

# Patterns and Trajectories of Behavioral and Neuropsychiatric Symptoms in Frontotemporal Dementia and Primary Progressive Aphasia

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## Abstract

### Background and Objectives

Behavioral and neuropsychiatric symptoms are common in frontotemporal dementia (FTD) and primary progressive aphasia (PPA). However, little is known about their patterns, time course, and association with brain atrophy. We, therefore, aimed to describe behavioral and neuropsychiatric phenotypes in patients with FTD and PPA, leveraging a hypothesis-free/data-driven approach.

### Methods

We included participants diagnosed with behavioral variant FTD (bvFTD) or PPA according to Rascovsky and Gorno-Tempini criteria from the German Center for Neurodegenerative Diseases Clinical Registry Study of Neurodegenerative Diseases-FTD prospective multicenter observational cohort study. Symptoms were assessed using the Neuropsychiatric Inventory—Questionnaire. Principal component analysis (PCA) was used to delineate symptom groups. Subsequently, frequency and severity across diagnostic groups were examined. We applied linear mixed-effects models to describe the longitudinal evolution of symptoms. Associations with MRI-assessed atrophy were investigated using linear regression models.

### Results

A total of 314 patients (42.4% female, mean age 65.52 [SD 9.0] years) with bvFTD or PPA were included. MRI was available for 134 of 314 individuals. PCA revealed 4 natural symptom groups, labeled active behavioral, passive behavioral, affective, and psychotic phenotypes. Symptom groups were observed at comparable frequencies across diagnostic groups. Time from symptom onset (0.130 [0.044–0.217],  $p < 0.003$ ), sex (1.376 [0.666–2.087],  $p < 0.001$ ), and the interaction between the nonfluent variant of PPA and sex (−1.940 [−3.242 to −0.638],  $p = 0.004$ ) showed a significant effect on the active behavioral phenotype, with symptom severity increasing over time and being most pronounced in men with bvFTD. Patients with bvFTD exhibited more severe passive behavioral symptoms compared with any other diagnostic group. For the affective phenotype, a significant interaction between time and sex (0.063 [0.010–0.117],  $p = 0.021$ ) indicated a progressive increase in symptom severity in men over time. Furthermore, we found robust neuroanatomical correlations of passive behavioral symptoms with subcortical and bilateral frontal and cingulate cortical atrophy.

### Discussion

Our findings demonstrate that behavioral and neuropsychiatric symptoms are prevalent in both bvFTD and PPA. Their severity depends on the disease duration, phenotypic group, and sex. This detailed understanding of symptomatology is crucial for optimizing patient care, diagnostic evaluations, and the design of clinical trials. Limitations comprise the lack of neuropathologic validation and the limited availability of MRI data.

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## Glossary

**A $\beta$**  =  $\beta$ -amyloid; **AD** = Alzheimer disease; **bvFTD** = behavioral variant of FTD; **DESCRIBE-FTD** = DZNE Clinical Registry Study of Neurodegenerative Diseases-FTD; **DZNE** = German Center for Neurodegenerative Diseases; **EMM** = estimated marginal mean; **FDR** = false discovery rate; **FTD** = frontotemporal dementia; **LME** = linear mixed-effects; **lvPPA** = logopenic variant of PPA; **MMSE** = Mini-Mental State Examination; **ncvPPA** = nonclassifiable variant of PPA; **nfvPPA** = nonfluent variant of PPA; **NPI-Q** = Neuropsychiatric Inventory–Questionnaire; **PCA** = principal component analysis; **PPA** = primary progressive aphasia; **PPD** = primary psychiatric disorder; **ROI** = region of interest; **RR** = relative risk; **svPPA** = semantic variant of PPA.

## Introduction

Frontotemporal dementia (FTD) comprises a heterogeneous group of neurodegenerative diseases, characterized by behavioral, emotional, and language disturbances. It typically manifests between the ages of 45 and 65.<sup>1</sup> While FTD is highly heritable, with approximately 30% of cases being familial and 10%–20% following an autosomal dominant inheritance pattern, most cases are considered sporadic.<sup>2</sup>

The most common phenotype is the behavioral variant of FTD (bvFTD), with clinical hallmarks including prominent changes in behavior and personality.<sup>3</sup> Language-predominant phenotypes, termed primary progressive aphasia (PPA), include the nonfluent variant of PPA (nfvPPA), marked by effortful speech and grammatical errors; the semantic variant of PPA (svPPA), characterized by impaired word comprehension and object recognition; and the logopenic variant of PPA (lvPPA), characterized by difficulties in word retrieval and repetition.<sup>4</sup> Despite clinical similarities with other PPA variants, lvPPA is frequently associated with Alzheimer disease (AD) pathology rather than frontotemporal lobar degeneration.<sup>5</sup>

Although neuropsychiatric and behavioral symptoms are most prominent in bvFTD, they may be present in PPA as well, complicating diagnosis and treatment.<sup>6</sup> Because symptoms overlap significantly with psychiatric conditions, FTD carries the highest risk, compared with other dementia syndromes, of being misdiagnosed as a primary psychiatric disorder (PPD).<sup>7,8</sup> Because of the clinical spectrum of FTD, a detailed understanding of potential symptoms is crucial for optimizing patient care and improving diagnostic accuracy. In light of upcoming clinical trials on disease-modifying drugs,<sup>9–11</sup> an early and precise diagnosis becomes increasingly relevant. We, therefore, aimed to characterize behavioral and neuropsychiatric symptoms in FTD cases from the German Center for Neurodegenerative Diseases (DZNE) Clinical Registry Study of Neurodegenerative Diseases-FTD (DESCRIBE-FTD) cohort, examine the longitudinal course of symptoms, and investigate structural brain changes associated with particular symptoms using a data-driven approach.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

The study was performed according to the Declaration of Helsinki (1991). Ethical approval for the study has been obtained from all participating centers. All participants provided written informed consent.

### Participants

We analyzed baseline and follow-up data of patients with FTD from the DESCRIBE-FTD prospective multicenter observational cohort study,<sup>12</sup> gathered between February 19, 2019, and May 7, 2021. The DESCRIBE-FTD study<sup>12</sup> is led by the DZNE, involving 10 participating research centers with specialized memory clinics across Germany, where patients are referred for diagnostic evaluation and study participation. DESCRIBE-FTD enrolls patients with a clinical diagnosis of FTD or PPA, according to Rascovsky<sup>3</sup> or Gorno-Tempini<sup>4</sup> criteria, respectively, regardless of their biomarker or genetic status. Follow-up visits are scheduled yearly. Participants with PPA not meeting Gorno-Tempini criteria for any variant are classified as nonclassifiable variant of PPA (ncvPPA). All participants underwent a standardized clinical assessment consisting of medical history, family history, physical examination, and neuropsychological testing. Lumbar puncture and MRI scans were conducted when possible. The Neuropsychiatric Inventory–Questionnaire (NPI-Q) was administered on the study day, and MRI was also typically performed on the same day, with some exceptions where MRI scans were conducted before or after the visit, but usually within 3 months. CSF biomarkers were measured using the Meso Scale Discovery platform (Rockville, MD).<sup>13</sup> For more detailed information on the DESCRIBE-FTD study design, we refer to the published cohort description.<sup>12</sup> Participants diagnosed with bvFTD or PPA and available (NPI-Q) data were included in this analysis.

### Assessment of Behavioral and Neuropsychiatric Symptoms

The presence and severity of the following symptoms were assessed by the NPI-Q<sup>14</sup> administered with the caregiver: delusions, hallucinations, agitation/aggression, depression, euphoria/ elation, apathy, disinhibition, irritability/lability, aberrant motor behavior, impaired sleep and hyperorality, and appetite changes.

**Table 1** Baseline Demographics and Biomarkers of the Study Cohort

	Total (n = 314)	bvFTD (n = 152)	nfvPPA (n = 61)	lvPPA (n = 32)	svPPA (n = 31)	ncvPPA (n = 38)
<b>Age, y, mean (SD)</b>	65.52 (9.0)	63.4 (9.6) <sup>b,e</sup>	67.4 (8.5) <sup>a</sup>	67.1 (8.8)	67.5 (6.0)	68.18 (7.9) <sup>a</sup>
<b>Age at onset, y, mean (SD)</b>	62.37 (9.3)	59.9 (9.8) <sup>b,e</sup>	64.5 (8.7) <sup>a</sup>	64.4 (8.7)	63.8 (7.1) <sup>a</sup>	65.53 (8.0)
<b>Disease duration, y, mean (SD)</b>	3.2 (2.7)	3.6 (3.1)	3.0 (2.1)	2.7 (2.0)	3.5 (2.5)	2.7 (2.2)
<b>Education, y, mean (SD)</b>	13.86 (5.7)	13.5 (3.3)	13.3 (2.7)	12.8 (3.1)	14.8 (2.7)	13.89 (2.7)
<b>Sex, female/male, n (%)</b>	133/314 (42.4)	59/93	31/30	12/30	16/15	15/23
<b>MMSE score, mean (SD)</b>	22.1 (7.4)	23.5 (6.4) <sup>c</sup>	21.8 (8.0)	18.19 (8.5) <sup>a</sup>	20.1 (7.5)	22.1 (7.7)
<b>MRI, n (%)</b>	134/314 (42.7)	66/152 (43.4)	29/61 (47.5)	16/32 (50.0)	16/31 (51.6)	7/38 (18.4)
<b>Pathogenic variant, n (%)</b>	34/314 (10.8)	19/152 (12.5)	5/61 (8.2)	3/32 (9.4)	2/31 (6.5)	5/38 (13.2)
<b>Availability of CSF biomarkers, n (%)</b>	103/314 (32.8)	45/152 (29.6)	24/61 (39.3)	14/32 (44.8)	5/31 (16.1)	15/38 (39.5)
<b>CSF A<math>\beta</math>1-42/1-40 ratio, mean (SD)</b>	0.0837 (0.0301)	0.0977 (0.0199) <sup>c</sup>	0.0908 (0.0274) <sup>c</sup>	0.0524 (0.0263) <sup>a,b</sup>	0.0854 (0.0299)	0.0706 (0.0350)
<b>AD biomarker-positive, n (%)</b>	36/103 (35.0)	6/45 (13.3) <sup>c,e</sup>	7/24 (29.17) <sup>c</sup>	12/14 (85.7) <sup>a,b</sup>	2/5 (40.0)	9/15 (60.0) <sup>a</sup>
<b>Follow-up duration, y, median (SD)</b>	0.79 (1.0)	0.83 (1.0)	0.92 (1.0)	0.0 (1.0)	0.67 (0.83)	0.92 (1.0)

Abbreviations: A $\beta$  =  $\beta$ -amyloid; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; lvPPA = logopenic variant of PPA; MMSE = Mini-Mental State Examination; ncvPPA = nonclassifiable variant of PPA; nfvPPA = nonfluent variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA. Significantly different ( $p < 0.005$ ) compared with <sup>a</sup>bvFTD, <sup>b</sup>nfvPPA, <sup>c</sup>lvPPA, <sup>d</sup>svPPA, <sup>e</sup>ncvPPA.

Severity of symptoms was scored as follows: score 0 = no impairment, score 0.5 = very mild impairment, score 1 = mild impairment, score 2 = moderate impairment, and score 3 = severe impairment.

### MRI Acquisition and Analysis

Standardized T1-weighted MRI scans were available for 134 of 314 participants at baseline. MRI scans were acquired on 3T Siemens scanners using different models (2 TrioTim, 3 Verio, 2

Skyra, and 1 Prisma). T1-weighted images were acquired using a magnetization-prepared rapid gradient-echo sequence with the following parameters: repetition time = 2,500 milliseconds, echo time = 4.37 milliseconds, inversion time = 1,100 milliseconds, flip angle = 7°, GRAPPA factor = 2, field of view = 256 × 256 mm<sup>2</sup>, slice thickness = 1 mm, and 192 contiguous sagittal slices.

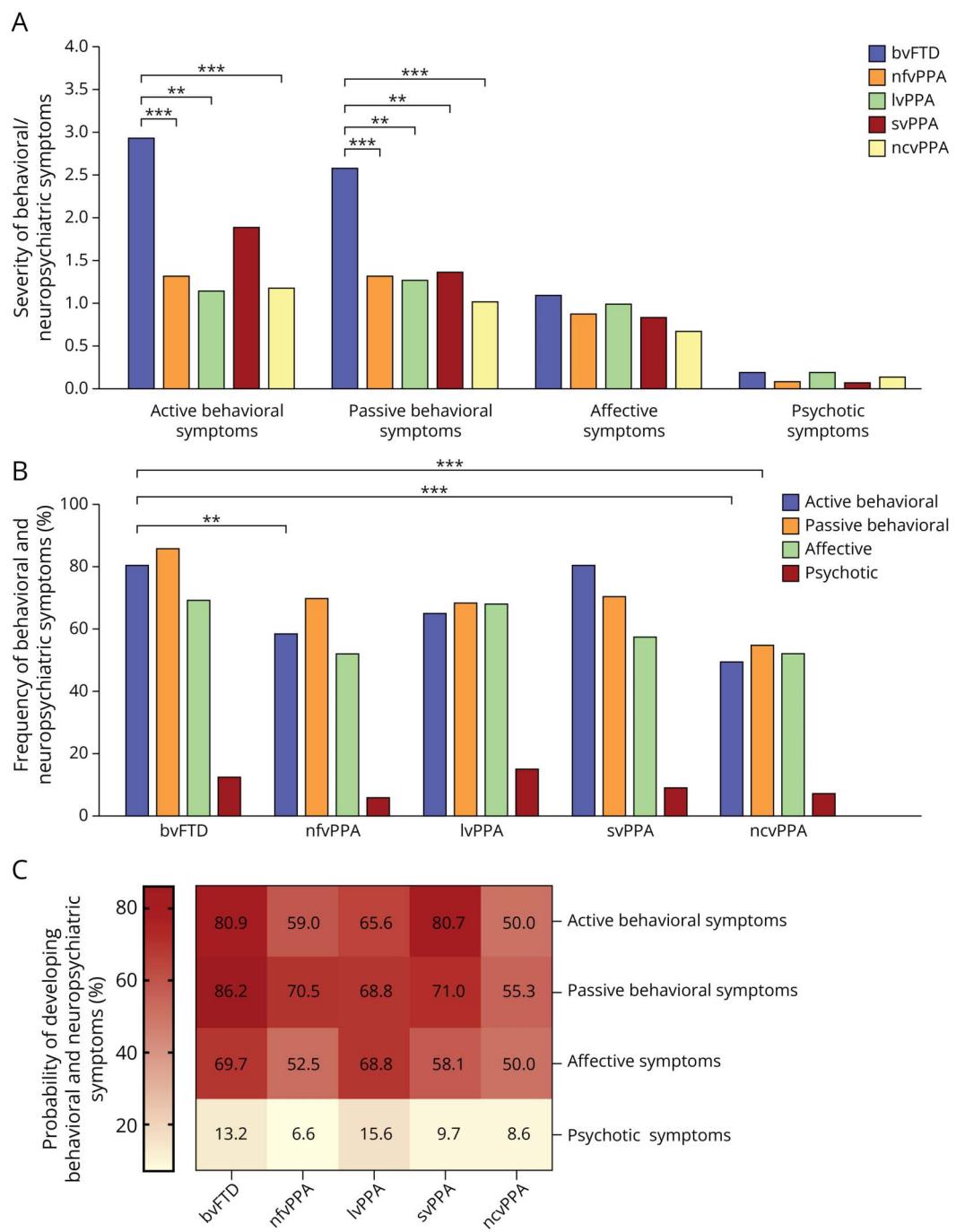
T1-weighted images were analyzed using the surface-based stream in FreeSurfer<sup>15</sup> to obtain cortical and subcortical volumes

**Table 2** Rotated Component Matrix

	Active behavioral phenotype	Passive behavioral phenotype	Affective phenotype	Psychotic phenotype
<b>Irritability/lability</b>	0.795	0.086	0.327	0.022
<b>Agitation/aggression</b>	0.790	0.082	0.232	0.142
<b>Disinhibition</b>	0.726	0.369	-1.36	0.055
<b>Euphoria/elation</b>	0.489	0.397	-0.223	0.262
<b>Hyperorality and appetite changes</b>	0.167	0.797	0.002	0.116
<b>Aberrant motor behavior</b>	0.190	0.728	0.127	-0.160
<b>Apathy</b>	0.256	0.530	0.317	0.073
<b>Impaired sleep</b>	-0.076	0.445	0.416	0.263
<b>Depression</b>	0.145	0.074	0.772	0.170
<b>Anxiety</b>	0.492	0.235	0.542	-0.086
<b>Delusions</b>	0.151	0.039	-0.024	0.818
<b>Hallucinations</b>	0.022	0.023	0.362	0.619

Factor loadings exceeding 0.4 are color-coded depending on the associated component.

**Figure 1** Severity and Frequency of Behavioral and Neuropsychiatric Symptoms at Baseline Visit

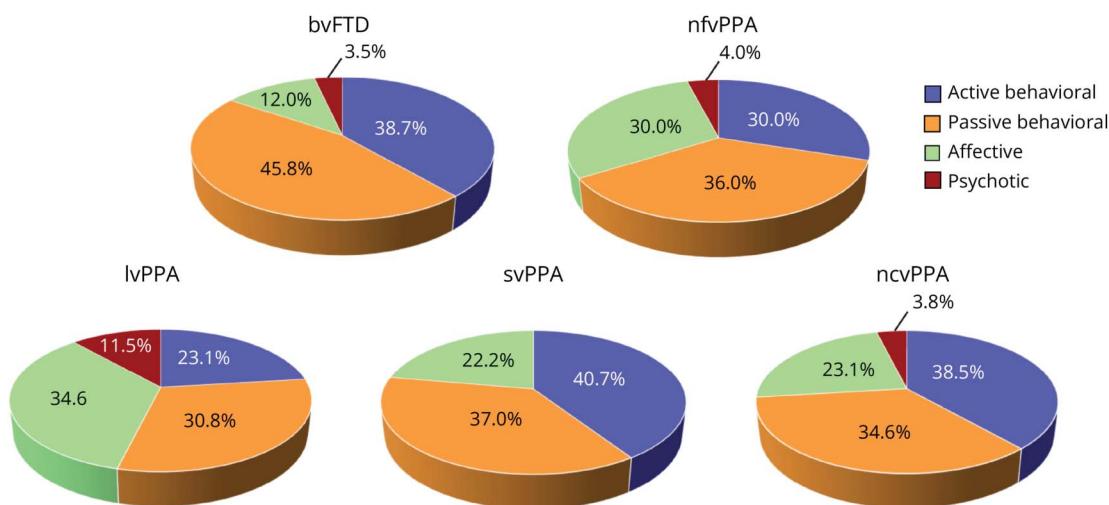


(A) Comparison of the severity of behavioral and neuropsychiatric symptoms as defined by the component scores of the individual phenotypes according to the clinical diagnoses. (B) Comparison of the frequency of symptom occurrence among distinct clinical groups. Patients may present symptoms of different behavioral or neuropsychiatric phenotypes at the same time. Therefore, the sum of frequencies does not add up to 100%. Bonferroni-corrected  $p$  values: \* $p$  < 0.005, \*\* $p$  < 0.001, \*\*\* $p$  < 0.0001 (C). Heatmap showing the probability (%) of developing behavioral and neuropsychiatric symptoms across FTD and PPA subtypes. Rows represent symptom groups; columns represent diagnostic groups. Color intensity corresponds to the probability of symptom occurrence. bvFTD = behavioral variant FTD; FTD = frontotemporal dementia; lvPPA = logopenic variant of PPA; ncvPPA = nonclassifiable variant of PPA; nfvPPA = nonfluent variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.

and cortical thickness. It included Talairach transformation, bias-field correction, removal of nonbrain tissues, and automated segmentation of data into gray and white matter.<sup>16</sup> Subsequently, cortical inflation, registration to a spherical atlas, and parcellation of the cerebral cortex into gyral and sulcal units were

performed.<sup>17</sup> Labeling of cortical regions was performed on the basis of the Desikan-Killiany atlas.<sup>18</sup> Cortical thickness was calculated by measuring the closest distance from pial to white matter boundary at each vertex.<sup>19</sup> In addition, automated volumetric processing based on a probabilistic atlas in FreeSurfer

**Figure 2** Proportion of the Predominant Phenotype Depending on the Clinical Diagnosis



Cases were assigned to the component with the highest PCA-based score. Because patients may present behavioral and neuropsychiatric symptoms of other phenotypes in addition to the symptoms of the predominant phenotype, Figure 2C is not congruent with Figure 2B. Owing to rounding, the sum of percentages may not add up to exactly 100%. bvFTD = behavioral variant frontotemporal dementia; lvPPA = logopenic variant of PPA; ncvPPA = nonclassifiable variant of PPA; nfvPPA = nonfluent variant of PPA; PCA = principal component analysis; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.

generated subcortical labels.<sup>19</sup> From these labels, volumetric measures of 7 subcortical gray matter structures (thalamus, caudate nucleus, nucleus accumbens, pallidum, putamen, hippocampus, and amygdala) were extracted for each hemisphere.

## Statistical Analysis

Data were analyzed using GraphPad Prism (version 10.5.0, GraphPad Software, Boston, MA) or IBM SPSS Statistics (version 28.0, IBM Corp., Armonk, NY). Nondichotomized demographic data were compared through Kruskal-Wallis and post hoc Bonferroni-corrected Mann-Whitney *U* tests. Fisher exact and  $\chi^2$  tests were performed to compare dichotomized variables. Median follow-up duration was compared between groups using the Brown-Mood median test. Standard statistical significance level was set at  $p < 0.05$ . Normality was assessed using the Shapiro-Wilk test.

Principal component analysis (PCA) with varimax rotation based on Pearson correlation was applied to NPI-Q data to delineate groups of behavioral and neuropsychiatric symptoms. Variables with factor loadings above 0.4 were considered as part of a group. Where appropriate, variables were assigned to multiple components. Labeling of the components was conducted post hoc, depending on the pattern of symptoms. No a priori assumptions regarding the grouping of symptoms were applied.

Component scores were calculated from the factor loading-weighted variable sum scores of each component and were compared using Kruskal-Wallis and post hoc Bonferroni-corrected Mann-Whitney *U* tests at baseline.

Participants exhibiting neuropsychiatric or behavioral symptoms were assigned to the PCA component with their highest

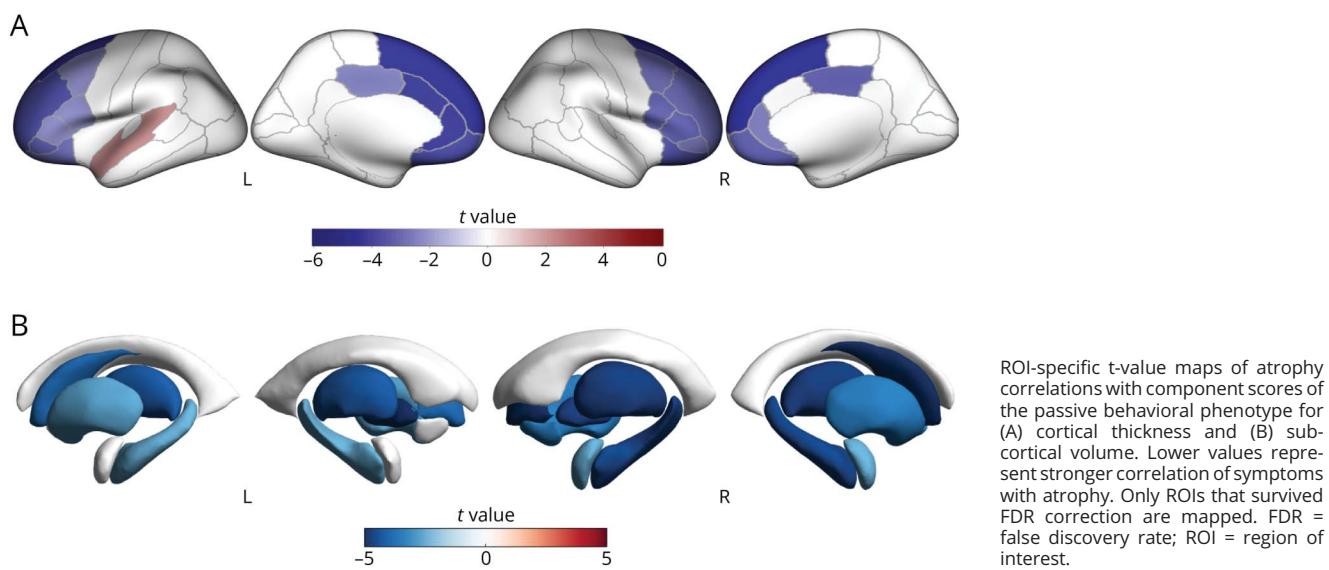
score to assess the distribution of the predominant phenotype across clinical diagnoses.

Linear regression models were used to test for significant associations between the FreeSurfer DKT (aparc + asec) atlas region-of-interest (ROI) thickness scores and the calculated component scores. All models were adjusted for age, sex, education, segmentation-based total intracranial volume, and site. All *p* values were then corrected for false discovery rate (FDR) at a level of  $\alpha = 0.05$ . R 4.4.1 (R Core Team, 2022) was used for statistical analysis. *fsbrain*<sup>20</sup> (version 0.5.5) and the ENIGMA Toolbox<sup>21</sup> (version 2.0.3) for MATLAB 2023b (The MathWorks Inc.) were used to visualize the results.

In addition, we applied linear mixed-effects (LME) models to examine the temporal evolution of the component scores and assess differences between groups. We tested several models, including a random intercept per participant. Fixed-effect variables included time from symptom onset, diagnostic group, sex, and years of education. Second-order contributions and logarithmic transformations were tested, with no significant improvement in the model.

We applied a type II Wald  $\chi^2$  test to the model, to estimate the relationship between the fixed variables and the component scores. Afterward, estimated marginal means (EMMs)<sup>22</sup> were calculated from the fitted models to assess the effect of group on the longitudinal evolution of the component scores while controlling for covariates such as age and sex. EMMs were preferred over simple means because of the unbalanced sample sizes across treatment groups. Standardized effect sizes were calculated using pairwise differences of the EMMs. These were evaluated in the time range from 0 to +15 years

**Figure 3** Correlation of Component Scores of the Passive Behavioral Phenotype With Cerebral Atrophy Using Linear Regression Models



from symptom onset. These analyses were conducted using R 4.1.2 (R Core Team, 2021), the *lme4*<sup>23</sup>, the *emmeans*<sup>24</sup> (version 1.8.8), the *interactions*<sup>25</sup> (version 1.1.0), and the *ggeplot2*<sup>26</sup> packages.

## Data Availability

The study data are subject to restrictions and are, therefore, not publicly available. Data can be obtained on reasonable request after submission of a formal data access application to the DZNE (klinische-studien@dzne.de) and with permission from the cohorts' steering committee. The analysis code is openly available at [github.com/pakitochus/describe\\_analysis.git](https://github.com/pakitochus/describe_analysis.git).

## Results

### Demographics

Data from 314 participants were used for delineating groups of associated behavioral and neuropsychiatric symptoms: 152 patients with bvFTD, 61 with nfvPPA, 32 with lvPPA, 31 with svPPA, and 38 with ncvPPA. Demographic data are provided in Table 1. Individuals diagnosed with bvFTD were significantly younger at symptom onset and baseline visit compared with patients with nfvPPA and ncvPPA. The Mini-Mental State Examination score was significantly lower in patients with lvPPA than in the bvFTD group at baseline. The CSF  $\beta$ -amyloid (A $\beta$ ) 1-42/1-40 ratio was lower in individuals with lvPPA compared with bvFTD and nfvPPA groups, and the rate of AD biomarker-positive cases (A $\beta$ 1-42/1-40 ratio  $<0.08$ <sup>13</sup>) was higher in lvPPA and ncvPPA groups compared with bvFTD and nfvPPA groups. Groups did not differ in education, sex, disease duration, frequency of genetic variants, follow-up duration, and number of follow-up visits (eTable 1). Participants with and

without MRI data did not differ significantly regarding clinical and demographic measures.

### Principal Component Analysis

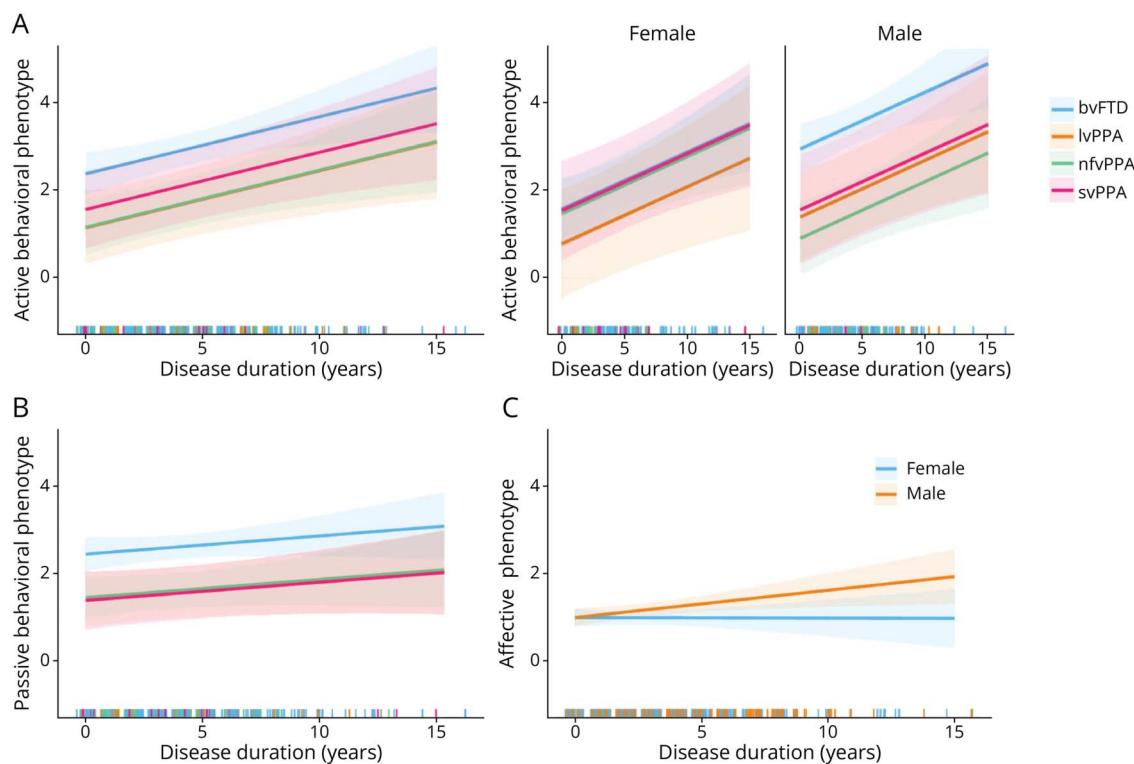
PCA with varimax rotation revealed the presence of 4 components with eigenvalues above 1, explaining 60.8% of variance (eFigure 1). The assessed symptoms grouped into the components as follows (Table 2):

1. Active behavioral phenotype: irritability/lability, agitation/aggression, disinhibition, euphoria/elation, anxiety
2. Passive behavioral phenotype: hyperorality and appetite changes, aberrant motor behavior, apathy, impaired sleep
3. Affective phenotype: impaired sleep, depression, anxiety
4. Psychotic phenotype: delusions, hallucinations

### Frequency and Severity of Neuropsychiatric and Behavioral Symptoms

When comparing component scores of active behavioral symptoms, we detected significant group differences ( $p < 0.0001$ ), with patients with bvFTD showing significantly higher component scores at baseline than individuals with lvPPA ( $r = -0.26$ ,  $U = 1,465$ ,  $p < 0.001$ ,  $n_1 = 152$ ,  $n_2 = 32$ ), ncvPPA ( $r = -0.30$ ,  $U = 1,643$ ,  $p < 0.0001$ ,  $n_1 = 152$ ,  $n_2 = 38$ ), and nfvPPA ( $r = -0.30$ ,  $U = 2,895$ ,  $p < 0.0001$ ,  $n_1 = 152$ ,  $n_2 = 61$ ) (Figure 1A). Although not significant, patients with svPPA demonstrated higher component scores of active behavioral symptoms compared with the other PPA subtypes. There were significant group differences for the passive behavioral phenotype ( $p < 0.0001$ ), with patients with bvFTD showing higher component scores than in nfvPPA ( $r = -0.33$ ,  $U = 2,674$ ,  $p < 0.0001$ ,  $n_1 = 152$ ,  $n_2 = 61$ ), lvPPA ( $r = -0.27$ ,  $U = 1,423$ ,  $p < 0.001$ ,  $n_1 = 152$ ,  $n_2 = 32$ ), svPPA ( $r = -0.24$ ,  $U =$

**Figure 4** Linear Mixed-Effects Models of Calculated Component Scores (With 95% CI) vs Years Since Symptom Onset



Individual data points are not plotted to prevent disclosure of genetic status. However, the time of the examination is marked on the x-axis by a colored dash. bvFTD = behavioral variant frontotemporal dementia; lvPPA = logopenic variant of PPA; nfvPPA = nonfluent variant of PPA; PPA = primary progressive aphasia; svPPA = semantic variant of PPA.

1,479,  $p < 0.0001$ ,  $n_1 = 152$ ,  $n_2 = 31$ ), and ncvPPA ( $r = -0.35$ ,  $U = 1,419$ ,  $p < 0.001$ ,  $n_1 = 152$ ,  $n_2 = 38$ ) groups. No significant group differences regarding the severity of affective and psychotic symptoms could be detected (Figure 1A).

Chi-squared analysis detected significant group differences regarding the frequency of active and passive behavioral symptoms at baseline visit (Figure 1B). Post hoc analysis revealed active behavioral symptoms being more frequent in bvFTD compared with nfvPPA (80.9% vs 59.0%, relative risk [RR] 1.440 [1.142–1.925],  $p < 0.001$ ) and ncvPPA (80.9% vs 50.0%, RR 1.434 [1.169–1.882],  $p < 0.001$ ). Passive behavioral symptoms were more frequent in bvFTD compared with ncvPPA (86.2% vs 55.3%, RR 1.560 [1.219–2.182],  $p < 0.0001$ ). There were no significant group differences regarding the frequency of affective and psychotic symptoms. In patients with bvFTD and nfvPPA, passive behavioral symptoms were most frequent (86.2% and 70.5%), followed by active behavioral (80.9% and 59.0%) and affective (69.7% and 52.5%) symptoms. In patients with svPPA, active behavioral symptoms were more prevalent than passive behavioral symptoms (80.7% and 71.0%), followed by affective symptoms (58.1%). In patients with lvPPA, affective and passive behavioral symptoms were most frequent (both 68.8%), closely followed by active behavioral symptoms (65.6%). In patients with ncvPPA, active and passive behavioral

symptoms, as well as affective symptoms, occurred at comparable frequencies (50.0%–55.3%). Psychotic symptoms were least common across all groups (15.6%–6.6%). Probabilities of developing specific symptom clusters across clinical diagnoses are displayed in Figure 1C.

### Predominant Phenotype

The  $\chi^2$  test revealed significant group differences regarding the presence of a predominant affective phenotype ( $p < 0.01$ ) (Figure 2). Post hoc analysis found the predominant affective phenotype to be significantly more frequent in patients with nfvPPA (30.0% vs 12.0%, RR 0.68 [0.463–0.900],  $p = 0.0033$ ) and lvPPA (34.6% vs 12.0%, RR 0.7428 [0.5228–0.9275],  $p = 0.0033$ ) compared with patients with bvFTD. No significant group differences regarding the frequency of the predominant active or passive behavioral and psychotic phenotypes could be detected. A predominant affective phenotype was present in 34.6% of patients with lvPPA and 30% of those with nfvPPA, but only in 12% of patients with bvFTD. Only in patients with lvPPA, the predominant affective phenotype was most common (34.6%), followed by the passive (30.8%) and behavioral (23.1%) phenotypes. In patients with bvFTD, the most common predominant phenotype was the passive behavioral phenotype (45.8%), followed by the active behavioral phenotype (38.7%). By contrast, in patients with svPPA, the active behavioral phenotype was most common (40.7%),

followed by the passive behavioral phenotype (37.0%). A predominant psychotic phenotype was the least frequent across all groups and was detected in 3.5% of patients with bvFTD, 4.0% of those with nfPPA, 3.8% of those with ncPPA, and 11.5% of those with lvPPA. None of the patients with svPPA exhibited a predominant psychotic phenotype.

## Atrophy Patterns

ROI-based regression identified a strong correlation of component scores of the passive behavioral phenotype with bilateral frontal lobe and anterior and posterior cingulate gray matter atrophy (Figure 3A). Regarding subcortical structures, component scores of the passive behavioral phenotype were associated with bilateral atrophy of the putamen, caudate nucleus, pallidum, thalamus, and hippocampus, with slightly stronger correlations for the right side (Figure 3B). Furthermore, there was a correlation with right-sided atrophy of the amygdala. Regarding the affective phenotype, the uncorrected analysis yielded a correlation with left-sided atrophy of the rostral and right-sided atrophy of the caudal anterior cingulate cortex (ACC). However, this finding was not significant after FDR correction. No significant correlation with brain atrophy could be detected for the component scores of the active behavioral and psychotic phenotypes.

## LME Models

The visual distribution of the calculated component scores over time for the 4 diagnostic categories, that is, bvFTD, nfPPA, lvPPA and svPPA, is illustrated in Figure 4 (eTable 2). Time from symptom onset (0.130 [0.044–0.217],  $p < 0.003$ ), sex (1.376 [0.666–2.087],  $p < 0.001$ ), and the interaction between nfPPA and sex (−1.940 [−3.242 to −0.638],  $p = 0.004$ ) showed a significant effect on the active behavioral phenotype, with symptom severity increasing over time and being most pronounced in men with bvFTD. Furthermore, there was a significant effect of the diagnostic category on the component scores of the passive behavioral phenotype, with symptoms being more pronounced in the bvFTD group than in any other diagnostic group. For the affective phenotype, a significant interaction between time and sex (0.063 [0.010–0.117],  $p = 0.021$ ) indicated a progressive increase in symptom severity in men over time. Owing to zero inflation with few nonzero observations, the assumptions for LME could not be met and no model could be calculated for the psychotic phenotype.

Because the interaction between time from symptom onset and diagnostic category had no significant effect on the severity of active and passive behavioral symptoms, groups did not differ in the progression of these symptoms over time. Component scores of the active behavioral phenotype were significantly higher in patients with bvFTD compared with nfPPA (1.315,  $p < 0.01$ ) and lvPPA (1.002,  $p < 0.05$ ) groups. This effect was primarily driven by men while no significant group differences were observed among women. In addition, component scores of the passive behavioral phenotype were higher in patients with bvFTD compared with nfPPA (0.635,

$p < 0.001$ ), lvPPA (0.662,  $p < 0.01$ ), and svPPA (0.678,  $p < 0.05$ ) groups. Regardless of the diagnostic category, the number of affective symptoms remained largely stable over time in women. By contrast, severity of affective symptoms increased progressively in men and was significantly higher compared with women (0.062,  $p < 0.01$ ).

When the 3 PPA variants were merged into a single group and a binary comparison between bvFTD and PPA was performed, the LME yielded comparable results (eFigure 2 and eTable 3). Wald tests revealed a significant effect of the diagnostic category on the active (1.19 [0.71–1.67],  $p < 0.001$ ) and passive (1.10 [0.74–1.46],  $p < 0.01$ ) behavioral phenotypes, with symptoms being more pronounced in bvFTD than in PPA. Furthermore, time from symptom onset (0.12 [0.04–0.20],  $p < 0.01$ ) and sex (0.57 [0.09–1.06],  $p < 0.05$ ) showed a significant effect on the active behavioral phenotype, with symptoms increasing over time and being more pronounced in men. Education had a small but significant effect on the affective phenotype, with symptom severity being inversely associated with years of education (−0.04 [−0.08 to −0.00],  $p < 0.05$ ).

## Discussion

We present a data-driven approach to characterize the phenotypic range of behavioral and neuropsychiatric symptoms and their association with time and brain atrophy in a large cohort of patients with FTD and PPA. We identified 4 natural symptom groups across the diagnostic categories: active behavioral, passive behavioral, affective, and psychotic phenotypes.

In line with previous work,<sup>6,27</sup> neuropsychiatric and behavioral symptoms were common across all groups, highlighting that PPA extends beyond aphasia and that neuropsychiatric and behavioral symptoms contribute significantly to the clinical presentation and symptom burden. Neither behavioral nor neuropsychiatric symptoms were significantly more frequent in the bvFTD group compared with the lvPPA and svPPA groups at baseline. Only in patients with nfPPA and ncPPA, active and passive behavioral symptoms were significantly less frequent compared with the bvFTD group but were still reported in 60%–70% of cases. Behavioral symptoms, though expected to predominate in bvFTD, were relatively evenly distributed across groups. Given that pronounced behavioral alterations are a hallmark of bvFTD,<sup>3</sup> it is not surprising that active and passive behavioral symptoms were most severe in bvFTD. We detected a nonsignificant trend toward active behavioral symptoms being more severe in svPPA compared with the other PPA subtypes. There was no significant difference between svPPA and bvFTD groups regarding frequency and severity of active behavioral symptoms. This observation did not apply to the severity of passive behavioral symptoms, consistent with previous smaller studies reporting a high prevalence of disinhibition, compulsiveness, and euphoria in svPPA.<sup>6,27–29</sup> In one of these studies,

more than 50% of the participants with svPPA also fulfilled clinical criteria for bvFTD within the first 5 years of disease.<sup>6</sup> As described previously,<sup>3</sup> we found the predominant passive behavioral phenotype to be more frequent than the active behavioral one in bvFTD.

Behavioral symptoms were more pronounced than neuropsychiatric symptoms in patients with bvFTD and svPPA, reflected by the high frequency of the predominant active and passive behavioral phenotypes and the lower frequency of the predominant affective and psychotic phenotypes in both groups. This contrasts with the comparable frequency of symptoms across groups. A potential explanation may lie in the data collection methodology using the caregiver-completed NPI-Q.<sup>14</sup> Highly noticeable symptoms with a significant impact on daily life such as behavioral disturbances correlate with caregiver distress<sup>30</sup> and may overshadow more subtle symptoms such as affective disturbances. Moreover, neuropsychiatric symptoms are often perceived as stigmatizing,<sup>31</sup> which may lead individuals to refrain from disclosing them. These biases could contribute to an underestimation of both their prevalence and severity. Considering the substantial impact of affective symptoms on patients' quality of life, clinicians should proactively assess these domains to facilitate proper treatment.

Affective symptoms were common across all groups, with prevalences ranging from 52% to 70% at baseline. A predominant affective phenotype was observed particularly frequently in patients with nfPPA and lvPPA, while being less common but still considerable in those with bvFTD and svPPA. Previous studies demonstrated that affective symptoms are common in FTD and PPA even before diagnostic criteria are met,<sup>32,33</sup> consistent with the high risk of FTD being misdiagnosed as PPD, such as major depressive disorder.<sup>8</sup> These data emphasize the need for a proper diagnostic workup, particularly in late-life affective symptoms, given that the age at onset of primary mental disorders is typically in adolescence and early adulthood.<sup>34</sup> In cases of diagnostic uncertainty, biomarkers such as neurofilament light chain can help differentiate FTD from PPD.<sup>35</sup> Longitudinal analyses yielded a sex-related effect on affective symptoms. The severity of affective symptoms in men increased over time, eventually surpassing the largely stable symptom burden in women. A similar observation has recently been made in genetic FTD.<sup>32</sup> These findings point to a disease-specific effect because, in the general population, affective symptoms are more prevalent in women and typically diminish with advancing age.

Psychotic symptoms constituted the least prevalent symptom group and occurred in 6.6%–15.6% of patients. Nevertheless, psychotic symptoms either were mildly expressed or occurred in patients with high component scores of other symptom groups, potentially reflecting a more progressed disease stage. A predominant psychotic phenotype was only observed in 3.5% of patients with bvFTD, 4.0% of those with nfPPA, and

11.5% of those with lvPPA, whereas none of the patients with svPPA exhibited a predominant psychotic phenotype. The comparatively high occurrence of the predominant psychotic phenotype among patients with lvPPA is noteworthy, particularly regarding the underlying AD neuropathology, but should be interpreted with caution and requires confirmation in larger cohorts. Altogether, a predominant psychotic phenotype was rare across all groups. Thus, the presence of pronounced psychotic symptoms in the absence of other neuropsychiatric or behavioral symptoms should prompt careful diagnostic evaluations with respect to other neurodegenerative conditions or PPD. However, psychotic symptoms remain consistent with an FTD diagnosis, particularly in *C9orf72* variant carriers,<sup>32</sup> where they occur in up to 60% of the variant carriers during the disease course.<sup>36</sup>

The correlation between symptomatology and histopathology and atrophy is a well-established concept in neurodegenerative diseases.<sup>37</sup> In agreement with previous work,<sup>37</sup> we found robust correlations between the passive behavioral phenotype and cortical atrophy of the frontal lobe as well as the anterior and posterior cingulate gyrus. Subcortical structures have been shown to play a key role in FTD, with some studies suggesting that their atrophy may precede cortical changes.<sup>38,39</sup> The thalamus, in particular, has been linked to the emergence of neuropsychiatric symptoms.<sup>39</sup> Consistent with previous work, passive behavioral symptoms strongly correlated with bilateral, right-predominant atrophy of the caudate nucleus, pallidum, putamen, hippocampus, thalamus, and amygdala.<sup>29</sup> Of interest, the passive behavioral symptom group includes changes in appetite. Previous studies demonstrated that right-sided orbitofrontal-insular-striatal atrophy is associated with alterations in eating behavior and may be linked to binge eating.<sup>40,41</sup> Strikingly, we did not identify a correlation between the active behavioral phenotype and regional atrophy. Based on previous studies, we hypothesized that component scores would most likely correlate with right-predominant atrophy of the prefrontal cortex, amygdala, nucleus accumbens, and hippocampus.<sup>37</sup> At present, we lack a clear explanation for this finding, but potential contributing factors could include the composition of the symptom group by PCA or the heterogeneity of the study population.

The uncorrected analysis linked affective symptoms to left rostral and right caudal ACC atrophy, but this finding did not remain significant after FDR correction. Previous studies demonstrated an association between reduced ACC activity and atrophy with depressive symptoms in PPD.<sup>42,43</sup> Similarly, in anxiety disorders, the ACC seems to play a key role, with reduced activation and disrupted connectivity to the amygdala being critical factors.<sup>44</sup> Our findings suggest that neural networks underlying affective symptoms in PPD and neurodegenerative conditions may overlap. Nevertheless, the neuroanatomical correlates of affective symptoms in FTD and PPA remain underexplored. A study on pure genetic FTD identified distinct neuroanatomical correlates for depression and anxiety related to different genetic groups.<sup>45</sup> This

widespread distribution of neurodegeneration underlying affective symptoms in FTD patients with distinct neuropathologies might have obscured groupwise atrophy patterns in our study.

No correlation between the psychotic phenotype and brain atrophy was identified in the current cohort, likely due to the restricted resolution of the analysis and the heterogeneity of the cohort. Psychotic symptoms in FTD and PPA, though less studied compared with other neurodegenerative diseases, are progressively gaining attention, particularly in *C9orf72*-associated cases. Specifically, thalamic atrophy plays a prominent role in *C9orf72* pathogenic variant carriers<sup>39</sup> and has been linked to the occurrence of hallucinations in this group,<sup>32</sup> whereas the neuroanatomical correlates of psychotic symptoms in sporadic cases seem to be more widespread.<sup>46</sup>

Longitudinal analyses revealed that the severity of active behavioral symptoms increases over time and is dependent on the diagnostic group. Symptoms were particularly severe in participants with bvFTD compared with those with nfPPA and lvPPA. This effect was primarily driven by men. A comparable observation was recently reported in genetic FTD,<sup>32</sup> supporting the idea of a greater executive and behavioral reserve in women.<sup>47</sup> A recent study demonstrated that men are more likely to present with bvFTD while women are more commonly diagnosed with a PPA variant.<sup>48</sup> These findings suggest a sex-specific influence on the predilection sites for neurodegeneration. Our data align with this hypothesis, particularly as we also observed a higher prevalence of bvFTD in men. However, the biological basis of these observations remains poorly understood, highlighting the need for further research on sex-related differences.

A strength of our study represents the large number of participants and the identification of natural symptom groups by PCA. By using a data-driven approach, we were able to conduct an objective analysis that diverges from traditional clinical categorizations and remains uninfluenced by preconceived assumptions. Moreover, the study population is expected to predominantly comprise sporadic cases, a cohort that is typically underrepresented in large-scale studies, allowing for comparisons with previous findings in genetic FTD.

However, we acknowledge the absence of healthy controls, although the primary objective of this work was to compare symptomatology across the FTD and PPA spectrum. Another limitation is the lack of neuropathologic validation. However, participants were classified based on clinical criteria,<sup>3,4</sup> which are likely to predict the underlying pathology with a reasonable degree of probability,<sup>3,5</sup> and percentages of A $\beta$ -positive cases were within the expected ranges.<sup>5,49</sup> Both specific fluid and imaging biomarkers for FTD are not yet available but are currently under development and should be integrated into future research.<sup>50-52</sup> While the multicenter design and the clinically diverse cohort strengthen the internal validity of our findings, generalizability may be limited because of the single-

country recruitment and lack of ethnic diversity. Because no external cohort was available, we could not confirm the external validity of our findings. Thus, broader international cohorts are warranted to validate our symptom-based phenotyping approach. Another limitation may be the correlation structure and measurement scale of our PCA. While we performed PCA using the Pearson correlation matrix with varimax rotation to maintain comparability with previous studies<sup>53</sup> and to achieve a clear, orthogonal component structure, we acknowledge that the NPI-Q items are ordinal and that a polychoric PCA with oblique rotation might better capture the underlying data structure. Sensitivity analyses, however, demonstrate that the main components and their clinical interpretability remain largely stable (eTables 4 and 5), and therefore, the original PCA provides a valid basis for the subsequent analyses. The high dropout rates, presumably among more severely affected patients, may have introduced a selection bias in the longitudinal analyses, as the estimated trajectories are likely driven by a healthier subsample. Last, standardized MRI scans were available for only 42.7% of participants, which may have reduced the interpretability and robustness of our analyses and could again have introduced selection bias, because this subgroup may not fully represent the entire cohort.

In summary, our study successfully categorized the range of behavioral and neuropsychiatric symptoms into 4 natural groups, which were observed in bvFTD and the different PPA subtypes at comparable frequencies. Symptom expression was influenced by the clinical diagnosis, disease duration, and sex. These findings are relevant to patients and clinicians as they provide a framework for understanding symptom patterns in FTD and PPA, potentially improving diagnostic accuracy and guiding tailored therapeutic approaches.

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