Received: 20 August 2024 | Revised: 4 February 2025 | Accepted: 10 February 2025

DOI: 10.1002/alz.70070

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

# Sex differences in the executive and behavioral reserve of autosomal dominant frontotemporal dementia

Jesús Garcia Castro[1,2,3] | Sara Rubio-Guerra[1,2,3] | Kaitlin B. Casaletto[4] | Judit Selma González[1,2,3] | Molly Memel[5] | Lídia Vaqué-Alcázar[1] | Alejandra Morcillo-Nieto[1,2,3] | José Arriola-Infante[1,2] | Oriol Dols-Icardo[1,2,3] | Alexandre Bejanin[1,2,3] | Olivia Belbin[1,2,3] | Juan Fortea[1,2,3] | Daniel Alcolea[1,2,3] | Maria Carmona-Iragui[1,2,3] | Isabel Barroeta[1,2,3] | Miguel Santos-Santos[1,2,3] | María Belen Sánchez Saudinós[1,2,3] | Isabel Sala Matavera[1,2,3] | Hilary W. Heuer[4] | Leah K. Forsberg[6] | Kejal Kantarci[7] | Adam M. Staffaroni[4] | Carmela Tartaglia[8] | Katherine P. Rankin[4] | Brad Boeve[6] | Adam Boxer[4] | Howard J. Rosen[4] | Alberto Lleó[1,2,3] | Ignacio Illán-Gala[1,2,3] | for the ALLFTD Consortium

[1]Sant Pau Memory Unit, Department of Neurology, Biomedical Research Institute Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[2]Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

[3]Departament de Medicina, Universitat Autònoma de Barcelona, Cerdanyola del Vallés, Spain

[4]Weill Institute for Neurosciences, Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA

[5]Ray Dolby Brain Health Center, San Francisco, California, USA

[6]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[7]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[8]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada

**Correspondence**
Ignacio Illán-Gala, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret 167, 08025 Barcelona, Spain.
Email: iillan@santpau.cat

**Funding information**
National Institute on Aging; National Institute of Neurological Diseases and Stroke; National Center for Advancing Translational Sciences; National Institute of Neurological Diseases and Stroke; NIH-NIA; Carlos III National Institute of Health of Spain, Grant/Award Numbers: CM23/00176, JR20/0018, PI21/00791, INT21/00073, PI20/01473, PI23/01786, CP20/00038, PI22/00307, PI18/00435, PI20/01330, PI21/01395,

## Abstract

**INTRODUCTION:** Self-reported sex influences brain resilience, but its role in genetic frontotemporal dementia (FTD) remains unclear.

**METHODS:** We analyzed 394 genetic-FTD patients and 279 controls from the ALLFTD consortium, assessing annual neuropsychological performance and MRI-based cortical thickness. Clinical characteristics and cortical thickness were compared between sexes. We used the residuals of linear regression models, which predict each participant's cognitive and behavioral performance levels relative to cortical thickness, as a proxy for reserve. We then modeled sex differences in longitudinal trajectories with linear mixed-effects models.

**RESULTS:** Symptomatic females with genetic FTD had lower frontal cortical thickness than males, and the *C9orf72* subgroup showed lower-than-expected frontal cortical

CM21/00243; European Union; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas Program 1; Fondo Europeo de Desarrollo Regional; Unión Europea; Una Manera de Hacer Europa; National Institutes of Health, Grant/Award Numbers: R01 AG056850, R21 AG056974, R01 AG061566, R01 AG081394, R61AG066543, AG032306, K24AG045333, AG038791, R01AG072475; Department de Salut de la Generalitat de Catalunya; Pla Estratègic de Recerca I Innovació en Salut, Grant/Award Numbers: SLT006/17/00119, SLT002/16/00408; Fundación Tatiana Pérez de Guzmán el Bueno, Grant/Award Number: IIBSP-DOW-2020-151; Horizon 2020–Research and Innovation Framework Programme from the European Union, Grant/Award Number: H2020-SC1-BHC-2018-2020; Alzheimer Association, Grant/Award Number: AARG-22-923680; Alzheimer's Association, Grant/Award Number: AARF-22-924456; Jerome Lejeune Foundation postdoctoral fellowship; Instituto de Salud Carlos III through the Río Hortega Fellowship, Grant/Award Number: CM21/00243″; European Union. L.V.-A., Grant/Award Number: UNI/551/2021; Global Brain Health Institute

thickness for a given level of executive functioning. Differences in cognitive reserve between sexes peaked near symptom onset but diminished thereafter.

**DISCUSSION:** Females with genetic FTD showed higher cognitive reserve than males, suggesting that self-reported sex modulates resilience to frontotemporal neurodegeneration.

**KEYWORDS**

cognitive reserve, diagnosis, frontotemporal dementia, magnetic resonance imaging, neuroimaging, progression, resilience, survival

### Highlights

- Females with genetic FTD showed higher cognitive reserve than males.
- Those differences were particularly pronounced in the *C9orf72* and *GRN* subgroups.
- The higher cognitive reserve in females declined as the disease progressed.

## 1 | BACKGROUND

Frontotemporal dementia (FTD) encompasses a heterogeneous group of neurodegenerative disorders characterized by progressive deterioration in social behavior, language, and executive functions.[1] FTD demonstrates significant heritability, with many affected individuals displaying a robust familial history[2–4] and up to 30% harboring autosomal dominant mutations.[5] The most common FTD mutations are the expansion in the chromosome 9 open reading frame 72 (*C9orf72*), and pathogenic mutations in the progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*)[3,6,7] genes. The study of families with autosomal dominant FTD offers a unique opportunity to delineate the sequence of clinical and biomarker alterations beginning at the preclinical or minimally symptomatic stages, potentially identifying pivotal factors that influence clinical outcomes and prognosis.[8]

Among these factors, biological sex, understood as the sex chromosome complement of a person, has emerged as a top priority in the research of neurodegenerative diseases,[9,10] and there is increasing evidence that sex and gender play a crucial role in modulating cognitive decline, biomarker trajectories, and responses to therapies in Alzheimer's disease (AD).[11–13] However, the specific impact of self-reported sex on FTD remains less understood. In a large multicenter study, we previously reported that females diagnosed with the most common clinical presentation of FTD, behavioral variant FTD (bvFTD), had more severe frontotemporal cortical thinning than males despite showing similar clinical features and disease severity at diagnosis.[14] These results align with the notion that females exhibit greater cognitive and behavioral reserve, namely, they might have a better ability to cope with neurodegeneration and preserve cognitive performance and social behavior.[14,15] Nevertheless, our previous work focused on symptomatic cases and only included a relatively small proportion of autosomal dominant FTD. Thus, it remains unclear to which extent sex differences in FTD can be explained by diagnosis-related factors[16] (i.e., delays in diagnosis due to later diagnosis in females[17]) and if sex-related differences could be observed at the preclinical stages of the disease. The study of genetically determined FTD cases followed from the preclinical phase to the symptomatic phase could provide valuable information to precise the role of self-reported sex in FTD.

In this study, we aimed to (1) characterize the impact of self-reported sex on the clinical presentation, cortical thickness, and cognitive and behavioral reserve in autosomal dominant FTD; and (2) leverage longitudinal clinical and imaging data to model cognitive and behavioral reserve progression from the preclinical stages to overt dementia, to understand how self-reported sex may influence the trajectory of genetic FTD.

## 2 | METHODS

### 2.1 | Study population

Participants included 394 carriers of the *C9orf72* hexanucleotide repeat expansion, a pathogenic mutation in *GRN* or *MAPT*, and 279 non-carrier controls from families harboring one of these mutations. Participants were recruited through the ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD; NCT04363684)

cohort, encompassing 18 centers across the United States and Canada. The subject inclusion flowchart is depicted in Figure. S1 Inclusion criteria were: (1) carriership of one of the three common pathogenic variants of autosomal dominant FTD, with no requirement for knowledge of their genetic status, (2) age over 18 years, (3) having a reliable informant in regular weekly contact, (4) English fluency sufficient for completing assessments, (5) availability of at least one MRI exam of acceptable quality, (defined by an image quality rating under 6 according to the CAT12 threshold).[18] Controls were included if they had a Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains Global Score (CDR+NACC-FTLD-GS) of 0, indicating no clinical impairment and no genetic mutation. Exclusion criteria included the presence of a structural brain lesion or any other neurological disorder that could affect outcomes. Participants underwent baseline and annual follow-up neurological and neuropsychological evaluations and cerebral MRI exams. Sex was considered as self-reported by the participants choosing among *Female*, *Male*, *Unknown*, or *Unspecified* options, and meant to reflect female or male reproductive organs.

## 2.2 | Genetic testing

Using a previously published method, participants underwent genetic testing at the University of California, Los Angeles.[19] The hexanucleotide repeat expansion in *C9orf72* was detected using fluorescent and repeat-primed polymerase chain reaction (PCR), and mutations in *GRN* and *MAPT* were identified by targeted sequencing.

## 2.3 | Disease severity assessment

CDR+NACC-FTLD-GS and CDR+NACC-FTLD Sum of Boxes (CDR+NACC-FTLD-SB)[20] were acquired at baseline and longitudinally as the primary measures of cognitive impairment severity. Asymptomatic status was established as CDR+NACC-FTLD-GS = 0, and a participant was deemed symptomatic if CDR+NACC-FTLD-GS≥0.5.

## 2.4 | Cognitive assessment

The ALLFTD protocol mandates annual multidisciplinary assessments, including neurological and neuropsychological evaluations and informant interviews. A selected subset of Uniform Data Set (UDS) Neuropsychological Battery, version 3.0[21] was administered at baseline and follow-up. The neuropsychological measures included the Digit Span Backward, Verbal Fluency Phonemic Test for F-Words and L-Words, Trail Making Test Part B (TMTB), where performance is quantified by dividing the total number of correct lines by the completion time in seconds, Multilingual Naming Test (MINT), Category Fluency (Animals and Vegetables), California Verbal Learning Test (CVLT) delayed recall, Benson Figure Copy delayed recall, and Craft Story 21 delayed recall (verbatim score).

To adjust for sex differences in cognitive performance, participant raw scores were standardized into z-scores based on the mean and standard deviation of healthy controls of the corresponding sex, following expert recommendations.[9,22,23] In line with previous ALLFTD studies,[24] cognitive composites were calculated by averaging the z-scores of tests reflecting similar neuropsychological functions. The executive composite score included Digit Span Backward, Verbal Fluency Phonemic Test, and TMTB; the language composite score encompassed MINT and Category Fluency; and the episodic memory composite score was derived from CVLT, Benson Figure Copy delayed recall, and verbatim Craft Story 21 delayed recall scores. A global cognitive composite was also computed by averaging all individual test scores.

## 2.5 | Social cognition and behavioral assessment

Because cognitive function can be relatively spared in the earliest symptomatic stages of FTD, we also included measures of social cognition. We included the Social Behavior Observer Checklist (SBOC)[25] to measure the observed social behavior. We also considered the Behavioral Inhibition Scale (BIS),[26] the Revised Self-Monitoring Scale (RSMS),[27] and the Interpersonal Reactivity Index (IRI)[28] as informant-based questionnaires of social cognition. As for cognitive measures,

### RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched PubMed for previous studies assessing sex differences in cognitive reserve and genetic frontotemporal dementia (FTD). The influence of biological sex in cortical thickness, cognitive or behavioral reserve, and functional decline has not been extensively studied for genetic FTD patients.
2. **Interpretation**: Symptomatic females with genetic FTD presented with higher frontal atrophy compared to males despite similar clinical manifestations. For equivalent executive impairment, females displayed higher atrophy than males, but the differences declined over time after symptom onset. Our findings add to the previous evidence suggesting a higher cognitive reserve in females with FTD.
3. **Future directions**: Females with genetic FTD might have greater cognitive resilience to frontotemporal neurodegeneration. Future studies in FTD should perform segregated analyses by sex and delve into the mechanisms underlying higher resilience in women with FTD, paving the path to precision medicine-based approaches.

the participants' raw scores were transformed into z-scores by considering the mean and standard deviation of the healthy controls of the corresponding sex.

## 2.6 | Neuroimaging

### 2.6.1 | MRI acquisition

All images at baseline and during the follow-up were acquired on 3T MRI scanners. T1-weighted images were obtained as Magnetization Prepared Rapid Gradient Echo images with the following parameters: 240 × 256 × 256 matrix, about 170 slices, voxel size = 1.05 × 1.05 × 1.25 $mm^3$, with flip angle, echo time, and repetition time varying by vendor. A standard imaging protocol was used across all centers, managed, and reviewed for quality at the Mayo Clinic, Rochester. Further details can be found elsewhere.[29]

### 2.6.2 | MRI processing

Images at baseline and during follow-up were processed with the CAT12 toolbox within SPM12 (Wellcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm), running in MATLAB R2023b.[30,31] Default settings were employed to compute cortical thickness, and the mean values for the frontal, parietal, temporal, and occipital lobes were extracted, using the Desikan-Killiany (DK40) atlas.[32] Cortical thickness analyses were chosen over volumetric approaches as recommended for studying sex differences in neurodegenerative dementias, as it is not correlated with total intracranial volume, a measure known to differ between sexes and a potential underlying confound.[9]

## 2.7 | Group comparison of cortical thickness

In alignment with consensus recommendations, analyses were segregated by sex to enhance sensitivity in detecting sex-related differences in neurodegenerative dementias.[9,22,23] Age and years of education were included as covariates when comparing pathogenic mutation carriers versus healthy controls. The significant differences were identified for all the analyses using a $p$-value threshold of $< 0.05$, adjusted for family-wise error (FWE), and an extent threshold based on the expected number of vertices per cluster. Cohen's d was calculated to quantify the effect size of cortical thickness reduction in regions showing significant differences between pathogenic mutation carriers and controls of the same self-reported sex. The net effect size was obtained after subtracting the effect size for female carriers compared to healthy female controls and the effect size for male carriers compared to healthy male controls. To find cortical areas where thickness reduction might respond to an interaction between the carrier status and self-reported sex, we conducted a two-way analysis of variance (ANOVA) analysis with group (pathogenic mutation carrier or healthy control) and self-reported sex (female or male) as main factors and age and years of education as covariates. Cortical thickness values between females and males carrying a pathogenic FTD mutation were also compared using $t$-test.

## 2.8 | Correlation of cognitive and behavioral measures with cortical regions

Spearman's correlation coefficient was used to assess the relationship between cortical regions and each cognitive and behavioral measure, with group (pathogenic mutation carrier or healthy control), symptomatic status (asymptomatic and symptomatic), age, and years of education as covariates (Figure S2). We selected the regions of interest as those areas showing a significant correlation after FWE correction with each specific cognitive composite or behavioral measure. Frontal lobe was found to be significantly correlated with the executive function composite; frontal and temporal regions with the memory composite; and frontal, temporal, and parietal regions with the language and global cognitive composites. Global cortical thickness (i.e., the mean value of cortical thickness for the entire cortex) was chosen for the cognitive measures, which showed no localized or statistically significant correlation.

## 2.9 | Residuals approach

Consistent with our previous studies,[14] we employed the residuals approach to model the relationships between cognitive and behavioral changes and cortical thinning, used as a proxy for pathology. This approach allowed us to predict each participant's cognitive and behavioral performance levels relative to cerebral cortical thickness, using individual residuals as reserve measures. The "residuals method" has been deemed a useful approach to measure and study cognitive reserve, and is conceptualized as a quantitative assessment of the variance in cognitive measures not explained by pathology or demographic factors (i.e., the discrepancy between the observed and expected cognitive function).[33,34] Although potential limitations of this method have been brought to attention when searching for associations between residuals and external variables,[35] it offers valuable insights as it allows quantitative comparisons. A linear regression model was developed for each cognitive composite z-score and the z-scores of SBOC, RSMS, BIS, IRI-Empathy, and IRI-Perspective-taking, serving as dependent variables, computing a total of nine models. Each model included age, years of education, and cortical thickness from the previously identified regions of interest (as defined in Section 2.8.) as independent variables. To explore the potential effect of the different pathogenic mutations and disease severity, we also included interaction terms for genotype and symptomatic status. As for cognitive variables, z-scores based on the mean and standard deviation of healthy controls of the corresponding sex were employed as a standardized measure to account for sex-related differences in cortical thickness.[36] Each model incorporated both female and male participants. One residual value was obtained per participant and timepoint.

### 2.10 | Statistical analyses of the residuals

Differences in the residuals between females and males carrying pathogenic mutations were analyzed using Welch *t*-tests. We performed these analyses in all carriers at baseline (both symptomatic and asymptomatic). To explore if sex differences in cognitive and behavioral reserve could be driven by a specific mutation group or were related to symptomatic status, we conducted post-hoc comparisons for subgroups adjusting for false discovery rate (FDR).

### 2.11 | Linear mixed-effects models

To further explore the observed differences in cognitive reserve in the transition from the asymptomatic to the symptomatic stage, we used linear mixed-effects (LME) models to examine how cortical thickness and cognitive changes vary by sex, using all the data obtained during the follow-up. We modelled the cognitive outcome obtained from every participant at each visit during the follow-up as the dependent variable, correcting for cortical thickness, in order to quantify the individual reserve as disease progresses. Time, age at baseline, and years of education were included as fixed effects, and the interaction between self-reported sex and symptomatic status with time were also included because sex differences are known to emerge by disease stage.[37–39] The model included random intercepts and slopes. We performed post-hoc comparisons for subgroups according to sex and symptomatic status, adjusting for FDR.

As cognitive trajectories could potentially follow a non-linear trajectory[40] and therefore LME models might not account for this possibility, we performed additional analyses following an alternative method to longitudinally quantify cognitive reserve.[41] This approach relies on a latent process mixed-effects (LPM) and approximates time by natural cubic splines with four knots placed at the quantiles of the distribution, thus avoiding assuming linearity of the trajectories. The model included the cognitive outcome as the dependent variable, and cortical thickness, time, age at baseline and years of education as fixed effects, as well as the interaction between sex and time. The model included random intercepts.

In addition, we also ran an LME model exploring the changes in cognitive reserve according to the global cognitive-functional decline. The cognitive outcome was included as the dependent variable. Cortical thickness, age at baseline, years of education, and CDR+NACC-FTLD-SB, as well as the interaction between self-reported sex and CDR+NACC-FTLD-SB were chosen as fixed effects, with random intercepts and slopes.

### 2.12 | Other statistical analyses

Baseline demographic and neuropsychological differences between groups were studied using the Wilcoxon rank sum test, Pearson's chi-squared test, or Fisher's exact test, as appropriate, and FDR correction for multiple testing applied. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with R version 4.3.2. (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) using the "gtsummary," "ggstatsplot," "lme4," and "lcmm" packages.[42–46]

## 3 | RESULTS

### 3.1 | Clinical and demographic analyses

The comparison of baseline demographic variables is depicted in Table 1 and Table S1. No significant differences were found between sexes regarding age at first visit, years of education, number of visits, number of MRIs, or image quality rating of MRI. The median number of annual visits during the follow-up was 2, ranging from 1 to 7. Carriers of pathogenic mutations exhibited a mean age of 50 years at baseline, with ages spanning from 18 to 80 years. The majority of the pathogenic mutation carriers showed no cognitive or behavioral impairment according to CDR+NACC-FTLD-GS. Among pathogenic mutation carriers at baseline, the most frequently encountered clinical diagnosis was clinically normal in 212 (54%), followed by mild cognitive impairment in 39 (9.9%), bvFTD in 94 (24%), and non-fluent primary progressive aphasia in 9 (2.3%). During follow-up, the percentage of asymptomatic mutation carriers decreased to 50% according to CDR+NACC-FTLD-GS at the last visit. The most frequently identified pathogenic mutations were found in the *C9orf72* gene in 189 (48%) participants, followed by *MAPT* in 112 (28%) and *GRN* in 93 (24%).

We replicated previously described cognitive and social cognition differences between males and females in the non-carrier and carrier group, showing higher memory and empathy scores for females (Table S2-S3)[10,47–49]. This observation and current recommendations to study sex differences in neurodegenerative diseases[9,22,23] justified our approach to z-score calculation segregating by sex. Table S4-S6 show detailed information about each mutation group's baseline cognitive and behavioral scores. As expected, the pathogenic mutation carrier group was older than the non-carrier group and was characterized by higher cognitive and behavioral impairment (Table S7). In the subgroup of participants that were asymptomatic at baseline and developed symptoms during the follow-up ($n = 28$), we observed consistently higher age at symptom onset in females compared to males, suggesting additional 6.5 symptom-free years in females. However, the effect did not reach statistical significance [mean (standard deviation), females vs. males: 55.6 (13.9) vs. 49.1 (10.8), Cohen's d = 0.54, $p = 0.178$]. We found no significant moderation by self-reported sex on the relationship between cortical thickness and the age of symptom onset, adjusting for years of education ($p = 0.118$). Males and females carrying pathogenic FTD mutations showed similar cognitive and behavioral changes compared to noncarriers at baseline (Table S8 and S9), however, some differences emerged at the asymptomatic stage for the MINT raw score and the copy of Benson figure z-score, in which females showed worse performance, and also for the IRI empathic concern raw and BIS scores, with females presenting better outcomes, in a pattern similar to the one found for healthy controls (Table S2).

**TABLE 1** Demographic and baseline characteristics of the participants.

| | Controls | | | | Mutation carriers | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristic | *N* | All controls, *N* = 279[a] | Female, *N* = 172[a] | Male, *N* = 107[a] | *N* | All carriers, *N* = 394[a] | Female, *N* = 213[a] | Male, *N* = 181[a] |
| Age** | 279 | 47 (13) | 47 (13) | 46 (14) | 394 | 50 (14) | 49 (14) | 50 (14) |
| Years of education | 279 | 15.9 (2.5) | 15.7 (2.5) | 16.1 (2.3) | 394 | 15.9 (4.9) | 15.6 (2.3) | 16.3 (6.7) |
| Number of visits | 279 | 2.1 (1.3) | 2.0 (1.3) | 2.2 (1.5) | 394 | 2.2 (1.4) | 2.2 (1.4) | 2.2 (1.4) |
| Number of MRIs | 279 | 2.0 (1.3) | 1.9 (1.2) | 2.1 (1.4) | 394 | 2.2 (1.4) | 2.2 (1.4) | 2.2 (1.4) |
| Image quality rating[b] | 279 | 2.2 (0.2) | 2.2 (0.2) | 2.3 (0.2) | 394 | 2.3 (0.3) | 2.2 (0.3) | 2.3 (0.3) |
| Executive function composite [c,**] | 273 | 0.0 (0.7) | 0.0 (0.7) | 0.0 (0.8) | 370 | −0.5 (1.2) | −0.5 (1.1) | −0.6 (1.2) |
| Language composite [d, **] | 273 | 0.0 (0.7) | 0.0 (0.7) | 0.0 (0.7) | 369 | −0.8 (1.7) | −0.8 (1.6) | −0.8 (1.8) |
| Memory composite [e, **] | 279 | 0.0 (0.7) | 0.0 (0.7) | 0.1 (0.6) | 379 | −0.5 (1.2) | −0.5 (1.2) | −0.5 (1.1) |
| Global cognitive composite [f, **] | 279 | 0.0 (0.6) | 0.0 (0.6) | 0.0 (0.6) | 380 | −0.6 (1.2) | −0.6 (1.2) | −0.6 (1.2) |
| CDR+NACC-FTLD-GS at baseline** | 279 | | | | 394 | | | |
| 0 | | 279 (100%) | 172 (100%) | 107 (100%) | | 230 (58%) | 130 (61%) | 100 (55%) |
| 0.5 | | | | | | 60 (15%) | 30 (14%) | 30 (17%) |
| 1 | | | | | | 42 (11%) | 20 (9.4%) | 22 (12%) |
| 2 | | | | | | 54 (14%) | 26 (12%) | 28 (15%) |
| 3 | | | | | | 8 (2.0%) | 7 (3.3%) | 1 (0.6%) |
| CDR+NACC-FTLD-GS at last visit** | 279 | | | | 394 | | | |
| 0 | | 279 (100%) | 172 (100%) | | | 197 (50%) | 111 (52%) | 86 (48%) |
| 0.5 | | | | | | 70 (18%) | 32 (15%) | 38 (21%) |
| 1 | | | | | | 41 (10%) | 21 (9.9%) | 20 (11%) |
| 2 | | | | | | 66 (17%) | 37 (17%) | 29 (16%) |
| 3 | | | | | | 20 (5.1%) | 12 (5.6%) | 8 (4.4%) |
| Age of symptom onset | | | | | 197 | 56.9 (11.2) | 57.9 (10.8) | 55.8 (11.7) |
| CDR+NACC-FTLD-SB at baseline** | 279 | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) | 394 | 2.7 (4.7) | 2.8 (5.1) | 2.7 (4.2) |
| Pathogenic mutation** | | | | | 394 | | | |
| C9orf72 | | | | | | 189 (48%) | 105 (49%) | 84 (46%) |
| GRN | | | | | | 93 (24%) | 44 (21%) | 49 (27%) |
| MAPT | | | | | | 112 (28%) | 64 (30%) | 48 (27%) |
| Control | | | | | | 0 (0%) | 0 (0%) | 0 (0%) |

Abbreviations: CDR+NACC-FTLD-GS, Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains Global Score; CDR+NACC-FTLD-SB, Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains Sum of Boxes; MRI, magnetic resonance imaging.

[a]Mean (SD); *n* (%).

[b]Quality rating is expressed as integers 0.5–6, being > 6 considered as unacceptable quality.

[c]Expressed as z-scores from controls of the same sex. The executive function composite comprises the average scores from Number Span Backward, Verbal Fluency Phonemic Test and Trail Making Test Part B.

[d]Expressed as z-scores from controls of the same sex. The language composite comprises the average scores from Multilingual Naming Test and Category Fluency.

[e]Expressed as z-scores from controls of the same sex. The memory composite comprises the average scores from California Verbal Learning Test, Benson Figure Copy delayed recall and Craft Story 21.

[f]Expressed as z-scores from controls of the same sex. The global cognitive composite comprises the average scores from the executive function, language and memory composites.

**Difference between pathogenic mutation carriers and healthy controls, $p < 0.05$. False discovery rate correction for multiple testing applied.

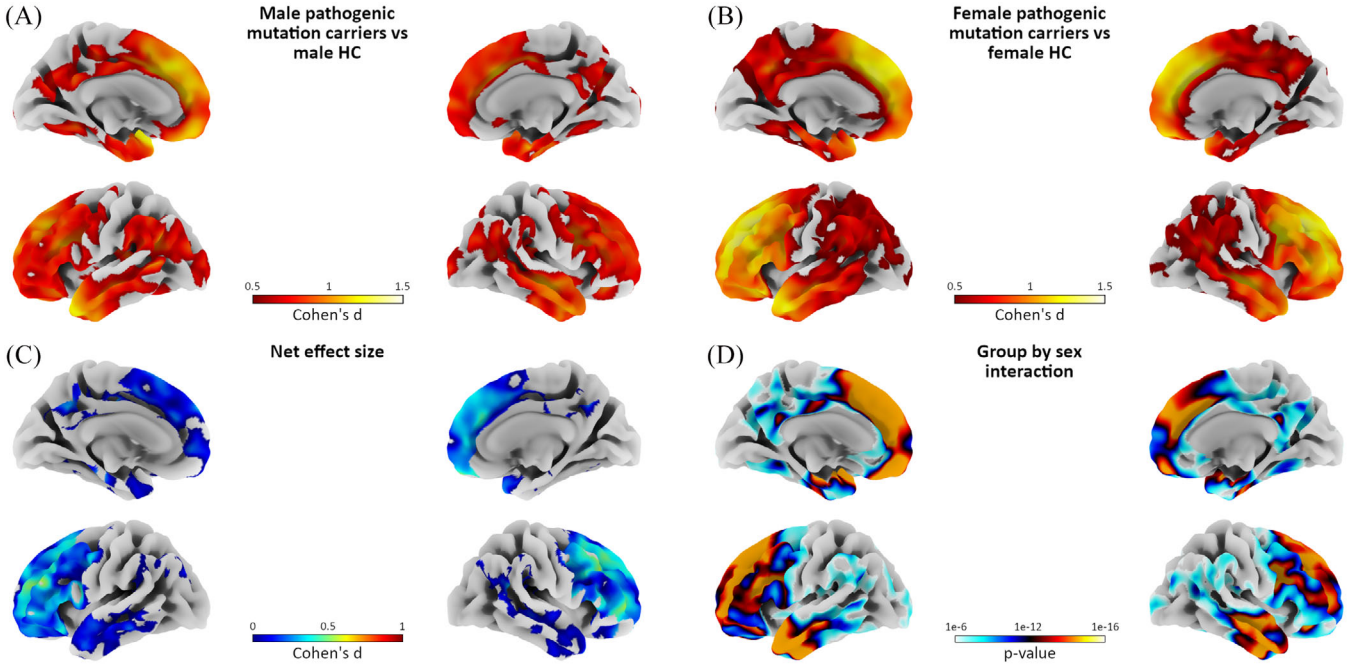


**FIGURE 1** Cortical thickness reduction in symptomatic FTD mutation carriers. Comparison of cortical thickness reduction in symptomatic (Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains ≥ 0.5) pathogenic mutation carriers and healthy controls of the same self-reported sex. (A) Group difference in cortical thickness between male FTD mutation carriers and healthy male controls. (B) Group difference in cortical thickness between female FTD mutation carriers and healthy female controls. (C) Net effect size shows greater cortical thinning in females carrying FTD mutations than in males. The effect size was obtained after subtracting the effect size map in panel B from the one in panel A. (D) Cortical areas where a significant group by sex interaction was found. The result was obtained from a 2-way ANOVA analysis with group (pathogenic mutation carrier or healthy control) and sex at birth (female or male) as main factors and age and years of education as covariates. Colored areas represent the *p*-values of the interaction between the pathogenic mutation carrier status (carrier vs. non-carrier) and self-reported sex (man vs. woman). ANOVA, analysis of variance; FTD, frontotemporal dementia; HC, healthy controls.

## 3.2 | Cortical thickness analyses

Each pathogenic mutation was associated with previously reported typical topography of neurodegeneration: more widespread in *C9orf72* carriers, a frontal, temporal, and parietal pattern in *GRN*, and a higher effect size in medial temporal regions and temporal poles for *MAPT* (Figure S3). Males and females carrying a pathogenic FTD mutation showed marked cortical thinning of the frontal, temporal, and parietal lobes compared to healthy controls of the same sex. Notably, the effect size of the cortical thinning was more prominent in females than in males (Figure S3). The difference between males and females in the amount of cortical loss was particularly evident at the symptomatic stage, with a significant sex-by-group interaction in frontotemporal regions (Figure 1). This difference was not observed in asymptomatic mutation carriers (Figure S4), where females showed no significant cortical thinning compared to healthy controls after FWE correction. Symptomatic females showed significant cortical thinning in frontal regions compared to symptomatic males across mutations. Figure S5 shows the comparison in cortical thickness between females and males carrying a pathogenic FTD mutation.

## 3.3 | Cognitive reserve analyses

To further evaluate potential cognitive and behavioral reserve differences by sex, we next used the residuals approach. The comparison of residual values between sexes showed that, at baseline, females (both asymptomatic and symptomatic) had greater frontal cortical thinning than males for the same level of executive functioning performance (Cohen's d = 0.30, 95% confidence interval [CI] [0.08, 0.51], t(331) = 2.331, $p = 0.007$, Figure 2). We found a significant effect for the interaction of the symptomatic status in the model ($p < 0.001$, Table S10). Post hoc FDR-adjusted analyses showed that, in the comparison among subgroups, the differences in the residuals remained statistically significant between symptomatic females and males carrying a pathogenic *C9orf72* expansion ($p = 0.026$), but not for the rest of the comparisons (Table S11). No significant differences in the cognitive reserve residuals were found for global ($p = 0.301$), language ($p = 0.500$), or memory ($p = 0.443$) composites (Figure S6, Table S12).

As we found a significant interaction for symptomatic status in the model, and due to the low proportion of symptomatic participants at baseline, we conducted an additional analysis using data from the first visit when symptoms appeared in participants who became

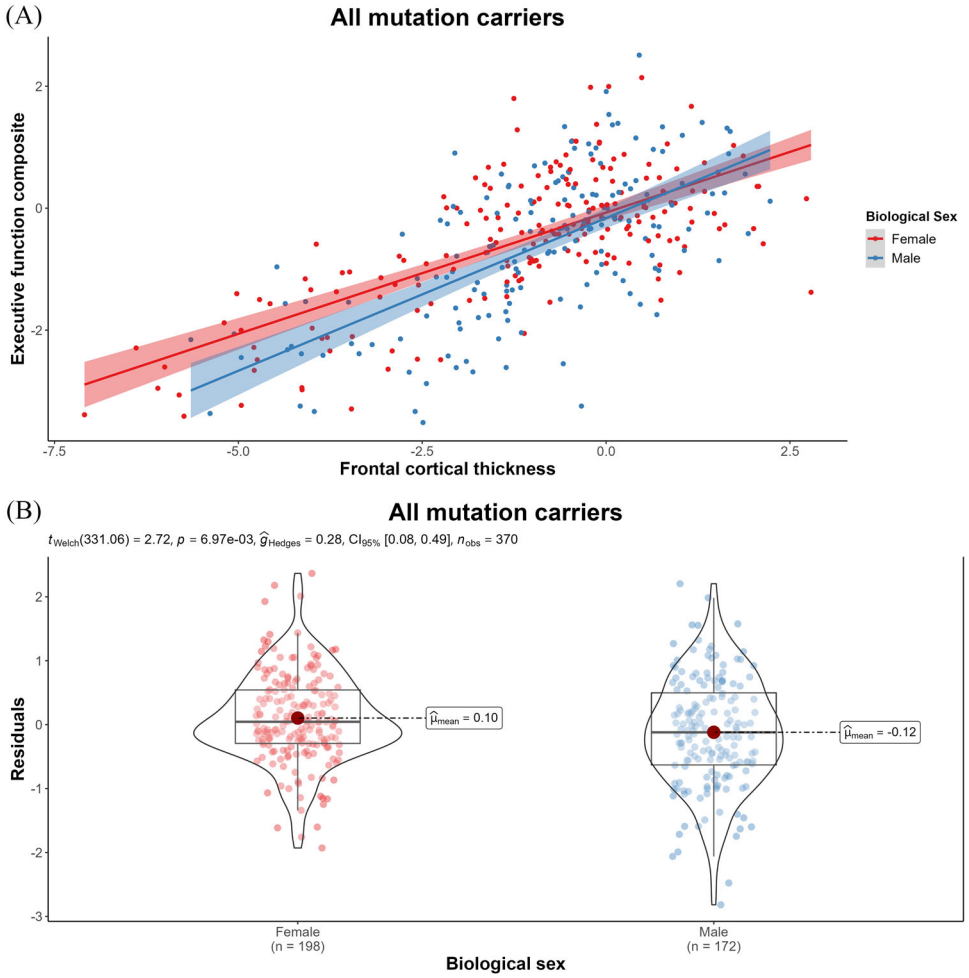


**FIGURE 2** Comparison of cognitive reserve between females and males carrying FTD mutations. The predicted cognitive performance for a certain level of cortical thinning in each subject was obtained using the individual residuals as a proxy of cognitive reserve. The model included data from all the mutation carriers at baseline. Differences in residuals between females and males were calculated with Welch *t*-tests. Panels show the linear model (A) and violin plot for the residuals (B). FTD, frontotemporal dementia.

symptomatic during follow-up. The results of this analysis can only be considered exploratory. The comparisons of the residuals indicated that females presented with greater frontal cortical thinning than males for an equivalent executive functioning performance (Cohen's d = 0.31, 95% CI [0.00, 0.62], t(163) = 1.9836, $p = 0.049$, Table S13). Post-hoc analyses showed that, when stratifying by genotype, the differences in residuals were statistically significant between females and males carrying a pathogenic *C9orf72* expansion ($p = 0.044$) or a *GRN* mutation ($p = 0.017$). However, no significant differences remained after adjusting for FDR (Table S14).

Examining social cognition and behavioral measures (Figure 3, Table S15), females carrying a pathogenic FTD mutation showed greater global cortical thinning compared to male carriers at equivalent IRI perspective-taking scores (Cohen's d = 0.30, 95% CI [0.09, 0.52], t(324) = 2.7432, $p = 0.006$). However, no differences remained significant in the post-hoc, FDR-adjusted stratified analyses (Table S16). No statistically significant differences were found in the IRI emphatic concern, RSMS, BIS, and SBOC residual analyses (Figure S7).

## 3.4 | Longitudinal analyses

To further explore the observed differences in cognitive reserve in the transition from the asymptomatic to the symptomatic stage, we fitted LME models leveraging all longitudinal measurements. The LME model for the executive function composite indicated a significant effect of the interaction between self-reported sex and symptomatic status with time when the whole cohort was analyzed (Table S17). Post-hoc comparison adjusting for FDR showed statistically significant differences between females and males in the asymptomatic status ($p = 0.012$), but not for symptomatic participants ($p = 0.455$). Asymptomatic FTD mutation carriers presented a divergent trajectory between sexes in the executive function composite. In the case of symptomatic FTD mutation carriers, the model indicated similar trajectories (Figure 4). Individual cognitive trajectories are shown in Figure S8.

This pattern of sex-specific trajectories was also found when longitudinally modeling the scores of IRI perspective-taking (Figure S9,

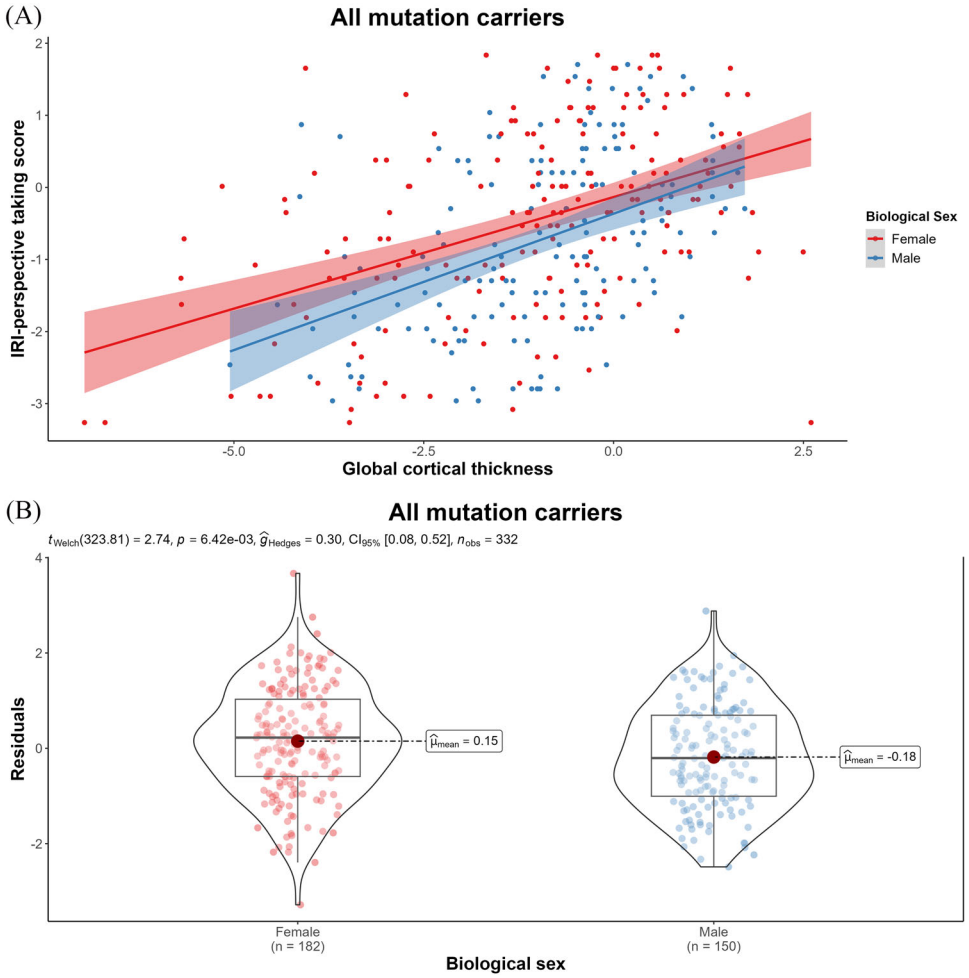


**FIGURE 3** Comparison of social cognitive reserve between females and males carrying FTD mutations. The predicted social cognitive performance for a certain level of cortical thinning in each subject was obtained using the individual residuals as a proxy of cognitive reserve. The model included data from all the mutation carriers at baseline. Differences in residuals between females and males were calculated with Welch *t*-tests Panels show the linear model (A) and violin plot for the residuals (B). FTD, frontotemporal dementia; IRI, Interpersonal Reactivity Index.

Table S18). Post-hoc comparison adjusting for FDR showed statistically significant differences between females and males only in the symptomatic status ($p = 0.007$).

We performed complementary longitudinal analyses fitting LPM to avoid assuming linearity in the trajectories of cognitive function. The model for the executive function composite showed a significant interaction between sex and the second timepoint of the follow-up ($p = 0.032$, Table S19), but not for the first ($p = 0.704$) and last ($p = 0.170$) time points. This finding supports the previously found sex-related differences in the trajectories in the middle part of the follow-up, but not in the later stages. No significant effect of the interaction between self-reported sex and time was found when modeling IRI perspective-taking (Table S20).

Finally, a significant effect of the interaction between self-reported sex and cognitive-functional decline as measured by CDR®+NACC-FTLD-SB was found, with females presenting with higher executive function than expected for cortical thickness compared to males as symptoms emerged (Figure S10, Table S21).

## 4 | DISCUSSION

In this large multicenter study of genetic FTD, we found that males and females showed remarkably similar clinical characteristics, but symptomatic females displayed more cortical thinning than males for an equal level of cognitive impairment and behavioral changes. To better understand this observation, we followed the residuals approach. We found that the observed cortical thinning in females was accompanied by better-than-expected executive function and social cognition, suggesting that females carrying FTD mutations have higher cognitive and behavioral reserve than males. Finally, we leveraged extensive longitudinal data to confirm that females with genetic FTD were characterized by increased cognitive reserve during the preclinical stage, reaching its maximum approaching symptom onset and decreasing as the disease progresses during the symptomatic stage. These observations seemed particularly pronounced in the subgroup of patients carrying the *C9orf72* repeat expansion and, to a lesser extent, the *GRN* subgroup.

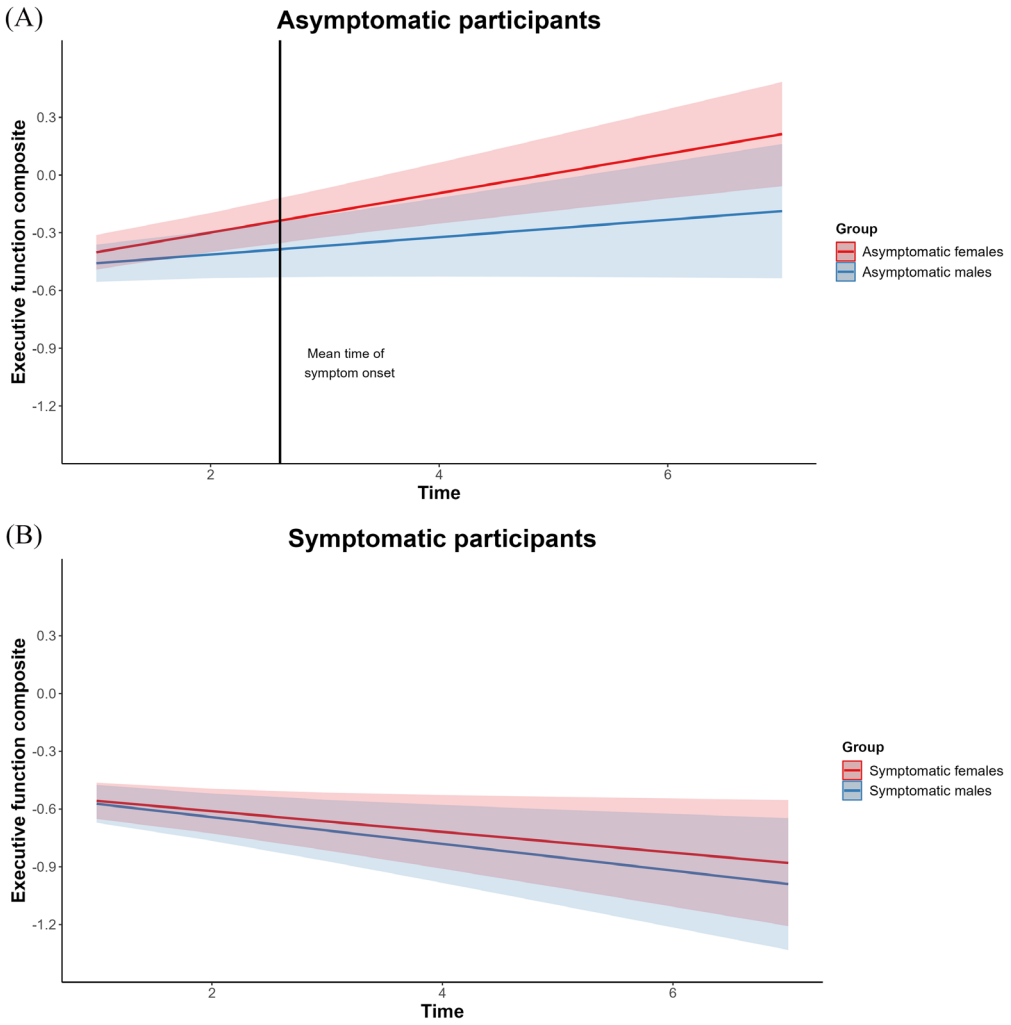


**FIGURE 4** Comparison of the cognitive reserve trajectories between females and males carrying FTD mutations. The image shows the differences in the executive function composite between males and females carrying FTD mutations through time, stratified by symptomatic status. The executive function composite obtained from every participant at each visit during the follow-up was included as the dependent variable, correcting for cortical thickness to quantify the individual reserve as the disease progresses. Time, age at baseline, and years of education were included as fixed effects, as well as the interaction between self-reported sex and symptomatic status with time. The model included random intercepts and slopes. The model included repeated measures from the mutation carriers during follow-up. The vertical line represents the mean time of symptom onset for the participants who transitioned from asymptomatic to symptomatic stage during the follow-up period. FTD, frontotemporal dementia.

Our findings complement another recent ALLFTD study, showing that females with genetic FTD also showed higher and faster increase than males of plasma neurofilament light chain (NfL) concentrations, an indicator of neuroaxonal degeneration.[24] Mirroring the results of the present work, males and females did not differ in cognitive and functional outcomes in the asymptomatic stages, and females evidenced better clinical trajectories for the intensity of neurodegeneration proxied by plasma NfL. Interestingly, symptomatic women presented steeper cognitive and functional declines compared to males, pointing to higher cognitive reserve in the early stages of the disease and greater subsequent vulnerability in females once the disease reaches a symptomatic stage. This pattern closely mirrors our study in which we also confirmed that with the emergence of symptoms, women showed loss of their reserve advantage over time.

The results of the present study also add to our previous observation in a large multicenter study of patients diagnosed with bvFTD.[14] Still, to our knowledge, our work is the first to demonstrate a higher executive and behavioral reserve in females with genetic FTD and a range of clinical phenotypes beyond bvFTD. In our previous study, we focused on patients with sporadic bvFTD who were, by definition, symptomatic. However, in the present work, we were able to delve into the preclinical stages, finding a similar pattern of cognitive reserve to the one found in AD, with females outperforming males early in the course of the disease but presenting a subsequent steeper decline.[50–53] Thus, females seem to have a premorbid advantage that translates into higher cognitive reserve and persists in the early disease phase but becomes equivalent to men after reaching a critical point of brain atrophy that is higher than men later in the disease

course. In this sense, we found a trend towards higher age at symptom onset in females, which aligns with previous studies of genetic FTD.[54–56] Although the differences were not statistically significant in our sample, probably due to lack of power, we observed similar mean age of onset distribution and effect sizes for the *C9orf72* and *MAPT* subgroups compared to previous extensive worldwide-scale studies.[55] Genetic (e.g., X chromosome), lifestyle[57], and hormonal[58] differences might be the underlying mechanisms, conferring greater flexibility and adaptability of brain networks to be able to cope with frontotemporal damage in females. Notably, by focusing on both symptomatic and asymptomatic participants with genetic FTD that were systematically followed over time in a longitudinal study, we reduced the potential confounding factor of diagnostic delays in females. Previous research has underscored sex and gender as potential modulators in FTD phenotype,[59,60] but the reason why it modulates the neurodegenerative pathway is yet to be elucidated. Notable differences in mechanisms known to play a role in neurodegeneration, like neuroimmune processes[61] and neuroendocrine dynamics[62–64] that add to the biological differences conferred by the X-chromosome[65] might impact protein accumulation. For instance, an X-linked single nucleotide polymorphism has been shown to modulate the age of onset in *C9orf72* hexanucleotide expansion carriers.[66] In AD, previous works have suggested a significant interaction between sex and microglia activation in relation to AD pathology, translating into a disproportionate effect of the immune system in females[61] but with a worse phagocytic activity.[67] Although this topic has been considerably less studied than in AD, immune responses have emerged as a potential pivotal mechanism in FTD.[68,69] Post-menopausal females also may present with a reduced glymphatic clearance as measured by functional MRI, thus having a predisposition to pathological protein accumulation.[70] Animal models of AD have shown increased amyloid plaque accumulation with estrogen depletion,[62] and females in perimenopausal ages present reduced cerebral metabolism compared to males, exceeding amyloid-$\beta$ deposition.[63,64] Future studies assessing the influence of menopause and perimenopause on how FTD manifests are therefore warranted.

Our results and previous studies conducted in sporadic and genetic FTD support the notion that females with FTD have a higher behavioral and executive reserve. However, the observed differences were not universal across mutations. In fact, the results from the present study indicate that sex-related differences seemed to be particularly driven by the *C9orf72* group and, to a lesser extent, by the *GRN* group. The *MAPT* group had a different pattern. Several reasons could explain the differences observed. First, individuals affected by either a *C9orf72* expansion or a *GRN* mutation present with a distinct pattern of cortical thinning compared to *MAPT* mutation carriers.[58] *C9orf72* and *GRN* may have a higher propensity to early neurodegeneration of the frontal lobe, where we observed the interaction between group and sex. Notably, cognitively healthy females have a thicker frontal cortex than men, and this baseline difference in cerebral structure may have contributed to the observed results in the *C9orf72* and *GRN* groups.[36] In sharp contrast, the topography of neurodegeneration in *MAPT* carriers involves the medial temporal lobe region, where sex-related differences in brain structure may favor males.[59] These differences could contribute to specific resilience mechanisms in the *MAPT* subgroup. Second, the associated pathology differs among mutations, with *C9orf72* and *GRN* causing TDP-43 accumulation and *MAPT* predisposing to tau aggregation.[1] The variability in the genetic and pathophysiological underpinnings between TDP-43 and tau subtypes of frontotemporal lobar degeneration (FTLD) may, therefore, also account for the observed differences.[71]

Our results have important implications for developing integrated models that combine clinical, genetic, biofluid, and imaging biomarker data to stage mutation carriers. Such models would enable the determination of "disease age" at the individual level and facilitate the prediction of longitudinal decline in single subjects. Previous studies have focused on elucidating the sequence of cortical thinning[72] and changes in fluid biomarkers[73] during the preclinical stage of FTD. These advancements are critical for designing and implementing more effective clinical trials, as they help establish a reliable staging system for the disease during its presymptomatic or minimally symptomatic phases, when potential treatments may have the greatest impact.[74] However, recent studies developing such models[75] or exploring longitudinal brain atrophy rates in genetic FTD[76] did not perform segregated analyses by sex; thus, resulting models may have mitigated the observed sex-related differences in brain structure.[77] Future studies aiming to develop data-driven models for staging FTD should consider defining segregated models by sex, and future trials in *C9orf72* should be designed and powered to address sex-specific endpoints for cognition, behavior, and clinical stage.

## 4.1 | Strengths and limitations

Our study has some limitations. This study lacks pathological confirmation, or in vivo biomarkers related to relevant pathophysiological processes, like specific protein aggregates or astroglial activation. However, we limited the participants to confirmed carriers of the most frequent FTD mutations regardless of symptomatic status or clinical phenotype, and thus, a diagnosis of definitive FTD could be made. Also, our results were restricted to macrostructural cortical thinning and did not include measures of functional cerebral connectivity that could help in understanding the mechanisms by which females' brains were able to cope with a higher neurodegenerative burden. While significant advances have shown that sex differences are crucial in shaping functional networks in the human brain,[78–82] there is a paucity of data in brain connectivity research accounting for differences by sex in FTD,[83] and future studies should perform segregated analyses in preclinical FTD.

We conducted segregated analyses when studying cognition, following current recommendations[9,13,22,23] to avoid overestimating potential baseline differences between females and males. Nevertheless, this approach leads to obtaining different reference values to quantify variables and might make the interpretation less straightforward. Another limitation of our study is its focus on differences related to self-reported sex, defined here as the complement of sex chromosomes that aligns with reproductive organs. This definition

is constrained when applied to humans, as social roles and identities significantly shape our understanding of self-reported sex, introducing the dynamic and nuanced concept of gender.[10] Furthermore, the study of sex-related differences in health has limitations as the presence of transgender, intersex, or non-binary individuals can result in a lack of clear alignment between self-reported sex and chromosomal sex.[84] Future studies should comprehensively address the individual interactions between sex and gender, as well as delve into the differences between biological sex, self-reported sex, and gender, in order to accurately assess the influence of these factors on health and disease. Lastly, we used the residual approach as a proxy of resilience. Although this method has been proven useful in capturing meaningful information and allowing for a quantitative analysis of cognitive resilience,[33,34] its conceptual limitations have also been brought to attention.[35] However, we performed complementary imaging and longitudinal analyses that supported our findings. Our results suggest that females with genetic FTD have higher executive and behavioral reserve than males and add to previous evidence supporting the existence of sex-related differences in the ability of females' brains to cope with frontal neurodegeneration. Future staging and prognosis studies in FTD should consider performing segregated analyses by sex to forward precision medicine-based approaches, particularly in *C9orf72* expansion carriers.

## ACKNOWLEDGMENTS

Data collection and dissemination of the data presented in this paper were supported by the ALLFTD Consortium (U19: AG063911, funded by the National Institute on Aging and the National Institute of Neurological Diseases and Stroke) and the former ARTFL and LEFFTDS Consortia (ARTFL: U54 NS092089, funded by the National Institute of Neurological Diseases and Stroke and National Center for Advancing Translational Sciences; LEFFTDS: U01 AG045390, funded by the National Institute on Aging and the National Institute of Neurological Diseases and Stroke). The ALLFTD Executive Committee reviewed the manuscript for scientific content. This work was supported by NIH-NIA grants R01AG072475 (PI: K.B.C.), and UCSF ADRC P50 AG023501. J.G.C. is supported by a *Río Hortega* grant (CM23/00176) from the Carlos III National Institute of Health of Spain, partly funded by the European Social Fund Plus. I.I.-G. is a senior Atlantic Fellow for Equity in Brain Health at the Global Brain Health Institute (GBHI), and receives funding from the GBHI, the Alzheimer's Association, and the Alzheimer Society (GBHI ALZ UK-21-720973 and AACSF-21-850193). I.I.-G. was also supported by the Juan Rodés Contract (JR20/0018). This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project PI21/00791 and co-funded by the European Union (FEDER) This study has been also funded by Instituto de ISCIII through the projects INT21/00073, PI20/01473 and PI23/01786 to J.F., CP20/00038 and PI22/00307 to A.B., PI18/00435 to D.A., PI20/01330 to A.L. and PI21/01395 to O.D.-I.) and co-funded by the European Union, and the Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas Program 1, partly jointly funded by Fondo Europeo de Desarrollo Regional, Unión Europea, Una Manera de Hacer Europa. This work was also supported by the National Institutes of Health grants (R01 AG056850, R21 AG056974, R01 AG061566, R01 AG081394 and R61AG066543 to J.F., AG032306 and K24AG045333 to H.J.R., AG038791 to A.B.), the Department de Salut de la Generalitat de Catalunya, Pla Estratègic de Recerca I Innovació en Salut (SLT006/17/00119 to J.F.; SLT002/16/00408 to A.L.). It was also supported by Fundación Tatiana Pérez de Guzmán el Bueno (IIBSP-DOW-2020-151 to J.F.) and Horizon 2020–Research and Innovation Framework Programme from the European Union (H2020-SC1-BHC-2018-2020 to J.F.; 948677). The Alzheimer Association also participated in the funding of this work (AARG-22-923680 to A.B.). O.D.-I. receives funding from the Alzheimer's Association (AARF-22-924456) and the Jerome Lejeune Foundation postdoctoral fellowship. J.A.-I. was supported by Instituto de Salud Carlos III through the Río Hortega Fellowship "CM21/00243" and co-funded by the European Union. L.V.-A. was supported by Margarita Salasjunior postdoctoral fellowship (UNI/551/2021, NextGenerationUE).

## CONFLICT OF INTEREST STATEMENT

J.G.C.: Declarations of interest: none; S.R-G.: Declarations of interest: none; K.B.C.: Declarations of interest: none; J.S.G.: Declarations of interest: none; M.M.: Declarations of interest: none; L.V.-A.: Declarations of interest: none; A.M.-N.: Declarations of interest: none; J.A-I.: Declarations of interest: none; O.D-I.: Declarations of interest: none; A.B.: Declarations of interest: none; O.B.: Declarations of interest: none; J.F.: Declarations of interest: none; D.A. participated in advisory boards from Fujirebio-Europe, Roche Diagnostics, Grifols S.A. and Lilly, and received speaker honoraria from Fujirebio-Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica S.L., Zambon S.A.U. and Esteve Pharmaceuticals S.A., and declares a filed patent application (WO2019175379 A1 Markers of synaptopathy in neurodegenerative disease); M.C.-I.: Declarations of interest: none; I.B.: Declarations of interest: none; M. S.-S.: Declarations of interest: none; M.B.S.S.: Declarations of interest: none; I.S.M.: Declarations of interest: none; H.W.H.: Declarations of interest: none; L.K.F: Declarations of interest: none; K.K.: Declarations of interest: none; A.M.S.: Declarations of interest: none; C.T.: Declarations of interest: none; K.P.R.: Declarations of interest: none; B.B.: Declarations of interest: none; A.B.: Declarations of interest: none; H.J.R.: Declarations of interest: none; A.L. reports holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0), and has served as a consultant or on advisory boards for Almirall, Fujirebio-Europe, Grifols, Eisai, Lilly, Novartis, Nutricia, Roche, Biogen and Zambon; I.I-G.: Declarations of interest: none. Author disclosures are available in the supporting information.

## CONSENT STATEMENT

The ALLFTD study was approved through the Trial Innovation Network at Johns Hopkins University. Local ethics committees at each of the sites approved the study, and all participants provided written informed consent or assent with proxy consent.

## ORCID

*Jesús Garcia Castro* https://orcid.org/0000-0003-1503-4775

*Ignacio Illán-Gala* https://orcid.org/0000-0002-5418-2052

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## SUPPORTING INFORMATION

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

**How to cite this article:** Garcia Castro J, Rubio-Guerra S, Casaletto KB, et al. Sex differences in the executive and behavioral reserve of autosomal dominant frontotemporal dementia. *Alzheimer's Dement*. 2025;21:e70070. https://doi.org/10.1002/alz.70070