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RESEARCH ARTICLE

# The impact of sex on clinical profiles of patients with behavioral variant frontotemporal dementia

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## Abstract

**INTRODUCTION:** Sex differences in behavioral variant frontotemporal dementia (bvFTD) remain understudied, especially when controlling for sex differences already existing in the general population.

**METHODS:** Clinical features were analyzed in 620 bvFTD participants. Sex-diagnosis interactions were examined in 1029 bvFTD and 1029 healthy control (HC) participants for neuropsychiatric symptoms, and in 1109 bvFTD and 1109 HC participants for cognitive, behavioral, and language measures.

**RESULTS:** Males with bvFTD showed greater-than-expected loss of empathy and nighttime behavioral symptoms relative to females, based on sex-by-diagnosis interactions. They also exhibited higher-than-expected punishment sensitivity. In contrast, females with bvFTD showed greater-than-expected impairments in semantic fluency and picture naming relative to HC females.

**DISCUSSION:** Findings reveal that males with bvFTD present with more prominent behavioral disturbances, while females with bvFTD experience greater language impairments. This work is an important step toward integrating social determinants of health, such as sex, into the diagnostic and care paradigms for bvFTD.

KEYWORDS
behavior, cognition, Frontotemporal dementia, language, neuropsychatric symptoms, sex differences

## Highlights

- Males with behavioral variant frontotemporal dementia (bvFTD) show more empathy loss and nighttime behavioral symptoms
- Females with bvFTD have greater deficits in naming and semantic fluency
- Findings support including sex in diagnostic and care models for bvFTD

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## 1 | INTRODUCTION

Frontotemporal dementia (FTD) is the second most common type of neurodegenerative disease among individuals under 65 years old following Alzheimer's disease.[1–3] In the United States, the prevalence of FTD among individuals aged 45 to 64 was estimated to be 15 to 22 per 100,000 people.[2,3] Behavioral variant FTD (bvFTD), the most prominent variant of FTD, is characterized by behavioral disinhibition, apathy, loss of empathy, compulsive/ perseverative behavior, hyperorality, and executive dysfunction.[4] Diagnosis of bvFTD still remains a challenging task due to a lack of awareness in general practitioners combined with the overlap of the symptoms with psychiatric disorders[5] or other neurodegenerative diseases such as Alzheimer's dementia or primary progressive aphasia[6,7].

Sex differences may contribute to the challenges in diagnosing bvFTD. Beyond the fact that previous investigations have shown that bvFTD is more prevalent among males,[8–10] the disease may also present differently in males and females.[11] Studying the differences in symptoms between males and females could improve our understanding of this specific type of dementia and ultimately decrease misdiagnosis and late diagnosis of those suffering from it. Nonetheless, in comparison to other types of dementia such as Alzheimer's disease,[12,13] very little research has focused on the sex differences in bvFTD[14].

A study by Logroscino and colleagues showed that males with bvFTD had better global cognition (as measured by the Mini-Mental State Exam [MMSE]) than females with bvFTD.[9] They hypothesized that this difference may be due to higher rates of misdiagnosis or late diagnosis in females, likely stemming from sex-related biases in the diagnosis of bvFTD.[9] In another study by Pengo and colleagues, while global cognitive impairment was comparable between the two sexes, males with bvFTD performed better than females with bvFTD in more detailed cognitive tests such as Trail Making Test (TMT) Parts A and B, semantic fluency, story recall, and Rey Complex Figure.[11] Conversely, they showed that males with bvFTD presented more severe behavioral problems compared to females with bvFTD, as demonstrated by higher frequencies of apathy, aggressiveness, hypersexuality, poor judgment, and irritability.[11] Finally, in a study by Illán-Gala and colleagues (2021), females with bvFTD showed more severe frontal and temporal atrophy at diagnosis, along with lower global cognition (MMSE) and higher levels of delusions, as measured by the Neuropsychiatric Inventory (NPI).[14] No differences were found in detailed cognitive tests, bvFTD symptoms, or depressive symptoms.[14] However, when controlling for the level of brain atrophy, they found that females performed better than expected on executive tasks and exhibited less apathy, appetite changes, and sleep disturbances than expected.[14] These findings suggested that females with bvFTD may have greater executive and behavioral reserve than males[14].

The studies mentioned have two major limitations: (1) small sample sizes and (2) the failure to account for sex differences in cognition that already exist in cognitively unimpaired older adults in the general population. Overall, it has been reported that healthy males outperform healthy females in visuospatial tasks and mathematics, while females outperform males in most other cognitive domains, including verbal abilities and episodic memory.[15,16] To account for this, an interesting approach, rather than strictly comparing males and females with bvFTD, would be to investigate potential interaction effects between sex (male, female) and group (bvFTD, healthy controls). In this context, interaction effects would suggest that behavioral or cognitive differences are either amplified or diminished by the presence of bvFTD in a specific sex.

In this study, we aim to leverage the extensive dataset from the National Alzheimer's Coordinating Center (NACC) to conduct a detailed investigation into sex differences in the clinical profiles of large sample of patients with bvFTD. First, we assessed sex differences in the frequency of six core bvFTD features and daily functioning. Second, we explored sex-diagnosis interactions in neuropsychiatric symptoms. Third, we investigated sex-diagnosis interactions across behavioral, language, and cognitive tests.

## 2 | METHODS

### 2.1 | Participants

bvFTD and healthy controls (HCs) participants were selected from National Alzheimer's Coordinating Center (NACC).[17] Patients were diagnosed according to bvFTD consensus criteria.[4] All patients fulfilled criteria for possible bvFTD, and in a minority of cases, information on whether they also met criteria for probable bvFTD was available. This study used data from 46 Alzheimer's Disease Research Centers (ADRCs) for Uniform Data Set (UDS) visits conducted between September 2005 and December 2022. All participants or their informants provided written informed consent. From the NACC database, three different samples were selected for each of the three aims to maximize participant inclusion and sample size for each analysis.

For aim 1 (bvFTD clinical features), we included bvFTD patients with available clinical feature assessments (i.e., whether they fulfilled each of the Racovsky et al. (2011) bvFTD consensus criteria),[4] a non-zero Sum of Boxes CDR Dementia Staging Instrument plus NACC Frontotemporal Lobar Degeneration (FTLD) Behavior & Language Domains.[18], and retained only the earliest time point when multiple time points were available. This yielded 620 participants (375 males, 245 females).

For aim 2 (neuropsychiatric features), we included bvFTD patients with NPI Questionnaire (NPI-Q) data, a non-zero Sum of Boxes CDR plus NACC FTLD score, age ≥40, retained only the earliest time point when multiple time points were available. HC participants were selected with NPI-Q data, a zero Sum of Boxes CDR plus NACC FTLD score, a Montreal Cognitive Assessment (MoCA) score within the normal range (adjusted for race/ethnicity),[19] and earliest available data. Downsampling was used to match the groups with respect to age and sex. All of this yielded a sample of 1029 bvFTD participants (609 males, 420 females) and 1029 HC participants (609 males, 420 females).

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For aim 3 (behavioral, language, and cognitive tests), we included bvFTD participants who had completed at least one of 16 cognitive, behavioral, or language tests, had a non-zero Sum of Boxes CDR plus NACC FTLD score, were aged ≥40, and retained only their earliest visit. HC participants were included if they completed at least 8 of the 16 tests (ensuring full coverage of the NACC UDS module) [20,21] had a Sum of Boxes CDR plus NACC FTLD score of zero, normal MoCA scores (adjusted for race/ethnicity),[19] and earliest available data. Downsampling was applied to match groups on the number of completed tests, age, and sex. The final sample included 1109 bvFTD participants (680 males, 429 females) and 1109 HC participants (680 males, 429 females).

Each of our three aims required different types of data, which were not consistently available across all participants. For transparency, the degree of bvFTD sample overlap across analyses is reported as follows: the overlap between Aim 1 and Aim 2 was 477 bvFTD participants, between Aim 2 and Aim 3 was 861 bvFTD participants, and between Aim 3 and Aim 1 was 607 bvFTD participants. A total of 473 bvFTD participants had complete data across all three aims. Regarding HC, the overlap between Aim 2 and Aim 3 was 356 HC participants (Aim 1 had no HC participants) (Table 1).

## 2.2 | Procedure

The behavioral (including clinical features and the NPI), cognitive, and language assessment tools used in this study were taken from the UDS version 3 and the FTLD Module (FTLD-MOD)[20,21].

### 2.2.1 | Clinical bvFTD features

Rated by a clinician, this symptom checklist is used to establish the presence of the six main symptoms of bvFTD (behavioral disinhibition, apathy, loss of sympathy/empathy, compulsive/preservative behavior, hyperorality, and deficits in neuropsychological executive tasks with relative sparing of episodic memory and visuospatial abilities). Additionally, impaired daily functioning was also considered. The features are indicated as "Absent", "Questionably Present", and "Present".

### 2.2.2 | Neuropsychiatric features

The NPI-Q is filled by a clinician based on the interview with the informant.[22] It evaluates 12 neuropsychiatric symptom domains (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behaviors, and appetite/eating disturbances) with "yes" or "no" questions, as well as a severity scale ranging from mild to severe. Only the absence/presence response was used in this study.

**RESEARCH IN CONTEXT**

1. **Systematic review**: The authors reviewed the literature using traditional sources to identify studies addressing sex differences in behavioral variant frontotemporal dementia (bvFTD). Very few studies have examined this question, and most lacked large samples, detailed clinical assessments, or consideration of sex differences in healthy aging.
2. **Interpretation**: Our findings demonstrate that sex significantly influences the clinical expression of bvFTD, with males showing greater behavioral symptoms (e.g., empathy loss, nighttime behaviors) and females exhibiting more severe language impairments. By controlling for differences observed in healthy controls, our study provides stronger evidence that these effects are specific to bvFTD.
3. **Future directions**: Future studies should explore the neurobiological mechanisms underlying these sex differences—such as brain network organization or atrophy patterns—as well as how other social determinants of health (e.g., education, occupation, language, race/ethnicity) interact with sex to shape symptom presentation, diagnosis, and care in bvFTD.

### 2.2.3 | Cognitive, behavioral, and language tests

A series of tests from the UDS3 and FTLD module from these three domains were selected for the current study. Behavioral tests included the Behavioral Inhibition Scale (BIS), the Social Norms Questionnaire (SNQ-22), the Revised Self-Monitoring Scale (RSMS) and the Social Behavior Observer Checklist (SBOCL; which yields three behavioral symptom scores derived through cluster modeling: (1) Disorganized (2) Reactive and (3) Insensitive [23]). Language tests included the Multilingual Naming Test (MINT), letter fluency test, semantic fluency test, irregular word reading, semantic associates, Northwestern Anagram Test, and sentence repetition test. Cognitive tests included the TMT Part A, TMT Part B, Benson Figure Copy, Benson Figure Delayed Recall, and Craft Story 21 Delayed Recall.

## 2.3 | Statistical analyses

All statistical analyses were conducted using R (version 4.4.1).

For aim 1, ordinal logistic regression controlling for age, education, and Sum of Boxes CDR plus NACC FTLD Dementia were used to compare the frequency of all clinical features (present/questionably present/absent) between males and females with bvFTD.

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**TABLE 1** Demographics and clinical characteristics for all groups for the three aims of the study.

| Parameter | bvFTD Females | bvFTD Males | HC Females | HC Males |
|---|---|---|---|---|
| Sample aim 1: bvFTD features | | | | |
| N | 245 | 375 | - | - |
| Years of education | 15.7±2.5 | 15.8±3.1 | - | - |
| MoCA | 16.6±7.0 | 18.0±6.7 | - | - |
| Age | 63.1±9.5 | 63.8±8.6 | - | - |
| Global CDR plus NACC FTLD | 1.8±0.8[b] | 1.6± 0.7[a] | - | - |
| Sum of boxes CDR plus NACC FTLD | 10.5±5.5[b] | 9.0±4.4[a] | - | - |
| Disease duration | 5.5±4.3 | 6.18± 5.0 | - | - |
| Possible/Probable/Unknown bvFTD[T] | 44/178/23 | 86/259/30 | - | - |
| White | 92.2% | 95.5% | - | - |
| Black or African American | 2.9% | 1.3% | - | - |
| American Indian or Alaska Native | 0.0% | 0.3% | - | - |
| Native Hawaiian or Pacific Islander | 0.4% | 0.0% | - | - |
| Asian | 3.3% | 2.1% | - | - |
| Multiracial | 0.8% | 0.0% | - | - |
| Sample aim 2: neuropsychiatric symptoms | | | | |
| N | 420 | 609 | 420 | 609 |
| Years of education | 15.0 ±3.3[b, c, d] | 15.6±3.2[a, c, d] | 16.2±2.4 [a, b, d] | 16.8±2.4 [a, b, c] |
| MoCA | 16.9±7.0[b, c, d] | 18.8±6.6[a, c, d] | 27.5±1.8 [a, b] | 27.3±1.7 [a, b] |
| Age | 64.1±9.4 | 64.6±8.6 | 64.1±9.4 | 64.5±8.5 |
| Global CDR plus NACC FTLD | 1.8±0.8[b] | 1.7±0.8[a] | - | - |
| Sum of boxes CDR plus NACC FTLD | 10.9±5.9[b] | 9.7±5.3[a] | - | - |
| Disease duration | 5.2±4.4 | 5.8±4.8 | - | - |
| Possible/Probable/Unknown bvFTD[T] | 38/139/243 | 69/214/326 | - | - |
| White | 89.8% | 95.1% | 77.4% | 82.3% |
| Black or African American | 3.1% | 1.6% | 18.3% | 14.1% |
| American Indian or Alaska Native | 0.2% | 0.2% | 1.7% | 0.8% |
| Native Hawaiian or Pacific Islander | 0.5% | 0.3% | 0.0% | 0.0% |
| Asian | 3.6% | 2.0% | 1.9% | 2.0% |
| Multiracial | 2.1% | 0.0% | 0.5% | 0.3% |
| Sample aim 3: behavioral/language/cognitive tests | | | | |
| N | 429 | 680 | 429 | 680 |
| Years of education | 15.1±3.1[b, c, d] | 15.7±3.1[a, c, d] | 17.1±2.2[a, b] | 17.2±2.5[a, b] |
| MoCA | 16.2±7.1[b, c, d] | 18.1±6.8[a, c, d] | 28.2 ±1.5[a, b, d] | 27.7±1.5[a, b, c] |
| Age | 64.7±9.2[c, d] | 64.4± 8.4[c, d] | 61.9±9.9[a, b, d] | 63.1±9.3[a, b, c] |
| Global CDR plus NACC FTLD | 1.7±0.8[b] | 1.6±0.7[a] | _ | _ |
| Sum of boxes CDR plus NACC FTLD | 10.2±5.5[b] | 8.8±4.4[a] | _ | _ |
| Disease duration | 5.3±4.2 | 5.7±4.6 | _ | _ |
| Possible/Probable/Unknown bvFTD[T] | 44/172/213 | 88/259/333 | - | - |
| White | 90.2% | 96.2% | 92.8% | 90.2% |
| Black or African American | 3.0% | 1.3% | 4.9% | 7.4% |
| American Indian or Alaska Native | 0.2% | 0.2% | 0% | 0.3% |
| Native Hawaiian or Pacific Islander | 0.5% | 0.3% | 0% | 0.2% |
| Asian | 3.0% | 1.6% | 1.6% | 1.5% |
| Multiracial | 2.1% | 0% | 0.2% | 0.3% |

*Note*: Significant differences between groups are denoted as * ($p \leq .05$). a = different from bvFTD females; b = from bvFTD males; c = from HC males; d = from HC females. TUnknown bvFTD refers to patients who met possible bvFTD diagnostic criteria, but for whom data on probable bvFTD status were unavailable. Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; HC, healthy control; MoCA, Montreal Cognitive Assessment; NACC, National Alzheimer's Coordinating Center.

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For Aim 2, logistic regression models were conducted to assess neuropsychiatric outcomes, with diagnosis (bvFTD vs. HC), sex (Male vs. Female), and their interaction (sex × diagnosis) as predictors, while controlling for age and education. Post-hoc group comparisons were conducted using contrasts of predicted probabilities, adjusted for covariates, to compare test scores between groups and sexes. Afterwards, for outcomes showing significant interaction effects, logistic regression analyses were repeated specifically within the bvFTD group, controlling for age, education, and Sum of Boxes CDR plus NACC FTLD score. This post-hoc approach confirmed whether sex differences in those specific neuropsychiatric outcomes persisted independently of disease severity. When no interaction effects were found, the main effect of group (bvFTD vs. HC) and the main effect of sex (Male vs. Female) were examined using the results of the logistic regression models controlling for age and education.

For Aim 3, two-way analyses of variance (ANOVAs) were used to compare cognitive, behavioral, and language data between the two groups (bvFTD and HC) and sexes (male and female), while controlling for age and education, to calculate sex–diagnosis interaction effects. Tukey's honestly significant difference (HSD) test was then performed to compare the estimated marginal means of test scores between groups and sexes. Finally, for tests with significant interaction effects, ANOVAs were run specifically within the bvFTD group, controlling for age, education, and Sum of Boxes CDR plus NACC FTLD score, to confirm whether sex differences persisted independently of disease severity. When no interaction effects were found, the difference between groups (main effect of group) and the difference between sexes (main effect of sex) were compared using the results of the two-way ANOVAs controlling for age and education.

## 3 | RESULTS

### 3.1 | bvFTD core features

#### 3.1.1 | Sample description (Table 1)

The sample comprised 245 females and 375 males with bvFTD. Both groups were equivalent in age, years of education, global cognitive impairment, and disease duration. However, females demonstrated significantly higher Global and Sum of Boxes CDR plus NACC FTLD scores.

#### 3.1.2 | Sex differences in bvFTD features (Figure 1)

Regarding the sex differences in the absence and presence of bvFTD features, a significant sex difference was only observed in loss of empathy (females: Presence = 57.4%, Questionably Present = 25.8%, & Absence = 16.8%; males: Presence = 66.1%, Questionably Present = 22.0%, & Absence = 11.8%), with loss of empathy being significantly more present in males with bvFTD ($p < 0.01$). This effect was significant when controlled for demographic and disease severity variables. No significant sex differences were found for the other five bvFTD core features (behavioral disinhibition, apathy, compulsive behavior, hyperorality, neuropsychological deficits) as well as for impaired daily functioning.

### 3.2 | Neuropsychiatric symptoms

#### 3.2.1 | Sample description (Table 1)

The bvFTD group included 420 females and 609 males, with matched HC groups of equal size. No significant age differences were observed across groups. Education levels were significantly higher in HC compared to bvFTD participants, and within both diagnostic groups, males reported more years of education than females. Among bvFTD participants, females had significantly lower MoCA scores and higher Global and Sum of Boxes CDR plus NACC FTLD scores than males, but equivalent disease duration.

#### 3.2.2 | Sex differences in neuropsychiatric symptoms (Figure 2)

Regarding the NPI-Q features, a significant sex-diagnosis interaction was only found in nighttime behaviors. Males with bvFTD significantly displayed more nighttime behavioral disturbances (48.7% in males with bvFTD vs. 36.6% in females with bvFTD) while no significant sex difference was observed in the HC group (8.9% in HC males vs. 11.9% HC females) ($p < 0.01$). This effect was significant when controlled for demographic and disease severity variables. No significant sex-diagnosis interactions were found for the other eleven neuropsychiatric symptoms (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, appetite disturbances). A main effect of sex (irrespective of the group) was found for irritability, with males presenting higher levels of irritability compared to females (Table S1).

### 3.3 | Behavioral/language/cognitive tests

#### 3.3.1 | Sample description (Table 1)

This sample included 429 females with bvFTD and 680 males with bvFTD with HC groups of equal size. Among the bvFTD groups, no age differences were found, but the HC group was significantly younger than the bvFTD group. Education levels were higher in HC participants, with no sex differences among HCs but significant differences among those with bvFTD, where females had less years of education than males on average. Among bvFTD participants, females had significantly lower MoCA scores and higher Global and Sum of Boxes CDR plus NACC FTLD scores than males, but equivalent disease duration.

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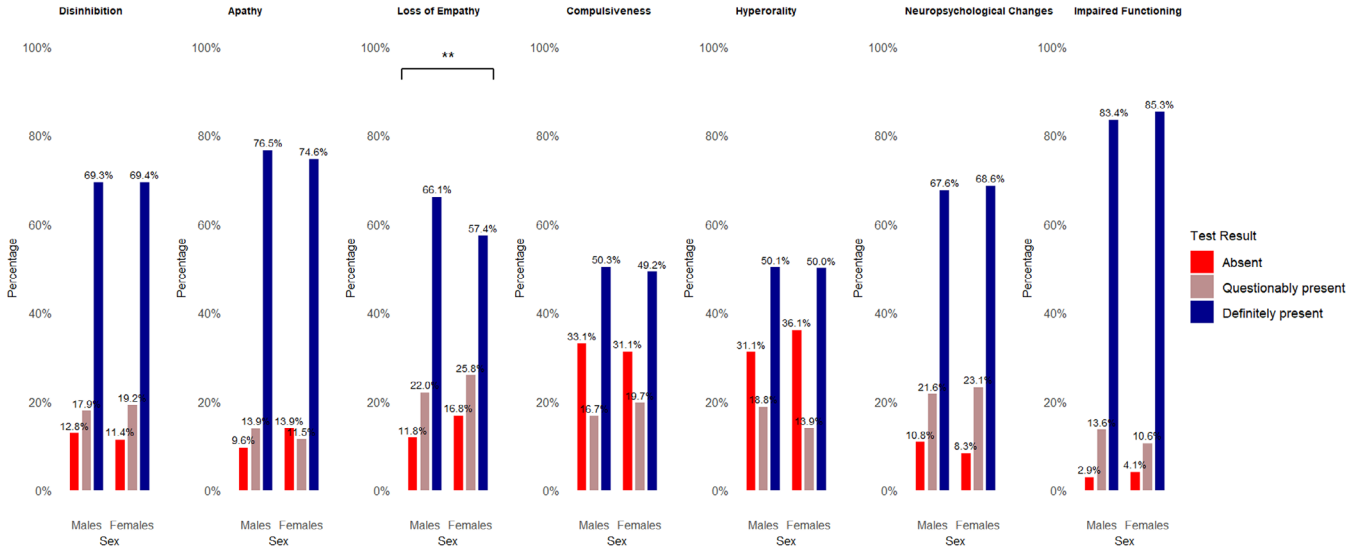


**FIGURE 1** Frequency of bvFTD clinical features according to sex in bvFTD patients. ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$). bvFTD, behavioral variant frontotemporal dementia.

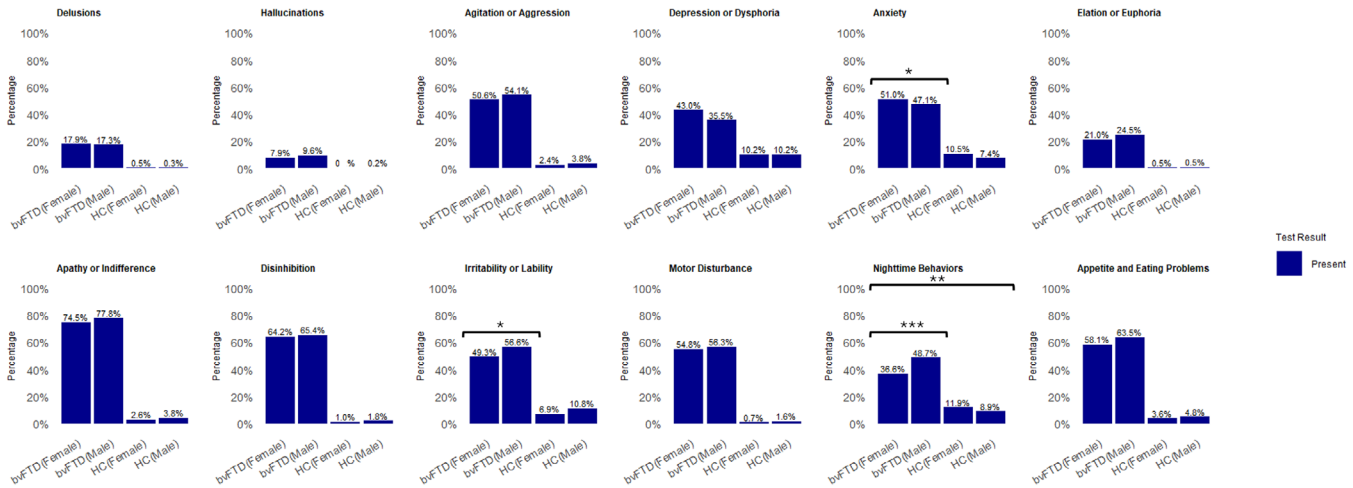


**FIGURE 2** Frequency of neuropsychiatric symptoms (NPI-Q) according to sex in bvFTD patients and HC participants. ($p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$). bvFTD, behavioral variant frontotemporal dementia; HC, healthy control; NPI-Q, Neuropsychiatric Inventory Questionnaire.

### 3.3.2 | Sex differences in behavioral/language/cognitive tests (Figure 3, Table 2, Figure S1)

For behavioral tests, the BIS was the only one with a significant sex-diagnosis interaction ($p < 0.05$). Significant sex differences were observed in both the bvFTD and HC groups, with females exhibiting higher sensitivity to punishment. However, while no group differences emerged among females (HC vs. bvFTD), males with bvFTD demonstrated higher levels of sensitivity to punishment compared to HC males. This effect was significant when controlled for demographic variables. No significant sex-diagnosis interactions were found in other behavioral tests (SNQ22, RSMS, SBOCL Disorganized, SBOCL Reactive, SBOCL Insensitive). A main effect of sex (irrespective of the group) was found for the SBOCL reactive cluster, with males showing less reactive behaviors during testing than females (Table S2).

For language tests, semantic fluency ($p < 0.001$) and MINT ($p < 0.001$) showed significant interaction effects. In semantic fluency, HC females demonstrated better performance than HC males; however, this advantage disappeared in the bvFTD group, where males and females performed at comparable levels, both performing significantly worse than HCs. On the MINT, no significant sex differences were observed in the HC group, but a pronounced sex effect emerged in bvFTD: females showed lower performance than males, with both groups performing below HCs. These effects were significant when controlled for demographic and disease severity variables. For the letter fluency test, although a significant interaction effect ($p < 0.01$) was initially observed, this effect did not remain significant in

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**TABLE 2** Results for behavioral/language/cognitive tests investigating sex (male/female) by group (bvFTD/HC) interactions.

| Parameter | Mean bvFTD females | Mean bvFTD males | Mean HC females | Mean HC males | Interaction effect | Interaction effect post-hoc | SME sex bvFTD | SME sex HC | SME group Females | SME group Males |
|---|---|---|---|---|---|---|---|---|---|---|
| Behavioral tests | | | | | | | | | | |
| Behavioral Inhibition Scale | 17.8 ± 0.3 | 16.7 ± 0.2 | 17.8 ± 0.4 | 15.2 ± 0.5 | <.05* | <.01** | <.05* | <.001*** | 1.00 | <.05* |
| SNQ22 (break score) | 1.5 ± 0.2 | 1.7 ± 0.1 | 0.3 ± 0.2 | 0.4 ± 0.2 | 0.9 | - | - | - | - | - |
| RSMS | 22.0 ± 0.8 | 20.5 ± 0.6 | 46.3 ± 1.0 | 47.6 ± 1.2 | 0.1 | - | - | - | - | - |
| SBOCL Disorganized | 1.4 ± 0.1 | 1.2 ± 0.1 | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.2 | - | - | - | - | - |
| SBOCL Reactive | 0.7 ± 0.1 | 0.4 ± 0.04 | 0.3 ± 0.1 | 0.1 ± 0.1 | 0.2 | - | - | - | - | - |
| SBOCL Insensitive | 0.7 ± 0.1 | 0.6 ± 0.1 | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.4 | - | - | - | - | - |
| Language tests | | | | | | | | | | |
| Letter Fluency Test | 14.8 ± 0.7 | 15.3 ± 0.5 | 34.7 ± 0.4 | 31.9 ± 0.3 | <.01** | .39 | - | - | - | - |
| Semantic Fluency | 15.5 ± 0.5 | 17.0 ± 0.4 | 48.4 ± 0.5 | 42.2 ± 0.4 | <.001*** | <.01** | .074 | <.001*** | <.001*** | <.001*** |
| Multilingual naming test (MINT) | 22.0 ± 0.4 | 25.0 ± 0.3 | 30.8 ± 0.2 | 30.9 ± 0.2 | <.001*** | <.001*** | <.001*** | 0.95 | <.001*** | <.001*** |
| Irregular Word Reading | 12.7 ± 0.2 | 12.8 ± 0.1 | 14.5 ± 0.2 | 14.6 ± 0.2 | 0.7 | - | - | - | - | - |
| Semantic Associates | 13.9 ± .2 | 14.2 ± .1 | 16.0 ± 0.2 | 16.0 ± 0.2 | 0.4 | - | - | - | - | - |
| Northwestern Anagram Test | 6.6 ± .2 | 6.6 ± .2 | 9.5 ± .2 | 9.3 ± 0.2 | 0.7 | - | - | - | - | - |
| Sentence Repetition Test | 3.8 ± .1 | 3.8 ± 0.1 | 4.4 ± 0.1 | 4.4 ± 0.1 | 0.8 | - | - | - | - | - |
| Cognitive tests | | | | | | | | | | |
| Trail Making Test A | 62.6 ± 1.5 | 59.5 ± 1.1 | 25.1 ± 1.3 | 26.6 ± 1.0 | 0.06 | - | - | - | - | - |
| Trail Making Test B | 173.6 ± 4.1 | 162.2 ± 2.9 | 58.6 ± 2.9 | 63.7 ± 2.3 | <.01** | .10 | - | - | - | - |
| Benson Figure Copy (Immediate) | 13.5 ± 0.2 | 14.0 ± 0.1 | 15.8 ± 0.1 | 15.8 ± 0.1 | 0.05 | - | - | - | - | - |
| Benson Figure Recall (Delayed) | 6.0 ± 0.3 | 6.9 ± 0.2 | 12.5 ± 0.2 | 12.7 ± 0.1 | 0.09 | - | - | - | - | - |
| Craft Story Recall (Delayed) | 8.7 ± 0.6 | 9.1 ± 0.4 | 22.3 ± 0.3 | 20.9 ± 0.3 | <.05* | .62 | - | - | - | - |

*Note*: p-Values for the interaction effect are first reported. When the interaction is significant, simple main effects (SME) of sex are reported separately for the bvFTD and HC groups, and SME of groups are reported separately for the females and males ($p$ <.05*, $p$ <.01**, $p$<.001***).

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; HC, healthy control; RSMS, Revised Self-Monitoring Scale; SBOCL, Social Behavior Observer Checklist; SNQ-22, Social Norms Questionnaire.



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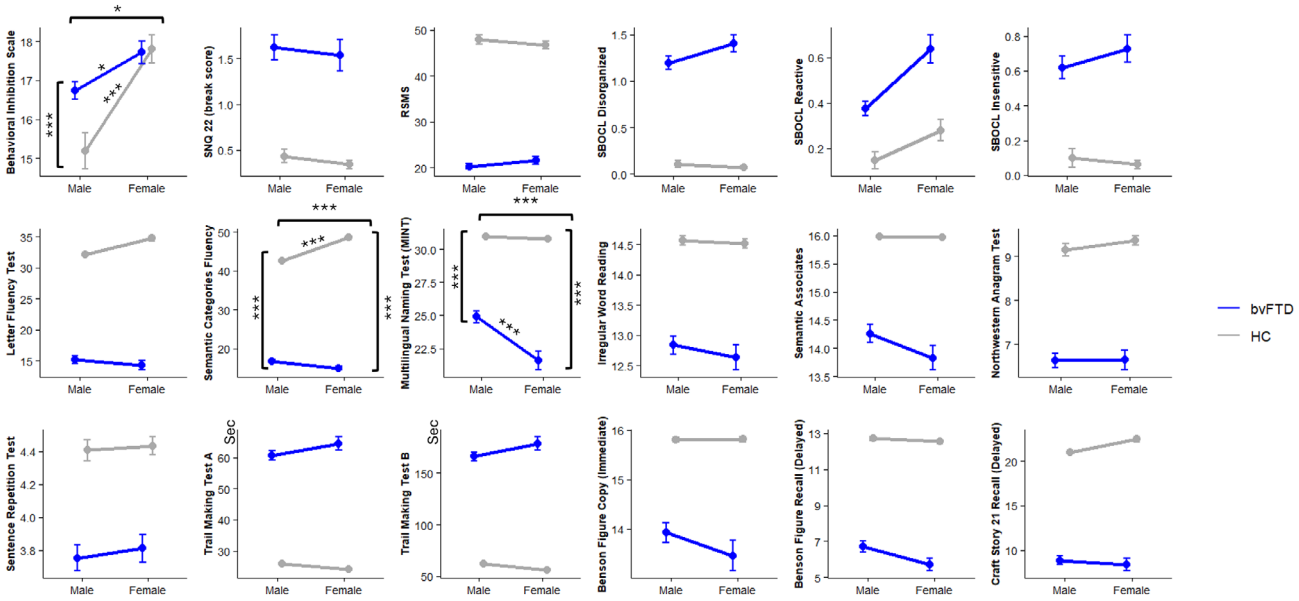


**FIGURE 3** Comparison of cognitive/behavioral/language test scores according to sex (male/female) and group (HC/bvFTD). ($p < 0.05$*, $p < 0.01$**, $p < 0.001$***). Error bars represent the standard error of the mean. bvFTD, behavioral variant frontotemporal dementia; HC, healthy control.

post-hoc comparisons controlling for age, education, and disease severity, suggesting that the apparent interaction may be explained by these covariates. No significant sex-diagnosis interactions were found in other language tests (irregular word reading, semantic associates, Northwestern anagram test, sentence repetition test).

In terms of cognitive tests, significant sex-diagnosis interactions were found for TMT Part B and Craft Story Recall (Delayed). However, similarly to what was observed for letter fluency, post-hoc tests controlling for age, education, and disease severity were not significant. No significant sex-diagnosis interactions were found in other cognitive tests (TMT Part A, Benson Figure Copy [Immediate], Benson Figure Recall [Delayed]). A main effect of sex (irrespective of the group) was found for the delayed recall of the Benson Figure, with males performing significantly better than females (Table S2).

## 3.4 | Post-hoc analyses

### 3.4.1 | Empathy

In Aim 1, we found that loss of empathy was reported significantly more often in males with bvFTD than in females with bvFTD. This was based on clinician ratings from the core diagnostic criteria for bvFTD. In contrast, when empathy was assessed with the informant-based Revised Self-Monitoring Scale (RSMS), no sex × diagnosis interaction emerged, nor were there sex differences in the combined sample (bvFTD + HC). To further examine these discrepant findings, logistic regression models were applied to each RSMS item and subscale, with diagnosis, sex, and their interaction as predictors, controlling for age and education. For items showing significant interaction effects, follow-up models were conducted within the bvFTD group, adjusting for age, education, and Sum of Boxes CDR plus NACC FTLD score. For the two subscale totals (Sensitivity to Socio-emotional Expressiveness and Ability to Modify Self-presentation), two-way ANOVAs were used, followed by Tukey's HSD tests to examine group and sex differences while controlling for age and education.

Significant sex-diagnosis interactions were observed in two items (Figure S2): "Can change projected image when it's not working" and "Usually detects when someone is lying." For the former, HC males demonstrated significantly greater ability to flexibly adjust self-presentation compared to HC females, whereas no sex differences were observed in bvFTD. For the latter, females with bvFTD showed better lie detection abilities than males with bvFTD, while in HC participants the pattern was reversed. Both results suggest lower-than-expected empathy skills in males with bvFTD, compared to females with bvFTD. This finding is also supported by the results in several socio-emotional expressiveness subscale, which expressed a similar pattern despite the absence of a global interaction effect. Notably, this was not observed in the Ability to Modify Self-presentation subscale. Taken together, these post-hoc findings point toward an alignment between clinician ratings and informant-reported questionnaires.

### 3.4.2 | Nighttime behaviors

In Aim 2, we found that males with bvFTD exhibited significantly more nighttime behavioral disturbances than females with bvFTD, whereas no sex difference was observed in the HC group. The Nighttime Behavior feature of the NPI-Q, however, encompasses a range of symptoms, including waking the informant during the night, waking too early in the morning, or engaging in excessive daytime napping.

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To further explore this finding, we first leveraged NACC data on specific sleep disorders (sleep apnea, rapid eye movement [REM] sleep behavior disorder, hyposomnia/insomnia, and other sleep disorders) to assess whether they could underlie the observed sex × diagnosis interaction. Data were available for 286 individuals with bvFTD and 674 HC participants (Figure S3). Ordinal logistic regression models were fitted with nighttime behavior as the outcome and self-reported sleep disorders, sex, and the sleep disorder × sex interaction term, while controlling for age, years of education, and disease severity. No significant interactions emerged, suggesting that sleep disorders did not interact with sex to influence nighttime behavior in bvFTD. Nevertheless, across sexes, hyposomnia/insomnia were significantly associated with nighttime behavior problems.

### 3.4.3 | Sensitivity to punishment

In Aim 3, we found that males with bvFTD showed higher-than-expected levels of sensitivity to punishment. To further investigate whether this effect reflected specific aspects of punishment sensitivity in males with bvFTD, we conducted logistic regression models for each item of the BIS, with diagnosis, sex, and their interaction as predictors, while controlling for age and education. Post-hoc group comparisons were conducted using contrasts of predicted probabilities, adjusted for covariates, to compare test scores between groups and sexes. For items showing significant interaction effects, additional logistic regression analyses were performed within the bvFTD group, adjusting for age, education, and disease severity. A significant sex-diagnosis interaction was identified for the item "Criticism or scolding hurts a lot." (figure S4). Among HC participants, females reported greater sensitivity to criticism and scolding compared to males. In contrast, no sex difference was observed in bvFTD participants, where males and females were equally affected. Interestingly, females with bvFTD and HC females reported comparable sensitivity, whereas males with bvFTD demonstrated significantly greater sensitivity than HC males.

Finally, we wanted to further examine whether interactions between neuropsychiatric symptoms and sex could impact the BIS scores. Two-way ANOVAs were conducted with NPI features as predictors, along with their interactions with sex, while controlling for age, education, and disease severity. No significant interaction effects were found, indicating that sex and NPI features did not interact to influence BIS scores (Figure S5). However, across sexes, the presence of agitation or aggression, depression or dysphoria, anxiety, and irritability or Lability was associated with significantly higher BIS total scores, suggesting that these symptoms increase sensitivity to punishment. In males with bvFTD, Delusions were additionally linked to higher BIS scores.

### 3.4.4 | Cognitive reserve

Post-hoc analyses were conducted to examine whether cognitive reserve, indexed by years of education, influenced the sex-related differences in bvFTD observed for loss of empathy, nighttime behaviors, the BIS, semantic fluency, and MINT. For these measures, education × sex interaction effects were tested using two-way ANOVAs and Ordinal logistic regressions, with sex, education, and their interaction entered as predictors while controlling for age and disease severity. No significant education × sex interaction effects were found. These exploratory results suggest that cognitive reserve did not modulate the sex-related differences in FTD symptoms.

## 4 | DISCUSSION

In this study, we aimed to leverage the extensive dataset from the NACC to investigate interaction effects that arise between sex (male/female) and group (bvFTD/HC) in core bvFTD features, neuropsychiatric symptoms, and behavioral/language/cognitive performance. This was done to account for sex differences that may already exist in the general population. Overall, we found sex-diagnosis interactions in (1) loss of empathy, being more frequent in males with bvFTD versus females; (2) nighttime behaviors, being significantly more present among males with bvFTD; (3) BIS, with males with bvFTD showing higher-than-expected sensitivity to punishment; (4) semantic fluency and picture naming, with deficits amplified in females with bvFTD in comparison to males with bvFTD. Overall, our results suggest that although many symptoms of bvFTD present similarly in males and females, certain clinically meaningful differences do emerge. These findings align with the emerging profile from the limited literature on sex differences in bvFTD, which suggests that males tend to exhibit more severe behavioral changes but less pronounced cognitive and linguistic impairments compared to females with bvFTD[9,11,14].

Interestingly, we found that loss of empathy was more frequently reported in males (66.1%) than in females (57.4%) with bvFTD, and our post hoc analyses suggest that this result might be specific to sensitivity to socio-emotional expressiveness. Several factors could account for this result. One possibility is that this represents a genuine sex-related difference in the clinical expression of bvFTD. Evidence from healthy populations suggests that females tend to exhibit higher baseline empathy.[24–26] Speculatively, this could represent a form of socio-emotional reserve, distinct from cognitive reserve, arising from lifelong differences in emotional attunement and socialization, and supported by the absence of any sex × education interaction in our post-hoc analyses. An alternative explanation is that empathy loss may manifest differently between sexes. In males, empathic deficits might present more overtly, whereas in females, underlying impairments could be partially masked by compensatory strategies. For example, women may rely on mimicking social cues or drawing on well-rehearsed emotional scripts, behaviors shaped by gendered social conditioning. Such strategies have been described in adults with autism spectrum disorder[27] and may similarly give the impression of preserved empathy in females with bvFTD, even when deficits are present. Furthermore, these symptoms may be misattributed to affective disorders such as depression or anxiety, as previous research has shown that females with bvFTD are disproportionately labeled as having psychiatric disorders.[28] Finally,

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previous research has shown that female informants tend to report greater disease severity in dementia compared to male informants,[29] and this discrepancy may be even more pronounced when it comes to ratings of empathy. In many cases, female informants—often spouses of male patients—may be particularly attuned to changes in empathic behavior, possibly due to superior social cognitive abilities (emotion recognition and theory of mind)[30,31] and/or higher expectations for emotional reciprocity in intimate relationships.

Additionally, our study found significantly elevated levels of nighttime behavioral problems in males with bvFTD. In our study, nearly half of the males with bvFTD exhibited nighttime behavioral symptoms, compared to approximately one-third of females. Our post-hoc analyses revealed that nighttime behaviors in bvFTD were linked to hyposomnia/insomnia, with no sex interactions in this association. Interestingly, this pattern contrasts with what is typically observed in Alzheimer's disease, where females more frequently present with nighttime disturbances.[32] Illán-Gala and colleagues[14] similarly reported that, at comparable levels of brain atrophy, females with bvFTD showed fewer behavioral symptoms (specifically, less apathy, appetite change, and sleep disturbances) than males, which they interpreted as indirect evidence of higher brain reserve in women. While our findings partially align with theirs, we did not observe sex differences in apathy or appetite. These discrepancies may be explained by the larger sample size in our study and our inclusion of healthy control data to account for baseline sex differences, as well as our control for disease severity across bvFTD groups.

In males with bvFTD, we also found greater-than-expected punishment sensitivity, particularly to criticism or scolding. This finding suggests that emotional reactivity in bvFTD is not uniformly reduced but may be selectively heightened in response to evaluative cues. Such sensitivity could reflect alterations in self-referential or social evaluative processes that make criticism particularly salient for males with bvFTD. The association of higher BIS scores with neuropsychiatric symptoms across sexes further indicates that punishment sensitivity is embedded within the broader psychopathological profile of the disease. Together, these results highlight the importance of considering sex-specific socio-emotional patterns when assessing and treating bvFTD.

Semantic fluency and picture naming were the two language tasks that showed significant sex-by-diagnosis interactions, with deficits being more pronounced in females with bvFTD compared to males. These results suggest that language impairments in bvFTD may be amplified in females, particularly in tasks requiring lexical access and semantic retrieval. Our findings are consistent with previous studies reporting greater language deficits in female patients with bvFTD.[11] A similar pattern is also seen in primary progressive aphasia and Alzheimer's disease.[33,34] In healthy aging populations, females typically outperform males on verbal fluency and naming tests.[35] Using the cognitive reserve hypothesis, one could interpret our result by saying that the greater decline observed in females with bvFTD may reflect a steeper drop from a higher premorbid baseline.[36] However, exploratory analyses do not support this interpretation, as education × sex interactions for measures that showed significant main effects revealed no significant interactions, suggesting that cognitive reserve, as indexed by years of education, did not modulate sex-related differences in bvFTD symptoms. Further research is needed to clarify the mechanisms underlying these differences. Prior functional magnetic resonance imaging (fMRI) studies have shown sex-related differences in language network organization and activation in healthy adults.[37] Whether these differences persist or are differentially disrupted in bvFTD remains unknown. Studies combining behavioral data with task-based or resting-state fMRI, as well as longitudinal structural imaging, are needed to determine whether disruptions in these networks may underlie the observed sex differences in linguistic function in bvFTD.

Beyond its clear strengths—including an elevated sample size, detailed clinical assessments, and rigorous control for both disease severity and baseline sex differences in healthy controls—our study also has several limitations. First, the NACC[17] does not report sex and gender separately and does not capture gender identities beyond the male/female binary; consequently, our analyses were limited to differences within this binary. Although disease duration and age were equivalent between sexes in our sample, baseline differences in MoCA and CDR plus NACC FTLD were observed. While we statistically controlled for CDR plus NACC FTLD scores in our post hoc analyses throughout the study, it could be argued that disease severity may itself be a meaningful sex-related variable, and adjusting for it might obscure true sex differences. Other studies have addressed this issue by controlling for degree of atrophy, which has its own strengths—namely, providing an objective measure of disease burden—but also limitations, such as variability in atrophy patterns across individuals and sexes. Future studies involving genetic mutation carriers, who are identified prior to symptom onset, may help clarify whether observed sex differences are intrinsic to disease expression or confounded by diagnostic and staging variability, although findings in genetic cohorts may not fully generalize to sporadic cases. A second major limitation of our study is that the sample was predominantly composed of white, American participants, which may limit the generalizability of our findings to more diverse populations. Cultural and ethnic factors could influence both the expression and the recognition of bvFTD symptoms, as well as caregiver reporting and access to healthcare, all of which may intersect with sex in shaping clinical profiles.

In conclusion, our study highlights the significant impact of sex on the clinical profiles of patients with bvFTD, independent of age, education, disease severity, and baseline sex differences observed in the general population. These findings have important implications for diagnosis and personalized care. Clinicians should be aware of how sex may shape symptom presentation and influence the interpretation of behavioral changes. Attention should also be given to potential sex-related biases in clinical assessment, including how symptoms are reported by informants depending on their own sex, which may subtly influence the recognition of socio-emotional deficits. Understanding these dynamics is essential for reducing diagnostic errors and improving early detection. Moreover, these sex-based clinical differences could inform the tailoring of treatment, management, and intervention strategies. For example, interventions for males may benefit from a greater focus on managing behavioral dysregulation,

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while those for females may prioritize cognitive-linguistic support. Overall, our findings contribute to the growing recognition of the role of social determinants of health in shaping neurodegenerative disease expression. While sex represents one critical factor, future research should further investigate the influence of other determinants—such as age, education, occupation, spoken language, and race/ethnicity—on the clinical presentation and progression of bvFTD. A more nuanced understanding of these factors will be essential to advancing equitable, individualized approaches to diagnosis and care in FTD.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

## CONSENT STATEMENT

All data used in this study were obtained from the National Alzheimer's Coordinating Center (NACC) database. Participant data were collected through the U.S. Alzheimer's Disease Research Centers (ADRCs), where informed consent was obtained at the time of enrollment in accordance with each center's local Institutional Review Board (IRB) guidelines. All data provided by NACC are fully de-identified and compliant with HIPAA regulations.

## DISCLOSURE STATEMENT

We confirm that we have used artificial intelligence (AI) tools, specifically OpenAI's ChatGPT, as a companion in the preparation of this manuscript. The AI was used to assist with refining language and improving clarity. However, we take full responsibility for reviewing and verifying the content, ensuring that all claims, arguments, and citations align with our research and expertise. We have ensured that the use of AI in the preparation of this manuscript adheres to all ethical and editorial standards outlined by Wiley. We have verified that no AI-generated content infringes upon intellectual property rights, and we maintain full ownership of the content. Additionally, we have carefully reviewed the terms and conditions of the AI tool used and confirm that it does not claim ownership of the manuscript or impose limitations on its use. We have disclosed the use of AI tools in accordance with Wiley's ethical publishing guidelines, and we are fully committed to transparency in the preparation process.

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