, PPD, etc.) cannot be discounted. This problem is mitigated by the study's reliance on expert clinicians establishing diagnosis using standard criteria in a formal consensus conference process. Another caveat is that the analyses do not take into account NPS severity; relying on a binary assessment of NPS (presence/absence) does not fully characterize psychiatric symptoms or their severity. In addition, assessments for many NPS domains were based on informant report which may not be as reliable as a formal clinical interview. Future studies will benefit from the use of more sophisticated assessments, including structured psychiatric interviews, to provide deeper phenotyping of bvFTD-related psychiatric phenomena. In addition, our use of factor analysis to define NPS clusters does not allow for a definitive examination of the neurobiology underlying psychiatric phenotypes in bvFTD. While useful for hypothesis generation, our findings will be strengthened by future studies that prospectively examine the functional and structural neural correlates of NPS in bvFTD. Our assessment of symptom fluctuations also did not account for any pharmacologic or non-pharmacologic interventions. Future studies will benefit from a comprehensive record of treatments prescribed, allowing for better characterization of the natural history of bvFTD-related NPS and the efficacy of existing interventions. Additionally, follow-up in our study was sparse after visit 2, limiting definitive conclusions about symptom fluctuations over time. Future studies with more robust longitudinal follow-up are necessary to replicate and confirm our observations about NPS fluctuations. Our baseline study population also consisted primarily of participants with CDR® plus NACC FTLD scores of 1 (33%) or 2 (50%), with less than 20% having scores of 0, 0.5 or 3. This may limit the generalizability of our findings to individuals with prodromal or highly advanced bvFTD. Future studies with representative distributions of prodromal and highly advanced cases are needed to confirm our findings. Finally, our study population is limited to participants recruited for participation at academic centers and consisted predominantly of white participants living in North America. This limits the generalizability of our results to other ethnocultural groups and geographic locations.

Conclusion

In this study, we show that NPS in bvFTD cluster into four distinct domains, with symptoms overlapping those seen in a variety of primary psychiatric conditions and other neurodegenerative disorders. We also observed that NPS have temporal variability, suggesting that while neuropsychiatric symptoms are central to the clinical presentation and lived experience of bvFTD, they may not be reliable markers of disease progression. Overall, our study highlights the potential for advancing treatment of psychiatric symptoms in bvFTD. Future studies are needed to clarify the early functional neuroanatomic changes accompanying these psychiatric phenotypes, as well as the neuropathological substrates, in order to inform the development of novel pharmacotherapies and methods for targeted neuromodulation.

Acknowledgments

This work was supported by CM: NCATS KL2TR003099, NIA K23AG088248; BP: NIH; DF: UW Clinician Scientist Training Program Award, NIH/NIA T32AG052354; NG: NIH U01AG045390-01A1, U54NS092089-01, U19AG063911, Tau Consortium, Association for Frontotemporal Degeneration; JK: U19AG063911; IL: NIH; CO: NIH, Alzheimer's Association, Robert and Nancy Hall Brain Research Fund; KDR: U19AG063911.

Disclosure statement

DW: Medical Education Speakers Network (honoraria); NG: Blue Cross Blue Shield, SSM Neuroscience Symposium, Blue Cross Blue Shield Medical Policy Panel Meeting, Florida Atlantic University New Horizons ADRD Symposium, AAN RITE Exam (payments), T-019989, US Application Serial No. 18/855,529 (patents), FSA, CS1P1 (DSMB), CureVCP, Northwestern University Medical Alumni Board (leadership); VK: R01AG064093, R01NS108452, U19AG063911 (grants); ML: U19AG063911 (grant); IL: NINDS, Michael J Fox Foundation, Parkinson's Foundation, EIP Pharmaceuticals, UCB, Amneal, Multiple System Atrophy Center of Excellence, Research Center of Excellence in Lewy Body Dementia, Novartis, Lundbeck, Roche, AbbVie, Alterity, Abbott, Transposon Therapeutics, CurePSP (grants), Davis Phinney Foundation (honoraria), Patent number: 10364452, Strip-based Electrochemical Quantification of L-DOPA in Whole Blood (patent planned); Rossy PSP Program at the University of Toronto, Aprinoia (DSMB), Frontiers in Neurology (editor); JM: NIH (grants), Wolters Kluwer Health, Elsevier (royalties), Coya Therapeutics, Eli Lilly (payments); CO: Alector, Transposon (grants), Acadia, Reata, Otsuka, Eli Lilly, Alexion, Lykos, Zevra, Neuvivo, LBD Association (payments), FTD Disorders Registry (DSMB), Tau Consortium, AFTD, ISFTD, ISTAART FTD PIA (leadership), Alector, Transposon, Denali (drugs/materials); AP: NIA K23 AG059891, NIA R44 AG080861, NINDS U01 NS102035 (grants); Ono Pharma, Ferrer Internacional, MedRhythms (consulting), CurePSP (leadership); JR: Ferrer (consulting), Eli Lilly, Eisai, Amylyx (site PI); KT: NIH/NIA R01AG068881, R01AG075111, R01AG075404 (grants); KDR: P30 AG066509, Lawton Health Research Institute (grants), MedBridge (payments).

Author contributions

CM, VK, BD, ME, NR, BW, SM, RD, AS, ML, BP, JR, JM, KT, EH, DF, AP, AB, ES, IL, KR, NG, KDR, JK, CO contributed to the conception and design of the study and drafting the manuscript. CM was responsible for acquisition and analysis of data and writing the initial manuscript draft.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.