UC Berkeley
UC Berkeley Previously Published Works

Title

Examining the relation between bilingualism and age of symptom onset in frontotemporal dementia.

Permalink

https://escholarship.org/uc/item/3ft1v13m

Journal

Bilingualism Language and Cognition, 27(2)

ISSN

1366-7289

Authors

de Leon, Jessica

Grasso, Stephanie

Allen, Isabel Elaine

et al.

Publication Date

2024-03-01

DOI

10.1017/s1366728923000226

Peer reviewed

Examining the relation between bilingualism and age of symptom onset in frontotemporal dementia

Jessica de Leon[a,*], Stephanie Grasso[b,*], Isabel Elaine Allen[c], Danielle P. Escueta[a], Yvette Vega[a], Malihe Eshghavi[d], Christa Watson[a], Nina Dronkers[e], Maria Luisa Gorno-Tempini[a], Maya L. Henry[b]

[a]Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA

[b]Department of Speech, Language and Hearing Sciences, University of Texas At Austin, Texas, USA

[c]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA

[d]Department of International and Multicultural Education, University of San Francisco, California, USA

[e]Department of Psychology, University of California, Berkeley, California, USA

Abstract

Bilingualism is thought to confer advantages in executive functioning, thereby contributing to cognitive reserve and a later age of dementia symptom onset. While the relation between bilingualism and age of onset has been explored in Alzheimer's dementia, there are few studies examining bilingualism as a contributor to cognitive reserve in frontotemporal dementia (FTD). In line with previous findings, we hypothesized that bilinguals with behavioral variant FTD would be older at symptom onset compared to monolinguals, but that no such effect would be found in patients with nonfluent/agrammatic variant primary progressive aphasia (PPA) or semantic variant PPA. Contrary to our hypothesis, we found no significant difference in age at symptom onset between monolingual and bilingual speakers within any of the FTD variants, and there were no notable differences on neuropsychological measures. Overall, our results do not support a protective effect of bilingualism in patients with FTD-spectrum disease in a U.S. based cohort.

Keywords

frontotemporal dementia; primary progressive aphasia; bilingualism; cognitive reserve; Alzheimer's dementia

Address for correspondence: Jessica de Leon, University of California, San Francisco, Memory and Aging Center Box 1207, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, **Telephone**: 415-476-2912, **Fax**: 415-353-8292, jessica.deleon@ucsf.edu.
*Jessica de Leon and Stephanie Grasso share first authorship and contributed equally to this study.

INTRODUCTION

Bilingualism is thought to contribute to cognitive reserve. The concept of cognitive reserve is evolving; at present, this term refers to a property of the brain that supports adaptability of cognitive processes that affect an individual's susceptibility to brain aging or neuropathology (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia, 2021; Y. Stern et al., 2020). Other factors that have been studied in terms of their contributions to cognitive reserve include education, occupation, exercise, diet and social activities. It is thought than an individual with high cognitive reserve may have a better ability to cope with the effects of brain aging or disease.

Bilingualism is thought to contribute to cognitive reserve by enhancing executive functioning, as bilinguals are constantly required to inhibit their non-target language(s) while selecting their target language for use (Green & Abutalebi, 2013; Marian & Spivey, 2003), and because of the need to constantly switch and select among their languages (Bialystok, 1999, 2011; Bialystok & Craik, 2010; Green, 1998). Several studies have shown higher performance on executive functioning tasks (Chen et al., 2022; Lamar et al., 2022; Valsdóttir et al., 2022) and evidence of brain reserve as shown by preserved white matter integrity in healthy older adult bilingual speakers compared to monolingual speakers (Berkes et al., 2021; DeLuca & Voits, 2022). However, the studies comparing executive functioning in bilingual relative to monolingual speakers have yielded mixed findings, and results may depend on the type of task, age of the persons being tested, and frequency of daily language switching (see (Ware et al., 2020), for a review). Statistical and methodological issues including the failure to report effect sizes and publication bias are also potential contributors to the diversity of findings on this topic (Paap et al., 2015; Ware et al., 2020).

Bilingualism is thought to contribute to enhanced brain volume and connectivity in healthy adults, and this may manifest as a form of cognitive reserve later in life. The increase in cognitive reserve may also present as a delay in onset of symptoms associated with neurodegenerative syndromes (Y. Stern et al., 2020; Voits et al., 2020). Several previous studies on Alzheimer's disease (AD) have shown that bilingualism may contribute to cognitive reserve. Bilingualism has been associated with a 5-year delay in symptom onset in AD (Bialystok et al., 2007; Craik et al., 2010; Guzmán-Vélez & Tranel, 2015), although some studies have reported a null effect (Mukadam et al., 2017; Paap et al., 2015; Zahodne et al., 2014). One potential contribution to the heterogeneity of previous findings is the differential effect of bilingualism relative to clinical phenotype. Recently, in a cohort of highly educated individuals in the U.S., we observed that bilingual speakers with logopenic variant primary progressive aphasia (lvPPA), a language-prominent variant of AD, had a 5-year delay in symptom onset compared to monolinguals (de Leon et al., 2020).. There was, however, no difference in age at symptom onset between monolingual and bilingual speakers with amnestic AD This study, along with others (Alladi et al., 2017; Alladi et al., 2013), shows that bilingualism can have differential effects across distinct phenotypes of neurodegenerative disease.

In this study, we explore the effects of bilingualism on age at symptom onset in frontotemporal dementia (FTD), a group of neurodegenerative disorders that is characterized by behavioral, executive, and speech/language dysfunction. There are three main variants: 1) behavioral variant FTD (bvFTD), which is characterized by personality and behavioral disturbances, executive dysfunction, frontal and/or anterior temporal atrophy on neuroimaging (often worse in the right hemisphere) and, most commonly, frontotemporal lobar degeneration (FTLD)-tau, FTLD-TDP-43, or FTLD-FUS pathology (Olney et al., 2017; Rascovsky et al., 2011; Younes & Miller, 2020); 2) non-fluent/agrammatic variant primary progressive aphasia (nfvPPA), which is characterized by motor speech deficits and agrammatism, left inferior frontal and insular atrophy and, most commonly, FTLD-tau pathology (Gorno-Tempini et al., 2011; Grossman, 2012; Spinelli et al., 2017); and 3) semantic variant primary progressive aphasia (svPPA), which is characterized by naming and word comprehension deficits, bilateral anterior temporal atrophy, and FTLD-TDP-43 type C pathology (Davies et al., 2005; Gorno-Tempini et al., 2011; Hodges et al., 1992). FTD typically presents between the ages of 40–75 years, although age of onset differs by FTD clinical variant and the underlying neuropathology, with bvFTD tending to present earlier and nfvPPA presenting latest (Hodges et al., 2004; Johnson et al., 2005; Leroy et al., 2021; Wagner et al., 2021).

In FTD, several studies have observed greater cognitive reserve in individuals with higher educational (Beyer et al., 2021; Gazzina et al., 2019; Perneczky, Diehl-Schmid, Pohl, et al., 2007; Premi et al., 2013; Premi et al., 2017) and/or higher occupational attainment (Dodich et al., 2018; Maiovis et al., 2018; Massimo et al., 2019; Premi et al., 2013) and more frequent engagement in active leisure activities (Casaletto et al., 2020; Kinney et al., 2021; Maiovis et al., 2018). Studies have also explored the role of biological sex (Illán-Gala et al., 2021; Perneczky, Diehl-Schmid, Förstl, et al., 2007), although these have yielded mixed findings, However, the role of bilingualism as a contributor to cognitive reserve has been relatively unexplored. In a previous study, Alladi et al. explored the effect of bilingualism on age at onset of FTD in India and found that bilingual speakers with bvFTD (n = 41) experienced a significant, nearly 6-year delay in symptom onset compared to monolingual speakers (n = 26). A significant effect was not observed in patients with PPA (Alladi et al., 2017). As previously described, it has been hypothesized that bilingualism may contribute to cognitive reserve through advantages in executive functioning (Bialystok, 1999, 2011; Bialystok et al., 2007; Green, 1998; Green & Abutalebi, 2013; Marian & Spivey, 2003). The authors concluded that, due to this advantage, bilingual bvFTD patients may show delayed onset of executive dysfunction, which is a core symptom of bvFTD. To our knowledge, this is the only study that has explored the effects of bilingualism on age at symptom onset within FTD variants.

In this study, we explored the effects of bilingualism on age at symptom onset in a large, well-characterized cohort of individuals with the variants of FTD. We hypothesized that bilingual speakers with bvFTD would demonstrate a later age at symptom onset when compared to monolingual speakers, but that these effects would not be seen in patients with nfvPPA or svPPA. In each variant, we also compared neuropsychological scores between monolingual and bilingual speakers in order to investigate potential differences in performance across cognitive domains.

METHODS

Participants

Participants were recruited through a longitudinal research study at the UCSF Memory and Aging Center (MAC) and were seen between August 2005 and March 2020.

All participants were administered an extensive research protocol, which included clinical history-taking, a neurological examination, neuropsychological testing performed in English (Kramer et al., 2003), and a caregiver interview to assess functional status. Each participant was evaluated by a team consisting of a neurologist, neuropsychologist, and nurse/nurse practitioner. Diagnosis was reached by a multidisciplinary team applying current diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). A research visit summary summarizing the clinical history, findings, and diagnosis was written for each participant.

Written consent for this longitudinal study was obtained from each participant and/or their decision-making surrogate. The study was approved by the UCSF institutional review board for human research.

Neuropsychological testing—Participants completed a comprehensive cognitive battery as part of the study. The battery included tasks evaluating processing speed (Stroop color naming; Trail Making Test, part A), executive functioning (digit span forward/backward; Trail Making Test, part B; Stroop inhibition; DKEFS design fluency; lexical fluency; abstraction), episodic memory (California Verbal Learning Test-3; Rey figure delayed recall), language (Boston Naming Test; semantic fluency; Peabody Picture Vocabulary Test; sentence repetition; verbal agility; sentence comprehension; irregular word reading), visuospatial processing (Rey figure copy; VOSP number location; calculations), and global cognition (Mini Mental State Examination). This battery has demonstrated high sensitivity to both age-related cognitive changes and impairments characteristic of distinct neurodegenerative syndromes (Casaletto et al., 2019; Casaletto et al., 2017; Kramer et al., 2003).

Determination of monolingual or bilingual status

A comprehensive chart review to determine speaker status (monolingual or bilingual) was performed (Figure 1). First, the UCSF MAC database containing comprehensive research visit summaries from the participants' research neurologists were searched for terms that could indicate bilingualism, which were determined prior to the start of the study (de Leon et al., 2020). Patients were classified as bilingual if their chart indicated that they could communicate in two or more languages in everyday interaction with other speakers of these same languages (Alladi et al., 2017; Grosjean, 2010; Mohanty, 1994). Based on this definition, we used the following criteria to determine bilingualism status:

- They used one of their two languages as a part of their job (e.g., translator, language teacher, or other indication that they used a second language at work)

- They used one of their two languages in the home environment that was different from the majority language (which they also reported speaking)

- The neuropsychological evaluation was conducted in English, and there was indication that English was the individual's second language

- They were educated partly in another country wherein the language of education was reported to be different than their second language and may have reported continuing to use the language of education with family/friends

On the other hand, participants were classified as monolingual if there was no evidence from the chart review that they had learned a second language. Participants were excluded from this study if it was unclear that they met the above criteria for monolingual or bilingualism. Participants assigned to this category included those who 1) took classes in a second language but their achieved proficiency was unclear (i.e., it could not be determined whether they achieved the ability to communicate with a native speaker of this language or regularly used this language outside of the classroom), 2) immigrated to another country where a different language from their native language was spoken but it remained unclear if they used the language of their adopted country (e.g. worked or attended classes in their adopted country), or 3) reported minimal use of their second language, therefore leaving it unclear if they achieved proficiency in this language and/or the ability to converse in this language with a native speaker.

A total of 2053 charts were reviewed for this study—1499 participants were classified as monolingual, while 375 participants were classified as bilingual. We excluded 179 participants due to inability to determine monolingual or bilingual status based on the criteria listed above. The monolingual and bilingual cases were then reviewed for clinical diagnosis. Patients who met clinical diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011) for bvFTD, nfvPPA, or svPPA (N = 366) were then selected for further analysis and inclusion in this study. The charts of these individuals were then reviewed more extensively. The neurologists' visit summary notes were once again read in detail, and any supplemental notes from additional clinicians (e.g., neuropsychologists, speech pathologists) were also reviewed. This resulted in the reclassification of 1 participant from monolingual to bilingual and the exclusion of 5 participants due to inability to determine monolingual or bilingual status. We also excluded 53 individuals who were known carriers of genetic mutations associated with FTLD syndromes. Because of the insidious onset and heterogeneity of initial symptoms in this group of individuals, it is difficult to pinpoint symptom onset (Benussi et al., 2021; Gossink et al., 2022; McCarthy et al., 2022; Russell et al., 2020). In addition, FTLD mutation carriers tend to present at younger ages, in general (Benussi et al., 2022; Heuer et al., 2020; Laaksovirta et al., 2022; Moore et al., 2020; Rosas et al., 2021).

The chart review process resulted in a final cohort of 308 participants (105 monolingual bvFTD, 26 bilingual bvFTD, 57 monolingual nfvPPA, 22 bilingual nfvPPA, 68 monolingual svPPA and 30 bilingual svPPA). The charts of this final cohort were then reviewed for information regarding first language (L1), second language (L2) and any additional languages; age of acquisition of L2; country of birth; immigration to another country; and occupation. Demographic information, including sex, education, handedness, age at UCSF MAC evaluation, and clinical diagnoses were available through an internal MAC database. Information regarding age at symptom onset was also available through this database. We

note that previous studies have used delayed age at symptom onset, later age at diagnosis, or a combination of the two as proxies of cognitive reserve (Bialystok et al., 2007; Chertkow et al., 2010; Gollan et al., 2011). Because the UCSF MAC is a tertiary care center, 1) many individuals have been diagnosed prior to referral to UCSF, and this information was not routinely collected in our database, and 2) age at testing at our center is therefore not equivalent to age at diagnosis. As such, we utilized age at symptom onset as the dependent variable for this study.

Statistical Analysis

Statistical analyses were performed using Stata 14.1 (StataCorp). 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP. Our study was powered (80%) to show a statistically significant (<0.05) difference between the monolingual and bilingual groups based on previous research (Alladi et al., 2017; Craik et al., 2010; de Leon et al., 2020).

Demographic variables (education, age at symptom onset, Clinical Dementia Rating (CDR) Scale) were compared between monolingual and bilingual speakers 1) within the entire cohort and 2) within each FTD variant using unequal samples Student's t-tests. Pearson Chi squared tests were used for comparison of monolingual and bilingual speakers on categorical demographic variables (sex, handedness, occupational level, immigrant status).

Scores from a comprehensive neuropsychological battery were compared between monolingual and bilingual speakers within each FTD variant using analyses of covariance (ANCOVAs) to evaluate the effect of speaker status (monolingual vs bilingual) while controlling for two covariates: age at evaluation and years of education. The tasks from the neuropsychological battery were then grouped by cognitive domain (i.e., episodic memory, speech and language, visuospatial, and executive/frontal), and a Bonferroni correction was applied to tests conducted within each domain.

ANCOVAs were used to evaluate the effect of speaker status and clinical diagnosis on age at symptom onset while controlling for sex and educational attainment, variables known to also influence cognitive reserve (Eissman et al., 2022; Ewers, 2020; Illán-Gala et al., 2021; Levine et al., 2021; Subramaniapillai et al., 2021; Wang et al., 2021). Our omnibus test consisted of a two-way ANCOVA with speaker status (monolingual or bilingual) and FTD variant (bvFTD, nfvPPA, svPPA) as independent variables, age at symptom onset as the dependent variable, and sex, and years of education as covariates. Since the average age of onset differs at baseline within each FTD variant (Johnson et al., 2005; Leroy et al., 2021; Wagner et al., 2021), ANCOVAs were also conducted *within* each FTD variant to examine the effect of speaker status on age of symptom onset. These models also included sex and years of education as covariates. For any significant effects resulting from the within-variant ANCOVAs, we conducted post-hoc ANOVAs in order to test for interactions between the significant variable and the other variables known to contribute to cognitive reserve (i.e., speaker status, sex, and education). Scheffe tests were used to conduct pairwise comparisons from significant interaction terms.

RESULTS

Characteristics of the entire cohort

A total of 308 patients with FTD-spectrum diagnoses were included in this study (Table 1). The cohort was 52% female. The average years of education was 16.0 years (SD 2.9). The average age at symptom onset was 59.6 years (SD 8.9), while the average age at evaluation was 64.5 years (SD 8.6).

The cohort consisted of 230 monolingual speakers and 78 bilingual speakers. The two groups did not differ in sex, handedness, occupational skill level, or disease severity as measured by the Clinical Dementia Rating (CDR) scale. Bilingual speakers had a higher number of years of education compared to monolingual speakers (16.7 ± 2.8 years, versus 15.8 ± 3.0 years; $p = 0.013$), and they were more likely to have immigrated from another country (51% of bilinguals compared to 2% of monolinguals; $p < .001$). All of the monolingual speakers were English speakers. The bilingual individuals spoke a variety of languages (see Supplementary Table S1, l for full list). All participants completed neuropsychological testing in English, which was L1 for 38%, L2 for 58%, and L3 for 4% of individuals.

Demographic measures within each FTD variant

Of the 131 patients diagnosed with bvFTD, there were 105 monolinguals and 26 bilinguals (Table 2). The two groups did not differ on the basis of sex, years of education, or occupational level. However, the bilingual bvFTD patients were more likely to be right-handed (92% of bilinguals versus 90% of monolinguals; $p = 0.036$) and were more likely to have immigrated from another country (73% of bilinguals vs 0% of monolinguals; $p < .001$). The monolingual and bilingual groups did not differ from each other at time of testing in terms of MMSE or disease severity as measured by the Clinical Dementia Rating (CDR).

A total of 79 patients were diagnosed with nfvPPA. Of these patients, 57 were monolingual and 22 were bilingual (Table 2). The two groups did not differ from each other on any demographic variables, except that bilinguals were more likely to have immigrated from another country (27% vs 5%; $p = 0.006$). Moreover, they did not differ in terms of MMSE or disease severity.

Of the 98 patients diagnosed with svPPA, 68 were monolingual speakers while 30 were bilingual speakers (Table 2). The two groups did not differ on any demographic measures except for immigration status (50% of bilinguals vs 1% of monolinguals; $p < .001$). The monolingual and bilingual svPPA groups did not differ in MMSE or disease severity.

Neuropsychological measures within each FTD variant

On neuropsychological testing, after adjusting for age at evaluation and years of education and correcting for multiple comparisons, the bvFTD bilingual speakers scored lower than monolinguals on sentence repetition (3.5 ± 1.5 vs 4.3 ± 1.0; $p = 0.003$), the Peabody Picture Vocabulary Test (PPVT) (11.8 ± 3.3 vs 13.8 ± 3.1; $p = 0.004$), and the 15-item Boston Naming Test (9.3 ± 3.7 vs 12.4 ± 3.9; $p = <.001$). The two nfvPPA groups did not differ

significantly on any neuropsychological measures. Like the nfvPPA group, the two svPPA groups did not differ significantly from each other on any neuropsychological measures.

Effects of speaker status on age at symptom onset

Immigrant status was not included in the models because of its strong collinearity with bilingual status. ANOVA revealed a significant main effect of bilingualism status on age of onset in the entire FTD cohort ($F(1,304)= 4.10$, $\eta p2 = .013$, $p = .04$), with bilinguals being 2.4 years older on average (monolingual M = 59.0 SD= 9.2; bilingual M= 61.4 SD= 7.9). However, after accounting for other variables known to contribute to cognitive reserve (i.e., education, sex), this result was no longer significant ($F(1, 300)= 2.14$, $\eta p2= .007$, $p= .14$).

We then conducted a planned omnibus ANCOVA, which did not reveal an effect of the interaction of speaker status and FTD variant on age of symptom onset ($F(2,296) = 1.93$, $\eta p2 = 0.013$, $p = 0.15$). Additional ANCOVAs also failed to demonstrate statistically-significant differences in age at symptom onset between speaker groups within any of the three FTD variants (Table 2, Figure 2). We report the results of these analyses by clinical variant below.

For patients with bvFTD, the ANCOVA revealed no significant difference between speaker groups and age at symptom onset ($F(1, 125) = 2.53$; $\eta p2 = 0.02$; $p = 0.11$; monolinguals M = 56.6 ± 10.0 years; bilinguals M = 60.3± 8.6 years). Although age of onset was not significantly different between monolingual and bilingual speakers, on average, bilingual speakers with bvFTD presented with symptoms an average of 3 years later than monolingual speakers. The ANCOVA did reveal a significant effect of sex on age at symptom onset ($F(1,124) = 6.69$; $\eta p2 = 0.051$; $p = 0.01$; female M = 59.8 years; male M = 55.6 years). We performed additional post hoc ANOVAs to further investigate whether sex interacted with other cognitive reserve variables in the bvFTD cohort. There were no significant interactions between sex and speaker status ($F(1, 126) = 0.56$; $\eta p2 = 0.004$; $p = 0.46$) or sex and years of education ($F(1, 125) = 0.09$; $\eta p2 = 0.0007$; $p = 0.77$).

For patients with nfvPPA, the ANCOVA revealed no significant difference between speaker groups and age at symptom onset ($F(1, 75) = 0.81$; $\eta p2 = 0.011$; $p = 0.37$; monolinguals M = 64.8 years; bilinguals M = 63.6 years), but there was a significant effect of sex on age at symptom onset ($F(1,75) = 4.20$; $\eta p2 = 0.053$; $p = 0.044$; female M = 65.5 years; male M = 62.3 years). Additional post hoc ANOVAs revealed a significant interaction of sex with speaker status ($F(1, 75) = 6.91$; $\eta p2 = 0.084$; $p = 0.01$). A Scheffe test revealed that male monolinguals were significantly younger at age at symptom onset compared to monolingual women ($p = .03$, male M= 61.0, female M = 66.8), with no other contrasts reaching statistical significance. There were no significant interactions between sex and years of education ($F(1,75) = 1.24$; $\eta p2 = 0.016$; $p = 0.27$).

For patients with svPPA, the ANCOVA revealed no significant difference between speaker groups for age at symptom onset ($F(1,92) = 2.03$; $\eta p2 = 0.022$; $p = 0.16$; monolinguals M = 58.0 years; bilinguals M = 60.7 years). Although age of onset was not significantly different between monolingual and bilingual speakers in this study, on average, bilingual speakers with svPPA presented with symptoms an average of 2 years later than monolingual speakers.

There were no significant effects of other cognitive reserve variables including sex or years of education on age at symptom onset resulting from the ANCOVA.

DISCUSSION

In this retrospective study, we did not observe any statistically significant differences in age at symptom onset between monolingual and bilingual speakers with the three main FTD variants in a highly-educated sample from the United States. The lack of observed differences in age at symptom onset between monolinguals and bilinguals within each FTD variant differs from previous studies (Alladi et al., 2017; Alladi et al., 2013). One possible explanation for this finding is that our cohort differs from previous cohorts in terms of years of education, which has been previously implicated as an important factor in studies of cognitive reserve (Stern, 2009, 2012; Yaakov Stern et al., 2020). Both the monolingual and bilingual speakers in our cohort were highly educated (monolinguals M = 15.8 years, bilinguals M = 16.7 years). Previous studies have suggested that there may not be an additive effect of bilingualism and educational attainment, such that bilingualism only boosts cognitive reserve in populations with fewer years of formal education (Gollan et al., 2011). Another potential explanation for our divergent findings is that the sociocultural context and bilingual experience of our cohort from the United States may differ from previously-studied bilingual FTD cohorts in India. For example, it has been postulated that frequency of language switching may be an important factor when considering the relation between bilingualism and cognitive reserve (Antoniou & Wright, 2017). Although we do not have data for this variable in our cohort, it is likely that our cohort engaged in code-switching less frequently than a previously-studied FTD cohort.

It is also important to note that, although not statistically significant, a trend was observed such that bilingual speakers with bvFTD were more than 3 years older than their monolingual counterparts at symptom onset (bilinguals M = 60.3 years; monolinguals M = 56.6 years), and bilingual speakers with svPPA were more than 2 years older than their monolingual counterparts (bilinguals M = 60.7; monolinguals M = 58.0). These results are congruent with previous studies that have shown a protective effect of bilingualism in FTD (Alladi et al., 2017; Alladi et al., 2013) and in Alzheimer's disease (Bialystok et al., 2007; Craik et al., 2010; Guzmán-Vélez & Tranel, 2015). We would also emphasize that these results are clinically meaningful from a treatment, caregiving burden, and economic standpoint. There are currently no medications to cure or alter the disease course in FTD, magnifying the importance of lifestyle factors that may delay or prevent the onset of symptoms. The caregivers of individuals with FTD are often younger in age, have children, and are strained by the increased rate of neuropsychiatric symptoms compared to those with other types of dementia (Besser & Galvin, 2019; Karnatz et al., 2019; Liu et al., 2018). In addition, the economic impact of an FTD diagnosis is substantial. A study by Galvin and colleagues (Galvin et al., 2017) found an annual per-patient cost of nearly $120,000 for patients with FTD, almost twice the reported costs for AD, as well as a decrease in household income due to missed workdays and early departure from the workforce. Compared to other patients with young and late-onset dementias, those with young-onset FTD have the highest costs, and over 40% of young-onset dementia patients in one study reported a loss of employment due to dementia (Kandiah et al., 2016). These studies

underscore the notion that a trend towards a later age of symptom onset, even by 2–3 years, may still be meaningful for patients and their families.

It is interesting that, in post-hoc analyses, there was a significant interaction effect of sex and speaker status in the nfvPPA cohort, revealing that male monolinguals were significantly younger than monolingual females at symptom onset. A recent study by Illán-Gala et al. (2021) found that women with bvFTD had a greater degree of cognitive and brain reserve as demonstrated by a greater amount of grey matter atrophy in frontotemporal regions and better-than-expected performance on executive functioning measures compared to men with similar clinical characteristics (Illán-Gala et al., 2021). Our finding indicate that bilingual speakers with nfvPPA may not show differences in age of onset on the basis of sex. The interaction of bilingualism with other cognitive reserve variables should be explored in future studies as the relative contribution and additive effects of these factors may, in fact, differ between bilingual and monolingual speakers. Given that studies investigating the effects of sex on the clinical presentation of FTD are only beginning to emerge in the literature, further work addressing these effects is warranted (Pengo et al., 2022).

It has been hypothesized that bilingualism may contribute to cognitive reserve through advantages in executive functioning (Bialystok, 1999, 2011; Bialystok et al., 2007; Green, 1998; Green & Abutalebi, 2013; Marian & Spivey, 2003). We performed exploratory analyses to examine whether different patterns of performance across cognitive domains (including executive functioning) were observed in monolingual versus bilingual speakers with FTD. We did not find any significant differences between monolingual and bilingual speakers on executive functioning measures or on most other cognitive measures. We note that the majority of our available executive functioning tasks contained a verbal component, such that any benefit to executive functioning in bilinguals may have been masked by 1) the need to perform testing in a second language for 62% of the participants or 2) relative disadvantages in bilinguals on tasks that rely on language functioning, as previously discussed (Gollan et al., 2005; Kaushanskaya & Marian, 2007; Luo et al., 2010; Runnqvist et al., 2013; Sandoval et al., 2010). It is important to acknowledge that previous studies have also shown that differences between monolinguals and bilinguals may only be seen on certain executive functioning tasks (see Ware et al. (2020), for a review) and that several studies have not found evidence of advantages in executive functioning in bilingual speakers (Paap & Greenberg, 2013; Paap et al., 2015; Paap & Sawi, 2014). Bilingual bvFTD patients performed significantly worse on certain language measures, including sentence repetition, irregular word reading, PPVT, and BNT. It is possible that the lower scores on these measures reflect decreased English proficiency. Future studies should include measures of proficiency to directly address this possibility.

Interestingly, the overall pattern of deficits on neuropsychological testing did not differ between monolingual and bilingual speakers despite the fact that testing was only conducted in English. This could be taken as evidence that such scores from bilingual speakers with sufficient mastery of the English language may still provide crucial information to aid in diagnostic decision making. Of course, it is crucial that this pattern be examined in more detail in future prospective cohorts that consider bilingualism factors such as L2 age at acquisition, proficiency, and number/types of languages.

Strengths of our study include the relatively large sample of patients who were evaluated at a tertiary care center that specializes in FTD and the availability of detailed neuropsychological testing, lending validity to the diagnostic accuracy of these relatively rare disorders. In addition, we note that our data represent the largest cohort of bilingual patients with FTD reported to date, and our group sizes by variant are commensurate or larger than previously reported studies (Alladi et al., 2017; Alladi et al., 2013). As such, this study provides crucial knowledge regarding the effects of bilingualism on age of onset in FTD.

Our study also has several limitations, including sample sizes that were not balanced between monolingual and bilingual participant groups. In addition, neuropsychological testing was only performed in English for both monolingual and bilingual participants, which may not have fully captured their true cognitive-linguistic abilities. The impact of language of testing on FTD diagnosis is an avenue for future research and will benefit from multi-site collaborations to support data collection in larger bilingual cohorts with FTD. Furthermore, there was limited information regarding several measures for participants, including social determinants of health, age of L2 acquisition, total number of spoken languages, language proficiency, language exposure and use, and daily switching between languages. We acknowledge that these factors are essential for characterizing bilingualism and its effects on cognitive and neural function. As such, future research should investigate the relation between these factors and age of FTD onset. This will provide a deeper and more nuanced understanding regarding the extent to which specific components of the bilingual experience most strongly associate with age at symptom onset in the FTD spectrum. Lastly, since age at symptom onset and performance on cognitive tasks are only some of the parameters that may show evidence of cognitive reserve, other modalities, including MRI or PET neuroimaging, may yield additional critical information regarding cognitive reserve and bilingualism (Anderson et al., 2021; Berkes et al., 2021; DeLuca & Voits, 2022; Olsen et al., 2015; Rosselli et al., 2019; Sala et al., 2022).

Conclusion

In conclusion, in our cohort of highly educated monolingual and bilingual speakers with the three main FTD variants in the United States, we did not observe an association between bilingualism and age at symptom onset. Future prospective studies should collect detailed information regarding bilingual factors (e.g., age of L2 acquisition, proficiency) that may impact underlying neural networks and should evaluate bilingual speakers in each of their spoken languages. Additionally, the interacting effects of bilingualism with other cognitive reserve variables should be explored further, with the potential to elucidate which combinations of life experiences are most strongly associated with a later age of dementia onset. As there is no known cure for these devastating neurogenerative diseases, life experiences associated with a delay in age at onset should continue to be considered at the broader societal level (Bialystok et al., 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Data availability

The data that support the findings of this study are available on request from the corresponding author [JD]. The data reported in this study are not publicly available due to the conditions of our ethics approval and other patient confidentiality requirements. Access will be granted through a formal data sharing agreement in accordance with existing institutional procedures.

REFERENCES

Alladi S, Bak T, Shailaja M, Gollahalli D, & Kaul S (2017). Bilingualism delays the onset of behavioral but not aphasic forms of frontotemporal dementia. Neuropsychologia, 99, 207–212. [PubMed: 28322905]

Alladi S, Bak TH, Duggirala V, Surampudi B, Shailaja M, Shukla AK, Chaudhuri JR, & Kaul S (2013). Bilingualism delays age at onset of dementia, independent of education and immigration status. Neurology, 81(22), 1938–1944. 10.1212/01.wnl.0000436620.33155.a4 [PubMed: 24198291]

Anderson JAE, Grundy JG, Grady CL, Craik FIM, & Bialystok E (2021). Bilingualism contributes to reserve and working memory efficiency: Evidence from structural and functional neuroimaging. Neuropsychologia, 163, 108071. 10.1016/j.neuropsychologia.2021.108071 [PubMed: 34715120]

Antoniou M, & Wright SM (2017). Uncovering the Mechanisms Responsible for Why Language Learning May Promote Healthy Cognitive Aging. Front Psychol, 8, 2217. 10.3389/fpsyg.2017.02217 [PubMed: 29326636]

Benussi A, Libri I, Premi E, Alberici A, Cantoni V, Gadola Y, Rivolta J, Pengo M, Gazzina S, Calhoun VD, Gasparotti R, Zetterberg H, Ashton NJ, Blennow K, Padovani A, & Borroni B (2022). Differences and similarities between familial and sporadic frontotemporal dementia: An Italian single-center cohort study. Alzheimers Dement (N Y), 8(1), e12326. 10.1002/trc2.12326 [PubMed: 35898667]

Benussi A, Premi E, Gazzina S, Brattini C, Bonomi E, Alberici A, Jiskoot L, van Swieten JC, Sanchez-Valle R, Moreno F, Laforce R, Graff C, Synofzik M, Galimberti D, Masellis M, Tartaglia C, Rowe JB, Finger E, Vandenberghe R, . . . Borroni B (2021). Progression of Behavioral Disturbances and Neuropsychiatric Symptoms in Patients With Genetic Frontotemporal Dementia. JAMA Netw Open, 4(1), e2030194. 10.1001/jamanetworkopen.2020.30194 [PubMed: 33404617]

Berkes M, Calvo N, Anderson JAE, & Bialystok E (2021). Poorer clinical outcomes for older adult monolinguals when matched to bilinguals on brain health. Brain Struct Funct, 226(2), 415–424. 10.1007/s00429-020-02185-5 [PubMed: 33432426]

Besser LM, & Galvin JE (2019). Perceived burden among caregivers of patients with frontotemporal degeneration in the United States. Int Psychogeriatr, 31(8), 1191–1201. 10.1017/s104161021800159x [PubMed: 30398132]

Beyer L, Meyer-Wilmes J, Schönecker S, Schnabel J, Sauerbeck J, Scheifele M, Prix C, Unterrainer M, Catak C, Pogarell O, Palleis C, Perneczky R, Danek A, Buerger K, Bartenstein P, Levin J, Rominger A, Ewers M, & Brendel M (2021). Cognitive reserve hypothesis in frontotemporal dementia: A FDG-PET study [Article]. NeuroImage: Clinical, 29. 10.1016/j.nicl.2020.102535

Bialystok E (1999). Cognitive Complexity and Attentional Control in the Bilingual Mind. Child Development, 70(3), 636–644. 10.1111/1467-8624.00046

Bialystok E (2011). Reshaping the mind: the benefits of bilingualism. Canadian journal of experimental psychology = Revue canadienne de psychologie experimentale, 65(4), 229–235. 10.1037/a0025406 [PubMed: 21910523]

Bialystok E, Abutalebi J, Bak TH, Burke DM, & Kroll JF (2016). Aging in two languages: Implications for public health. Ageing Res Rev, 27, 56–60. 10.1016/j.arr.2016.03.003 [PubMed: 26993154]

Bialystok E, Craik FI, & Freedman M (2007). Bilingualism as a protection against the onset of symptoms of dementia. Neuropsychologia, 45(2), 459–464. 10.1016/j.neuropsychologia.2006.10.009 [PubMed: 17125807]

Bialystok E, & Craik FIM (2010). Cognitive and Linguistic Processing in the Bilingual Mind. Current Directions in Psychological Science, 19(1), 19–23. 10.1177/0963721409358571

Casaletto KB, Elahi FM, Staffaroni AM, Walters S, Contreras WR, Wolf A, Dubal D, Miller B, Yaffe K, & Kramer JH (2019). Cognitive aging is not created equally: differentiating unique cognitive phenotypes in "normal" adults. Neurobiology of Aging, 77, 13–19. 10.1016/j.neurobiolaging.2019.01.007 [PubMed: 30772736]

Casaletto KB, Marx G, Dutt S, Neuhaus J, Saloner R, Kritikos L, Miller B, & Kramer JH (2017). Is "Learning" episodic memory? Distinct cognitive and neuroanatomic correlates of immediate recall during learning trials in neurologically normal aging and neurodegenerative cohorts. Neuropsychologia, 102, 19–28. 10.1016/j.neuropsychologia.2017.05.021 [PubMed: 28549937]

Casaletto KB, Staffaroni AM, Wolf A, Appleby B, Brushaber D, Coppola G, Dickerson B, Domoto-Reilly K, Elahi FM, Fields J, Fong JC, Forsberg L, Ghoshal N, Graff-Radford N, Grossman M, Heuer HW, Hsiung GY, Huey ED, Irwin D, . . . Yaffe K (2020). Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. Alzheimers Dement, 16(1), 91–105. 10.1002/alz.12001 [PubMed: 31914227]

Chen S, Lin Y, Zuo S, Wang Z, Liang J, Jiang Z, Xu Y, Wang P, Jing X, & Lin L (2022). Cognitive advantage of bilingualism over monolingualism in older adults: A meta-analysis. Curr Alzheimer Res. 10.2174/1567205019666220920092234

Chertkow H, Whitehead V, Phillips N, Wolfson C, Atherton J, & Bergman H (2010). Multilingualism (but not always bilingualism) delays the onset of Alzheimer disease: evidence from a bilingual community. Alzheimer Dis Assoc Disord, 24(2), 118–125. 10.1097/WAD.0b013e3181ca1221 [PubMed: 20505429]

Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia. (2021). Framework for Terms Used in Research of Reserve and Resilience. https://reserveandresilience.com/

Craik FI, Bialystok E, & Freedman M (2010). Delaying the onset of Alzheimer disease: bilingualism as a form of cognitive reserve. Neurology, 75(19), 1726–1729. 10.1212/WNL.0b013e3181fc2a1c [PubMed: 21060095]

Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, & Xuereb JH (2005). The pathological basis of semantic dementia. Brain, 128(Pt 9), 1984–1995. 10.1093/brain/awh582 [PubMed: 16000337]

de Leon J, Grasso SM, Welch A, Miller Z, Shwe W, Rabinovici GD, Miller BL, Henry ML, & Gorno-Tempini ML (2020). Effects of bilingualism on age at onset in two clinical Alzheimer's disease variants. Alzheimers Dement, 16(12), 1704–1713. 10.1002/alz.12170 [PubMed: 32881346]

DeLuca V, & Voits T (2022). Bilingual experience affects white matter integrity across the lifespan. Neuropsychologia, 169, 108191. 10.1016/j.neuropsychologia.2022.108191 [PubMed: 35227709]

Dodich A, Carli G, Cerami C, Iannaccone S, Magnani G, & Perani D (2018). Social and cognitive control skills in long-life occupation activities modulate the brain reserve in the behavioural variant of frontotemporal dementia. Cortex, 99, 311–318. 10.1016/j.cortex.2017.12.006 [PubMed: 29328983]

Eissman JM, Dumitrescu L, Mahoney ER, Smith AN, Mukherjee S, Lee ML, Scollard P, Choi SE, Bush WS, Engelman CD, Lu Q, Fardo DW, Trittschuh EH, Mez J, Kaczorowski CC, Hernandez Saucedo H, Widaman KF, Buckley RF, Properzi MJ, . . . Hohman TJ (2022). Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. Brain, 145(7), 2541–2554. 10.1093/brain/awac177 [PubMed: 35552371]

Ewers M (2020). Reserve in Alzheimer's disease: update on the concept, functional mechanisms and sex differences. Curr Opin Psychiatry, 33(2), 178–184. 10.1097/yco.0000000000000574 [PubMed: 31789678]

Galvin JE, Howard DH, Denny SS, Dickinson S, & Tatton N (2017). The social and economic burden of frontotemporal degeneration. Neurology, 89(20), 2049–2056. 10.1212/wnl.0000000000004614 [PubMed: 28978658]

Gazzina S, Grassi M, Premi E, Cosseddu M, Alberici A, Archetti S, Gasparotti R, Van Swieten J, Galimberti D, Sanchez-Valle R, Laforce RJ, Moreno F, Synofzik M, Graff C, Masellis M, Tartaglia MC, Rowe JB, Vandenberghe R, Finger E, . . . Borroni B (2019). Education modulates brain maintenance in presymptomatic frontotemporal dementia. J Neurol Neurosurg Psychiatry, 90(10), 1124–1130. 10.1136/jnnp-2019-320439 [PubMed: 31182509]

Gollan TH, Montoya RI, Fennema-Notestine C, & Morris SK (2005). Bilingualism affects picture naming but not picture classification. Mem Cognit, 33(7), 1220–1234. 10.3758/bf03193224

Gollan TH, Salmon DP, Montoya RI, & Galasko DR (2011). Degree of bilingualism predicts age of diagnosis of Alzheimer's disease in low-education but not in highly educated Hispanics. Neuropsychologia, 49(14), 3826–3830. 10.1016/j.neuropsychologia.2011.09.041 [PubMed: 22001315]

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, & Grossman M (2011). Classification of primary progressive aphasia and its variants. Neurology, 76(11), 1006–1014. 10.1212/WNL.0b013e31821103e6 [PubMed: 21325651]

Gossink F, Dols A, Stek ML, Scheltens P, Nijmeijer B, Cohn Hokke P, Dijkstra A, Van Ruissen F, Aalfs C, & Pijnenburg YAL (2022). Early life involvement in C9orf72 repeat expansion carriers. J Neurol Neurosurg Psychiatry, 93(1), 93–100. 10.1136/jnnp-2020-325994 [PubMed: 33906932]

Green DW (1998). Mental control of the bilingual lexico-semantic system. Bilingualism: Language and Cognition, 1(2), 67–81. 10.1017/S1366728998000133

Green DW, & Abutalebi J (2013). Language control in bilinguals: The adaptive control hypothesis. Journal of cognitive psychology (Hove, England), 25(5), 515–530. 10.1080/20445911.2013.796377 [PubMed: 25077013]

Grosjean F (2010). Bilingual: Life and reality. In Bilingual: Life and reality. [doi:10.4159/9780674056459]. Harvard University Press.

Grossman M (2012). The non-fluent/agrammatic variant of primary progressive aphasia. The Lancet. Neurology, 11(6), 545–555. 10.1016/S1474-4422(12)70099-6 [PubMed: 22608668]

Guzmán-Vélez E, & Tranel D (2015). Does bilingualism contribute to cognitive reserve? Cognitive and neural perspectives. Neuropsychology, 29(1), 139–150. 10.1037/neu0000105 [PubMed: 24933492]

Heuer HW, Wang P, Rascovsky K, Wolf A, Appleby B, Bove J, Bordelon Y, Brannelly P, Brushaber DE, Caso C, Coppola G, Dickerson B, Dickinson S, Domoto-Reilly K, Faber K, Ferrall J, Fields J, Fishman A, Fong J, . . . Boxer AL (2020). Comparison of sporadic and familial behavioral variant frontotemporal dementia (FTD) in a North American cohort. Alzheimers Dement, 16(1), 60–70. 10.1002/alz.12046 [PubMed: 31914226]

Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, Kril JJ, & Halliday GM (2004). Clinicopathological correlates in frontotemporal dementia. Annals of Neurology, 56(3), 399–406. 10.1002/ana.20203 [PubMed: 15349867]

Hodges JR, Patterson K, Oxbury S, & Funnell E (1992). Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain, 115 (Pt 6), 1783–1806. 10.1093/brain/115.6.1783 [PubMed: 1486461]

Illán-Gala I, Casaletto KB, Borrego-Écija S, Arenaza-Urquijo EM, Wolf A, Cobigo Y, Goh SYM, Staffaroni AM, Alcolea D, Fortea J, Blesa R, Clarimon J, Iulita MF, Brugulat-Serrat A, Lladó A, Grinberg LT, Possin K, Rankin KP, Kramer JH, . . . Rosen HJ (2021). Sex differences in the behavioral variant of frontotemporal dementia: A new window to executive and behavioral reserve. Alzheimers Dement, 17(8), 1329–1341. 10.1002/alz.12299 [PubMed: 33590953]

Johnson JK, Diehl J, Mendez MF, Neuhaus J, Shapira JS, Forman M, Chute DJ, Roberson ED, Pace-Savitsky C, Neumann M, Chow TW, Rosen HJ, Forstl H, Kurz A, & Miller BL (2005). Frontotemporal lobar degeneration: Demographic characteristics of 353 patients [Article]. Archives of Neurology, 62(6), 925–930. 10.1001/archneur.62.6.925 [PubMed: 15956163]

Kandiah N, Wang V, Lin X, Nyu MM, Lim L, Ng A, Hameed S, & Wee HL (2016). Cost Related to Dementia in the Young and the Impact of Etiological Subtype on Cost. J Alzheimers Dis, 49(2), 277–285. 10.3233/jad-150471 [PubMed: 26444788]

Karnatz T, Monsees J, Wucherer D, Michalowsky B, Zwingmann I, Halek M, Hoffmann W, & Thyrian JR (2019). Burden of caregivers of patients with frontotemporal lobar degeneration - a scoping review. Int Psychogeriatr, 1–21. 10.1017/s1041610219000176 [PubMed: 30729909]

Kaushanskaya M, & Marian V (2007). Bilingual language processing and interference in bilinguals: Evidence from eye tracking and picture naming. Language Learning, 57(1), 119–163.

Kinney NG, Bove J, Phillips JS, Cousins KAQ, Olm CA, Wakeman DG, McMillan CT, & Massimo L (2021). Social and leisure activity are associated with attenuated cortical loss in behavioral variant frontotemporal degeneration. Neuroimage Clin, 30, 102629. 10.1016/j.nicl.2021.102629 [PubMed: 33770546]

Kramer JH, Jurik J, Sha SJ, Rankin KP, Rosen HJ, Johnson JK, & Miller BL (2003). Distinctive Neuropsychological Patterns in Frontotemporal Dementia, Semantic Dementia, and Alzheimer Disease [Article]. Cognitive and Behavioral Neurology, 16(4), 211–218. 10.1097/00146965-200312000-00002 [PubMed: 14665820]

Laaksovirta H, Launes J, Jansson L, Traynor BJ, Kaivola K, & Tienari PJ (2022). ALS in Finland: Major Genetic Variants and Clinical Characteristics of Patients With and Without the C9orf72 Hexanucleotide Repeat Expansion. Neurol Genet, 8(2), e665. 10.1212/nxg.0000000000000665 [PubMed: 35295181]

Lamar M, Tarraf W, Wu B, Perreira KM, Lipton RB, Khambaty T, Cai J, Llabre MM, Gallo LC, Daviglus ML, & González HM (2022). The Spanish-English bilingual experience and cognitive change in Hispanics/Latinos from the Hispanic Community Health Study/Study of Latinos-Investigation of Neurocognitive Aging [10.1002/alz.12703]. Alzheimer's & Dementia, n/a(n/a). 10.1002/alz.12703

Leroy M, Bertoux M, Skrobala E, Mode E, Adnet-Bonte C, Le Ber I, Bombois S, Cassagnaud P, Chen Y, Deramecourt V, Lebert F, Mackowiak MA, Sillaire AR, Wathelet M, Pasquier F, Lebouvier T, Abied R, Adnet C, Barois A, . . . the Méotis, n. (2021). Characteristics and progression of patients with frontotemporal dementia in a regional memory clinic network. Alzheimer's Research & Therapy, 13(1), 19. 10.1186/s13195-020-00753-9

Levine DA, Gross AL, Briceño EM, Tilton N, Giordani BJ, Sussman JB, Hayward RA, Burke JF, Hingtgen S, Elkind MSV, Manly JJ, Gottesman RF, Gaskin DJ, Sidney S, Sacco RL, Tom SE, Wright CB, Yaffe K, & Galecki AT (2021). Sex Differences in Cognitive Decline Among US Adults. JAMA Netw Open, 4(2), e210169. 10.1001/jamanetworkopen.2021.0169 [PubMed: 33630089]

Liu S, Liu J, Wang XD, Shi Z, Zhou Y, Li J, Yu T, & Ji Y (2018). Caregiver burden, sleep quality, depression, and anxiety in dementia caregivers: a comparison of frontotemporal lobar degeneration, dementia with Lewy bodies, and Alzheimer's disease. Int Psychogeriatr, 30(8), 1131–1138. 10.1017/s1041610217002630 [PubMed: 29223171]

Luo L, Luk G, & Bialystok E (2010). Effect of language proficiency and executive control on verbal fluency performance in bilinguals. Cognition, 114(1), 29–41. 10.1016/j.cognition.2009.08.014 [PubMed: 19793584]

Maiovis P, Ioannidis P, Gerasimou G, Gotzamani-Psarrakou A, & Karacostas D (2018). Cognitive Reserve Hypothesis in Frontotemporal Dementia: Evidence from a Brain SPECT Study in a Series of Greek Frontotemporal Dementia Patients. Neurodegener Dis, 18(23), 69–73. 10.1159/000486621 [PubMed: 29514157]

Marian V, & Spivey M (2003). Competing Activation in Bilingual Language Processing: Within- and between-Language Competition. Bilingualism: Language and Cognition, 6, 97–115. 10.1017/S1366728903001068

Massimo L, Xie SX, Rennert L, Fick DM, Halpin A, Placek K, Williams A, Rascovsky K, Irwin DJ, Grossman M, & McMillan CT (2019). Occupational attainment influences longitudinal decline

in behavioral variant frontotemporal degeneration. Brain Imaging Behav, 13(1), 293–301. 10.1007/s11682-018-9852-x [PubMed: 29542053]

McCarthy J, Borroni B, Sanchez-Valle R, Moreno F, Laforce R Jr., Graff C, Synofzik M, Galimberti D, Rowe JB, Masellis M, Tartaglia MC, Finger E, Vandenberghe R, de Mendonça A, Tagliavini F, Santana I, Butler C, Gerhard A, Danek A, . . . Ducharme S (2022). Data-driven staging of genetic frontotemporal dementia using multi-modal MRI. Hum Brain Mapp, 43(6), 1821–1835. 10.1002/hbm.25727 [PubMed: 35118777]

Mohanty AK (1994). Bilingualism in a multilingual society: Psycho-social and pedagogical implications. Central Institute of Indian Languages.

Moore KM, Nicholas J, Grossman M, McMillan CT, Irwin DJ, Massimo L, Van Deerlin VM, Warren JD, Fox NC, Rossor MN, Mead S, Bocchetta M, Boeve BF, Knopman DS, Graff-Radford NR, Forsberg LK, Rademakers R, Wszolek ZK, van Swieten JC, . . . Rohrer JD (2020). Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol, 19(2), 145–156. 10.1016/s1474-4422(19)30394-1 [PubMed: 31810826]

Mukadam N, Sommerlad A, & Livingston G (2017). The Relationship of Bilingualism Compared to Monolingualism to the Risk of Cognitive Decline or Dementia: A Systematic Review and Meta-Analysis. J Alzheimers Dis, 58(1), 45–54. 10.3233/jad-170131 [PubMed: 28387680]

Olney NT, Spina S, & Miller BL (2017). Frontotemporal dementia. Neurologic Clinics, 35(2), 339–374. 10.1016/j.ncl.2017.01.008 [PubMed: 28410663]

Olsen RK, Pangelinan MM, Bogulski C, Chakravarty MM, Luk G, Grady CL, & Bialystok E (2015). The effect of lifelong bilingualism on regional grey and white matter volume. Brain Res, 1612, 128–139. 10.1016/j.brainres.2015.02.034 [PubMed: 25725380]

Paap KR, & Greenberg ZI (2013). There is no coherent evidence for a bilingual advantage in executive processing. Cogn Psychol, 66(2), 232–258. 10.1016/j.cogpsych.2012.12.002 [PubMed: 23370226]

Paap KR, Johnson HA, & Sawi O (2015). Bilingual advantages in executive functioning either do not exist or are restricted to very specific and undetermined circumstances. Cortex, 69, 265–278. 10.1016/j.cortex.2015.04.014 [PubMed: 26048659]

Paap KR, & Sawi O (2014). Bilingual advantages in executive functioning: problems in convergent validity, discriminant validity, and the identification of the theoretical constructs. Frontiers in Psychology, 5, 962–962. 10.3389/fpsyg.2014.00962 [PubMed: 25249988]

Pengo M, Alberici A, Libri I, Benussi A, Gadola Y, Ashton NJ, Zetterberg H, Blennow K, & Borroni B (2022). Sex influences clinical phenotype in frontotemporal dementia. Neurol Sci, 43(9), 5281–5287. 10.1007/s10072-022-06185-7 [PubMed: 35672480]

Perneczky R, Diehl-Schmid J, Förstl H, Drzezga A, & Kurz A (2007). Male gender is associated with greater cerebral hypometabolism in frontotemporal dementia: evidence for sex-related cognitive reserve. Int J Geriatr Psychiatry, 22(11), 1135–1140. 10.1002/gps.1803 [PubMed: 17479980]

Perneczky R, Diehl-Schmid J, Pohl C, Drzezga A, & Kurz A (2007). Non-fluent progressive aphasia: Cerebral metabolic patterns and brain reserve [Article]. Brain Research, 1133(1), 178–185. 10.1016/j.brainres.2006.11.054 [PubMed: 17184752]

Premi E, Gazzina S, Bozzali M, Archetti S, Alberici A, Cercignani M, Bianchetti A, Gasparotti R, Turla M, Caltagirone C, Padovani A, & Borroni B (2013). Cognitive reserve in granulin-related frontotemporal dementia: from preclinical to clinical stages. PLoS One, 8(9), e74762. 10.1371/journal.pone.0074762 [PubMed: 24040338]

Premi E, Grassi M, van Swieten J, Galimberti D, Graff C, Masellis M, Tartaglia C, Tagliavini F, Rowe JB, Laforce R Jr., Finger E, Frisoni GB, de Mendonça A, Sorbi S, Gazzina S, Cosseddu M, Archetti S, Gasparotti R, Manes M, . . . Borroni B (2017). Cognitive reserve and TMEM106B genotype modulate brain damage in presymptomatic frontotemporal dementia: a GENFI study. Brain, 140(6), 1784–1791. 10.1093/brain/awx103 [PubMed: 28460069]

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, . . . Miller BL (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134(Pt 9), 2456–2477. 10.1093/brain/awr179 [PubMed: 21810890]

Rosas I, Martínez C, Coto E, Clarimón J, Lleó A, Illán-Gala I, Dols-Icardo O, Borroni B, Almeida MR, van der Zee J, Van Broeckhoven C, Bruni AC, Anfossi M, Bernardi L, Maletta R, Serpente M, Galimberti D, Scarpini E, Rossi G, . . . Menéndez-González M (2021). Genetic variation in APOE, GRN, and TP53 are phenotype modifiers in frontotemporal dementia. Neurobiol Aging, 99, 99.e15–99.e22. 10.1016/j.neurobiolaging.2020.08.018

Rosselli M, Loewenstein DA, Curiel RE, Penate A, Torres VL, Lang M, Greig MT, Barker WW, & Duara R (2019). Effects of Bilingualism on Verbal and Nonverbal Memory Measures in Mild Cognitive Impairment. J Int Neuropsychol Soc, 25(1), 15–28. 10.1017/s135561771800070x [PubMed: 30334507]

Runnqvist E, Gollan TH, Costa A, & Ferreira VS (2013). A disadvantage in bilingual sentence production modulated by syntactic frequency and similarity across languages. Cognition, 129(2), 256–263. 10.1016/j.cognition.2013.07.008 [PubMed: 23948209]

Russell LL, Greaves CV, Bocchetta M, Nicholas J, Convery RS, Moore K, Cash DM, van Swieten J, Jiskoot L, Moreno F, Sanchez-Valle R, Borroni B, Laforce R Jr., Masellis M, Tartaglia MC, Graff C, Rotondo E, Galimberti D, Rowe JB, . . . Rohrer JD (2020). Social cognition impairment in genetic frontotemporal dementia within the GENFI cohort. Cortex, 133, 384–398. 10.1016/j.cortex.2020.08.023 [PubMed: 33221702]

Sala A, Malpetti M, Farsad M, Lubian F, Magnani G, Frasca Polara G, Epiney JB, Abutalebi J, Assal F, Garibotto V, & Perani D (2022). Lifelong bilingualism and mechanisms of neuroprotection in Alzheimer dementia. Hum Brain Mapp, 43(2), 581–592. 10.1002/hbm.25605 [PubMed: 34729858]

Sandoval TC, Gollan TH, Ferreira VS, & Salmon DP (2010). What causes the bilingual disadvantage in verbal fluency? The dual-task analogy. Bilingualism: Language and Cognition, 13(2), 231–252. 10.1017/S1366728909990514

Spinelli EG, Mandelli ML, Miller ZA, Santos-Santos MA, Wilson SM, Agosta F, Grinberg LT, Huang EJ, Trojanowski JQ, Meyer M, Henry ML, Comi G, Rabinovici G, Rosen HJ, Filippi M, Miller BL, Seeley WW, & Gorno-Tempini ML (2017). Typical and atypical pathology in primary progressive aphasia variants. Ann Neurol, 81(3), 430–443. 10.1002/ana.24885 [PubMed: 28133816]

Stern Y (2009). Cognitive reserve. Neuropsychologia, 47(10), 2015–2028. 10.1016/j.neuropsychologia.2009.03.004 [PubMed: 19467352]

Stern Y (2012). Cognitive reserve in ageing and Alzheimer's disease. The Lancet. Neurology, 11(11), 1006–1012. 10.1016/S1474-4422(12)70191-6 [PubMed: 23079557]

Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, Ewers M, Franzmeier N, Kempermann G, Kremen WS, Okonkwo O, Scarmeas N, Soldan A, Udeh-Momoh C, Valenzuela M, Vemuri P, & Vuoksimaa E (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement, 16(9), 1305–1311. 10.1016/j.jalz.2018.07.219 [PubMed: 30222945]

Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, Ewers M, Franzmeier N, Kempermann G, Kremen WS, Okonkwo O, Scarmeas N, Soldan A, Udeh-Momoh C, Valenzuela M, Vemuri P, Vuoksimaa E, and the Reserve, R., Definitions, P. F. P. E., & Workgroup, C. F. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's & Dementia, 16(9), 1305–1311. 10.1016/j.jalz.2018.07.219

Subramaniapillai S, Almey A, Natasha Rajah M, & Einstein G (2021). Sex and gender differences in cognitive and brain reserve: Implications for Alzheimer's disease in women. Front Neuroendocrinol, 60, 100879. 10.1016/j.yfrne.2020.100879 [PubMed: 33137359]

Valsdóttir V, Magnúsdóttir BB, Chang M, Sigurdsson S, Gudnason V, Launer LJ, & Jónsdóttir MK (2022). Cognition and brain health among older adults in Iceland: the AGES-Reykjavik study. Geroscience. 10.1007/s11357-022-00642-z

Wagner M, Lorenz G, Volk AE, Brunet T, Edbauer D, Berutti R, Zhao C, Anderl-Straub S, Bertram L, Danek A, Deschauer M, Dill V, Fassbender K, Fliessbach K, Götze KS, Jahn H, Kornhuber J, Landwehrmeyer B, Lauer M, . . . The German, F. c. (2021). Clinico-genetic findings in 509 frontotemporal dementia patients. Molecular Psychiatry, 26(10), 5824–5832. 10.1038/s41380-021-01271-2 [PubMed: 34561610]

Wang H, Rosenthal BS, Makowski C, Lo MT, Andreassen OA, Salem RM, McEvoy LK, Fiecas M, & Chen CH (2021). Causal association of cognitive reserve on Alzheimer's disease with putative sex difference. Alzheimers Dement (Amst), 13(1), e12270. 10.1002/dad2.12270 [PubMed: 35005200]

Ware AT, Kirkovski M, & Lum JAG (2020). Meta-Analysis Reveals a Bilingual Advantage That Is Dependent on Task and Age. Front Psychol, 11, 1458. 10.3389/fpsyg.2020.01458 [PubMed: 32793026]

Younes K, & Miller BL (2020). Frontotemporal Dementia: Neuropathology, Genetics, Neuroimaging, and Treatments. Psychiatr Clin North Am, 43(2), 331–344. 10.1016/j.psc.2020.02.006 [PubMed: 32439025]

Zahodne LB, Schofield PW, Farrell MT, Stern Y, & Manly JJ (2014). Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. Neuropsychology, 28(2), 238–246. 10.1037/neu0000014 [PubMed: 24188113]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- No significant difference in age at onset for bi- vs mono-linguals in FTD variants

- Trend for older age at onset (by 3 yrs) for bvFTD bilingual vs monolingual speakers

- No notable differences in neuropsychological scores between speaker groups

- Need for future study of bilingualism's role in socioculturally diverse FTD cohorts
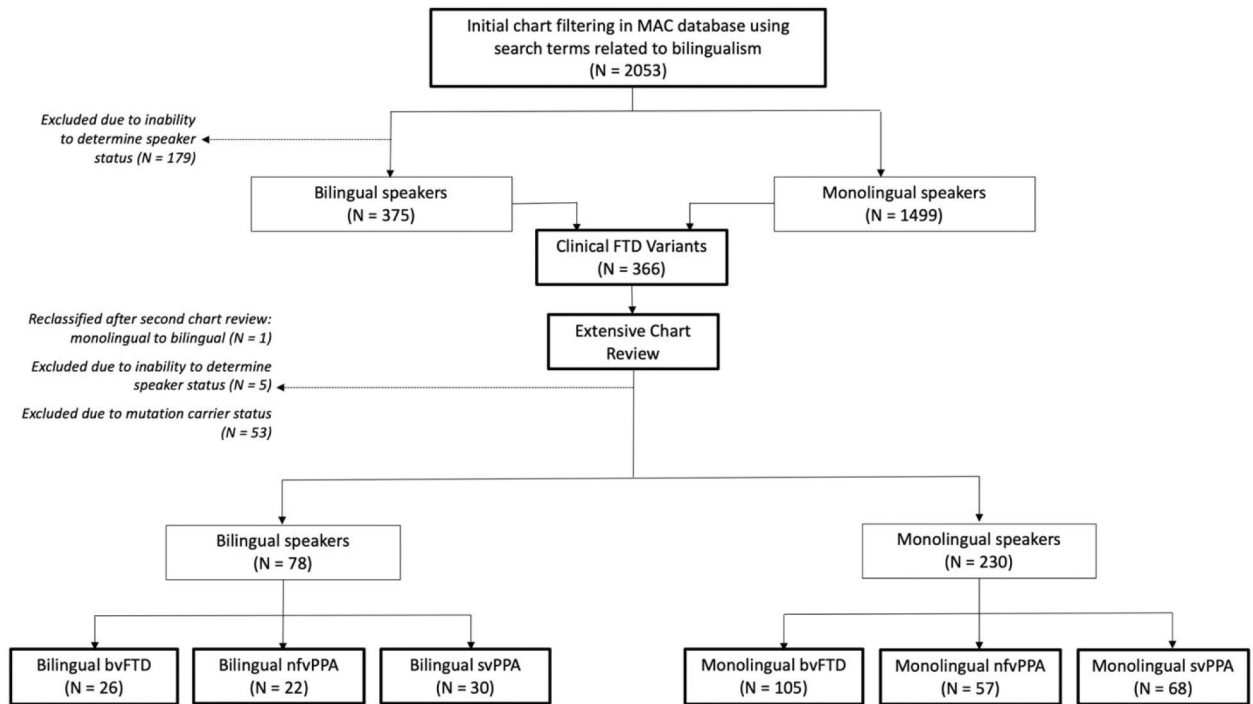
Figure 1.
Flowchart demonstrating selection and classification of study participants
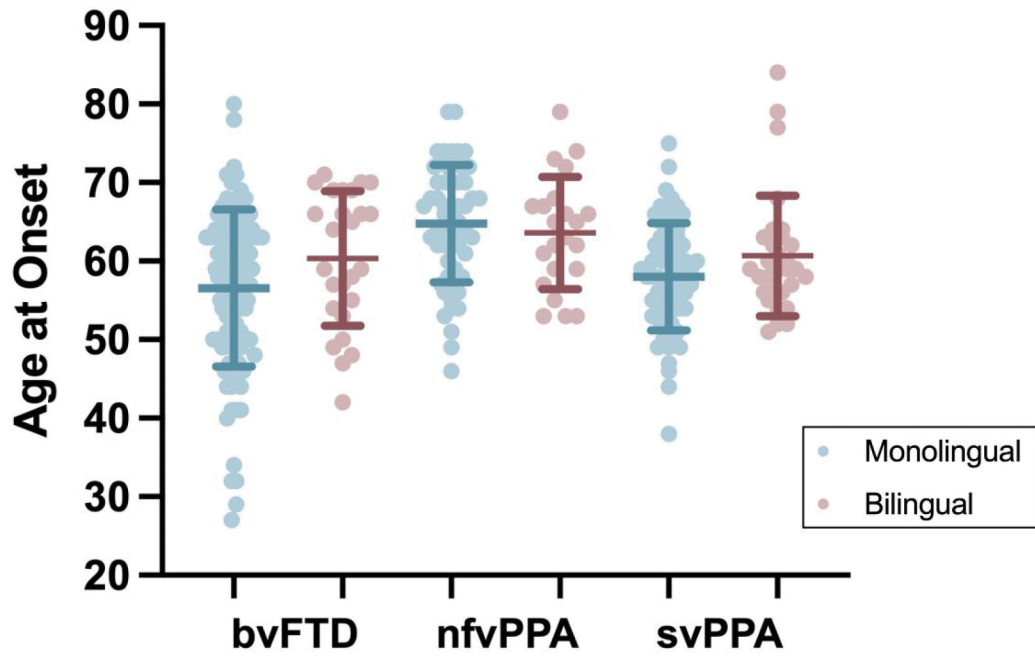
Figure 2.
Age at symptom onset by clinical FTD variant and speaker group (means, standard deviations, and individual participant data).

Table 1.

Demographic information for monolingual/bilingual speakers (full cohort)

Characteristics	All patients (N = 308)	Monolinguals (N = 230)	Bilinguals (N = 78)	*p* (mono vs. bi)	N (mono/bi)
Sex, Female, n (%)	159 (52)	114 (50)	45 (58)	0.215	-
Education, mean (SD), y	**16.0 (2.9)**	**15.8 (3.0)**	**16.7 (2.8)**	**0.013**	**228/78**
Right-handed, n (%)	275 (89)	205 (89)	70 (90)	0.273	-
Occupation					202/78
Professionals, n (%)	169 (60)	121 (60)	48 (62)	0.802	
Associate professionals, n (%)	51 (18)	39 (19)	12 (15)	0.446	
Skilled workers, n (%)	57 (20)	40 (20)	17 (22)	0.710	
Elementary, n (%)	3 (1)	2 (1)	1 (1)	0.832	
Race					220/78
Asian, n (%)	**19 (6)**	**4 (2)**	**15 (19)**	**<.001**	
Black/African-American, n (%)	1 (0.3)	1 (0.5)	0 (0)	1.000	
More than one race, n (%)	**6 (2)**	**2 (1)**	**4 (5)**	**0.042**	
Other, n (%)	5 (2)	2 (1)	3 (4)	0.114	
White, n (%)	**267 (90)**	**211 (96)**	**56 (72)**	**<.001**	
Hispanic Origin, n (%)	**11 (5)**	**3 (2)**	**8 (15)**	**0.001**	**150/55**
Immigrant, n (%)	**44 (14)**	**4 (2)**	**40 (51)**	**<.001**	-
CDR Total (3), mean (SD)	0.9 (0.6)	0.9 (0.6)	0.8 (0.6)	0.286	217/75

* Note: CDR = Clinical Dementia Rating scale. A dash (-) in the N column indicates that the full dataset was available. Occupational skill level was determined using the International Standard Classification of Occupations (ISCO-08).

Table 2.

Demographic information for monolingual/bilingual speakers by clinical syndrome

	bvFTD				nfvPPA				svPPA			
	Monolingual (N = 105)	Bilingual (N = 26)	p	N (mono/bi)	Monolingual (N = 57)	Bilingual (N = 22)	p	N (mono/bi)	Monolingual (N = 68)	Bilingual (N = 30)	p	N (mono/bi)
Sex, Female, n (%)	42 (40)	12 (46)	0.568	-	37 (65)	15 (68)	0.784	-	35 (51)	18 (60)	0.435	-
Education, mean (SD), y	15.6 (3.0)	16.4 (3.4)	0.224	104/26	15.6 (3.2)	16.9 (2.2)	0.097	-	16.1 (2.8)	16.9 (2.7)	0.214	67/30
Right-handed, n (%)	**94 (90)**	**24 (92)**	**0.036**	-	**52 (91)**	**20 (91)**	**0.227**	-	**59 (87)**	**26 (87)**	**0.590**	-
Occupation				95/26				48/22				59/30
Professionals, n (%)	56 (59)	15 (58)	0.908		26 (54)	15 (68)	0.269		39 (66)	18 (60)	0.571	
Associate professionals, n (%)	16 (17)	3 (12)	0.510		10 (21)	3 (14)	0.472		13 (22)	6 (20)	0.825	
Skilled workers, n (%)	23 (24)	7 (27)	0.777		12 (25)	4 (18)	0.528		5 (8)	6 (20)	0.118	
Elementary, n (%)	0 (0)	1 (4)	0.215		0 (0)	0 (0)	-		2 (3)	0 (0)	0.308	
Immigrant, n (%)	**0 (0)**	**19 (73)**	**<.001**	-	**3 (5)**	**6 (27)**	**0.006**	-	**1 (1)**	**15 (50)**	**<.001**	-
Age at onset*, mean (SD), y	56.6 (10.0)	60.3 (8.6)	0.121	104/26	64.8 (7.5)	63.6 (7.1)	0.177	-	58.0 (6.8)	60.7 (7.7)	0.083	67/30
CDR Total (3), mean (SD)	1.2 (0.7)	1.2 (0.6)	0.604	96/25	0.5 (0.4)	0.4 (0.4)	0.604	56/21	0.7 (0.5)	0.8 (0.4)	0.763	65/29

Note: CDR = Clinical Dementia Rating scale. A dash (–) in the N column indicates that the full dataset was available. Occupational skill level was determined using the International Standard Classification of Occupations (ISCO-08). p-values derived from t-tests or chi square tests, where appropriate.

*
indicates results derived from ANCOVAs.

Table 3.

Neuropsychological battery results for monolingual/bilingual speakers by clinical variant

	bvFTD				nfvPPA				svPPA			
	Monolingual (N = 101)	Bilingual (N = 25)	p	N (mono/bi)	Monolingual (N = 55)	Bilingual (N = 22)	p	N (mono/bi)	Monolingual (N =66)	Bilingual (N = 30)	p	N (mono/bi)
Age at Testing, mean (SD), y	**61.5 (10.0)**	**65.6 (8.2)**	**0.038**	-	**68.3 (7.5)**	**67.5 (7.8)**	**0.693**	-	**63.3 (6.0)**	**65.7 (7.4)**	**0.137**	-
MMSE (30)	23.0 (7.2)	23.9 (4.1)	0.689	98/23	25.1 (4.7)	25.3 (4.9)	0.889	54/21	23.1 (6.3)	21.7. (7.5)	0.230	66/29
GDS (30)	6.9 (5.9)	7.2 (7.6)	0.544	78/19	8.7 (6.9)	6.9 (5.2)	0.377	46/18	8.4 (6.2)	10.5 (8.2)	0.143	52/25
Episodic Memory												
CVLT Trials 1–4 (36)	19.2 (8.1)	16.8 (6.7)	0.131	85/23	21.7 (6.2)	21.1 (6.7)	0.752	45/20	15.8 (7.3)	16.2 (6.7)	0.912	57/25
CVLT 10 min (9)	3.3 (2.8)	2.5 (2.3)	0.193	83/23	5.6 (2.3)	5.2 (2.8)	0.812	45/20	1.9 (2.4)	1.6 (2.5)	0.367	57/25
Rey recall (17)	7.0 (4.6)	5.4 (4.0)	0.137	95/24	10.0 (3.6)	9.9 (3.0)	0.854	53/21	6.3 (4.5)	6.9 (4.5)	0.499	62/30
Speech and Language												
Sentence repetition (5)	**4.3 (1.0)**	**3.5 (1.5)**	**0.003**	**86/20**	**2.7 (1.5)**	**3.0 (1.9)**	**0.919**	**46/20**	**3.6 (1.4)**	**3.5 (1.4)**	**0.686**	**54/27**
Animal fluency	10.9 (6.8)	8.6 (4.3)	0.112	90/22	11.6 (7.0)	10.2 (6.0)	0.287	51/21	7.7 (4.6)	10.5 (8.2)	0.082	62/26
BNT (15)	**12.4 (3.9)**	**9.3 (3.7)**	**<.001**	**91/23**	**12.3 (2.9)**	**11.7 (3.6)**	**0.292**	**55/21**	**4.7 (3.7)**	**5.3 (4.4)**	**0.919**	**62/28**
Sentence comprehension (5)	3.8 (1.5)	3.8 (1.1)	0.646	84/20	3.9 (1.1)	4.3 (1.0)	0.223	46/20	4.5 (1.0)	4.0 (1.2)	0.049	52/27
Verbal agility (6)	5.0 (1.6)	5.1 (1.3)	0.695	80/20	2.5 (1.5)	2.9 (1.6)	0.716	44/20	5.1 (1.3)	5.2 (0.9)	0.873	50/27
PPVT (16)	**13.8 (3.1)**	**11.8 (3.3)**	**0.004**	**81/17**	**14.4 (1.8)**	**14.1 (2.6)**	**0.396**	**48/20**	**8.2 (3.9)**	**9.1 (4.6)**	**0.730**	**51/24**
Irregular word reading (6)	5.6 (1.2)	5.0 (1.8)	0.012	83/20	5.5 (0.7)	5.1 (1.5)	0.115	43/19	4.5 (1.4)	4.6 (1.3)	0.796	50/26
Visuospatial												
VOSP (10)	8.3 (1.9)	7.6 (1.7)	0.055	84/22	8.7 (1.5)	7.8 (2.3)	0.041	52/19	9.0 (1.7)	8.8 (1.6)	0.763	55/29
Rey copy (17)	13.9 (3.0)	14.8 (1.5)	0.231	95/24	14.4 (2.3)	14.1 (2.4)	0.486	54/20	15.3 (1.5)	15.5 (0.9)	0.741	64/30
Calculations (5)	3.7 (1.4)	4.0 (1.1)	0.433	95/23	4.1 (1.3)	4.0 (1.0)	0.502	55/21	4.2 (1.3)	4.4 (0.6)	0.672	65/28
Frontal/Executive												
Digits Forward	5.8 (1.5)	5.4 (1.0)	0.219	73/18	5.1 (1.4)	5.2 (1.5)	0.928	39/19	6.2 (1.5)	6.6 (1.9)	0.656	38/23
Digits Backward	3.6 (1.5)	3.8 (1.3)	0.662	73/24	3.2 (1.4)	3.7 (1.2)	0.181	51/21	4.8 (1.5)	5.0 (1.5)	0.726	63/27

	bvFTD				nfvPPA				svPPA			
	Monolingual (N = 101)	Bilingual (N = 25)	p	N (mono/bi)	Monolingual (N = 55)	Bilingual (N = 22)	p	N (mono/bi)	Monolingual (N =66)	Bilingual (N = 30)	p	N (mono/bi)
D words	7.3 (4.7)	7.2 (4.7)	0.481	88/22	6.0 (4.2)	5.0 (2.8)	0.221	51/21	7.4 (4.5)	7.5 (4.9)	0.816	62/27
Trails (lines/sec)	0.3 (0.2)	0.2 (0.2)	0.211	78/22	0.2 (0.2)	0.3 (0.2)	0.518	50/20	0.3 (0.2)	0.4 (0.3)	0.279	57/25
Design Fluency	5.3 (3.9)	5.2 (3.2)	0.572	85/23	5.6 (2.9)	7.2 (3.8)	0.105	52/21	7.3 (3.5)	7.5 (3.6)	0.889	52/26
Stroop color naming	61.2 (22.0)	55.3 (20.3)	0.265	69/17	42.8 (16.9)	39.8 (21.1)	0.579	41/16	68.2 (19.2)	62.8 (28.3)	0.171	37/23
Stroop inhibition	31.9 (18.4)	25.6 (15.6)	0.175	75/19	24.8 (13.5)	23.1 (12.3)	0.496	44/16	37.1 (13.8)	35.8 (20.5)	0.605	50/24
Abstraction (6)	1.9 (1.4)	2.3 (1.8)	0.658	61/11	2.9 (1.6)	3.1 (1.6)	0.971	37/13	1.9 (1.3)	1.9 (1.8)	0.652	44/15

Abbreviations: BNT = Boston Naming Test, CVLT = California Verbal Learning Test, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination, PPVT = Peabody Picture Vocabulary Test, VOSP = Visual Object and Space Perception battery, mono = monolingual, bi =bilingual.

*
Note. Results derived from ANCOVAs (covariates = age and education). Red denotes significance with Bonferroni correction applied within each cognitive domain. These measures are derived from a neuropsychological battery described further in Kramer, et al..[35]