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Gaps in clinical research in frontotemporal dementia: A call for diversity and disparities focused research

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Abstract

Frontotemporal dementia (FTD) is one of the leading causes of dementia before age 65 and often manifests as abnormal behavior—in behavioral variant FTD—or language impairment—in primary progressive aphasia. FTD's exact clinical presentation varies by culture, language,

education, social norms, and other socioeconomic factors; current research and clinical practice, however, is mainly based on studies conducted in North America and Western Europe. Changes in diagnostic criteria and procedures as well as new or adapted cognitive tests are likely needed to take into consideration global diversity. This perspective paper by two professional interest areas of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment examines how increasing global diversity impacts the clinical presentation, screening, assessment, and diagnosis of FTD and its treatment and care. It subsequently provides recommendations to address immediate needs to advance global FTD research and clinical practice.

Keywords

frontotemporal dementia; primary progressive aphasia; cultural diversity; ethnicity; language; literacy; neuropsychological tests; diagnosis

1. Introduction

Frontotemporal dementia (FTD) comprises neurodegenerative disorders usually characterized by onset in middle age or earlier and heterogeneity in the clinical presentations, neuropathological features, and genetic linkages. The canonical syndromes are defined by abnormal behaviors or defective language and communication, which have been codified in formal diagnostic criteria[1,2]. The behavioral variant FTD (bvFTD) is defined by aberrant temperament, judgment, self-control and conduct. Two language variants have been defined: non-fluent variant primary progressive aphasia (nfvPPA), which is characterized by labored, dysfluent and agrammatical speech, and difficulty understanding sentences; and semantic variant primary progressive aphasia (svPPA), in which speech is fluent but empty on account of anomia and of agnosia for words and objects. Other phenotypes have been described, featuring cognitive deficits (especially executive, attention, and language dysfunctions) alongside motor symptoms (apraxia and parkinsonism)[3]. FTD, defined in terms of the behavioral and language phenotypes in epidemiological studies, is a leading cause of young-onset dementia.

FTD appears to affect individuals of all races, ethnicities, and cultures, with incidence reports in over 30 population-based studies from many research and clinical centers in different world regions[4]. However, the impact of ethnic and cultural diversity in FTD care and research is often overlooked. Given that FTD mainly manifests as deficits in social behavior and communication it is reasonable to surmise that the wide global ethnocultural diversity—with over 3800 cultures and over 6000 different languages[5]—results in disparities in FTD clinical practice and research across the world.

This paper focuses on the intersection between ethnocultural diversity and clinical research and practice. It is now widely acknowledged that aspects of diversity, which encompasses differences in language, social norms, socioeconomic status (SES), and education, influence the performance and outcomes of cognitive and behavioral assessments. As such, ethnocultural diversity can be expected to influence all aspects of the FTD clinical process, including help-seeking, access to healthcare, diagnostic practice and treatment[4]. It

is also to be noted that the FTD clinical research literature has relied heavily on data from individuals of European descent living in North America, Western Europe, and Australia—owing to advantages in social and medical capital, expertise, expendable resources, and public health priorities[6]. Furthermore, in most low- and middle-income countries (LMICs), poverty, low literacy, cultural norms and local practices are barriers to neurodegenerative disease research[7–9].

Today, diagnostic and monitoring tools, standard-of-care practices, and preferred treatments mainly reflect what has been learned from research and published, without systematic adaptations that take into account the worldwide disparities in local context, knowledge, expertise and resources. There is, for example, a need for clinical assessment instruments adapted or adaptable to differing social and linguistic contexts, to facilitate case detection, diagnosis, clinical care and research.

Two Professional Interest Area (PIA) groups supported by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), i.e., the Frontotemporal Dementia (FTD) and Diversity and Disparities PIAs, convened a workgroup to bring together international expertise for the purpose of examining and addressing questions about diversity and equity in current FTD research and care. Here, we examine what is known of how diversity in culture, language, education, SES, and other factors impact the clinical presentation and diagnosis of FTD and its subsequent treatment and care. We conclude by describing next steps and recommendations for future research.

2. Clinical features

2.1 Clinical presentation and diagnostic challenges in diverse populations

Ascertaining a clinical diagnosis of FTD is challenging. First, the wide familiarity with Alzheimer's disease dementia (AD) may cause patients, caregivers, and even clinicians to implicitly associate dementia with memory deficits—which are not considered among the core features of FTD syndromes. Most formal cognitive assessments focus heavily on detecting memory impairment; assessment of social cognition and behavior, which are often impaired in FTD, is rarely included in routine cognitive assessments[10,11]. Moreover, bvFTD is frequently confounded with primary psychiatric disorders due to overlap in initial symptoms and its young age of onset—about 50% of bvFTD patients receive a psychiatric diagnosis prior to the bvFTD diagnosis[12]. Furthermore, dementia is generally underrecognized and undertreated in LMICs and in underrepresented populations in high-income countries[13,14]. This lack of recognition, diagnosis, and related treatment is likely due to the small number of medical specialists, particularly psychiatrists and neurologists, as well as due to the limited training these specialists have received in identifying bvFTD specifically.

Depending on the ethnocultural context, FTD may be associated with longer illness duration, or a more advanced clinical state (more severe brain atrophy, lower cognitive test scores, and more florid symptomatology) at presentation[15–18]. In other words, later diagnosis of FTD is common in many underrepresented populations[15,17,19,20]. These delays are due to factors at the level of the individual/family, and those at the level of the medical/health

system (summarized in Table 1). In preparation for a 2021 Externally Led Patient-Focused Drug Development meeting on FTD, The Association for Frontotemporal Degeneration and the FTD Disorders Registry collaborated on the FTD Insights Survey, a community based online survey of nearly 1,800 diagnosed patients, care partners, and family members designed to better understand the lived experience of FTD in the United States, Canada, and United Kingdom. This survey revealed that, among patients who received a diagnosis of FTD, the subset of Black/African American and Latino/Latina respondents took longer and consulted with more doctors to obtain their diagnosis[21,22]. It has also been shown that neighborhood-level disadvantage (i.e., low access to care) occurs in association with a lower likelihood of receiving standard diagnostic tests (for example, structural neuroimaging, laboratory studies[23]).

The cultural contexts also influences the expression and interpretation of cognitive and behavioral symptoms[24,25]. For example, studies from India and Japan have shown their bvFTD patients to have a higher frequency of utilization and imitation behaviors compared to studies from North America or Europe[16,26]. It has been observed that alterations in eating behaviors occur at similar frequencies in bvFTD patients in Japan and the UK, but, in contrast to the UK, are not associated with severe weight gain in Japan due to culture-related differences in diet[27]. Comparisons of attitudes regarding bvFTD in Turkey, Greece, and the US suggest that, at first, behavioral symptoms are often accepted as normal behavior in Greece and Turkey, and therefore overlooked[17]. These examples illustrate the challenges in framing awareness, public health messages and diagnostic practices in ways that maximize case identification and access to care in different ethnocultural contexts.

Interest in the potential impact of biological sex in the clinical presentation of FTD is increasingly being studied. The existence of both patient- and study partner-related biases associated with sex and gender may influence the diagnosis of the behavioral variant and language variants of FTD, possibly withholding an accurate representation of both sexes. But other biological factors like those noted in AD or ALS may also play a role[28,29]. The clinical presentation, longitudinal decline, and cortical thickness in bvFTD has recently been characterized by Illán-Gala et al.[30], showing that at diagnosis, women with bvFTD showed a more severe frontotemporal atrophy burden in comparison to men despite showing similar clinical characteristics. Altogether, these studies warrant clinicians and researchers to be aware of the existence of sex-linked differences in the clinical presentation of FTD and its possible impact on diagnostics and prognostics.

2.2 Language Diversity in Primary Progressive Aphasia

The global diversity in languages presents us with challenges in the recognition and diagnosis of language impairment across the FTD spectrum, but particularly in the primary progressive aphasias (PPA). Many studies have demonstrated that language typology influences PPA symptomatology. The most frequently reported feature is the over-regularization phenomenon, one of the core linguistic features in the formal diagnostic criteria for svPPA[2]. In English language speakers, this phenomenon manifests as surface dyslexia or surface dysgraphia, where there is a failure to read and spell irregular words (i.e., words with discordant grapheme-phoneme correspondence). In other words, irregular

words are incorrectly read or spelled phonetically. This phenomenon appears to be absent in languages such as Spanish and Portuguese[31,32]. In languages such as German and Spanish, words are almost always pronounced in the same way as they are spelled, and irregular words are uncommon. In these contexts, regularization manifests as inaccurate usage of articles with atypical gender nouns or difficulties with past tense verb inflectional morphology[33,34]. In French and Hebrew, the over-regularization phenomenon presents as errors in derivational morphology[35–37]. Japanese language speakers with svPPA have contrasting performances in reading the syllable-based script *kana* (a script that lacks irregular words) versus the ideogram script *kanji* (a script that is rich with irregular words)[38,39]. In terms of motor speech and morphosyntactic functions, monolingual English speakers have been shown to produce more distortions in connected speech compared to monolingual Italian speakers, but they performed better on syntactic comprehension and complexity tasks, reflecting distinct linguistic features of these languages[40]. Similarly, Chinese-speaking patients with nfvPPA have tone production and tone perception deficits in lexical selection processing, which are linguistic features probably more significant in tonal languages[41]. Chinese language users with PPA have also been shown to have various linguistic dysgraphia errors unique to logographic script, such as homophone or compound word errors[41]. Without adequate linguistic diversity in the PPA research field, we lack understanding regarding the generalizability of the current PPA diagnostic criteria and treatment guidelines, which potentially contributes to underdiagnosis or misdiagnosis of PPA in non-English language speakers.

There is still much to learn about how bilingualism or multilingualism affects the progression of symptoms in PPA. Bilingual speakers with neurodegenerative disease experience either a parallel decline in the first (L1, usually the mother tongue) and second (L2) acquired languages, or a differential decline[42,43]. To date, most studies have shown either disproportionately severe loss of L2 or parallel decline of both languages[44–56]. However, in the largest series of bilingual patients with svPPA to date, the less proficient language prior to disease onset was lost, regardless of whether the language was L1 or L2[57]. Beyond the need to understand the patterns of language decline in bilingual speakers, there is also a gap in investigating their unique symptoms, such as inappropriate mixing or code-switching[42,58–61]. Future prospective studies should include for all of a subject's languages, information on age and manner of acquisition, patterns of use, objective measures of proficiency, measures of education and literacy, and culturally and linguistically appropriate testing.

3. Diagnostic and monitoring tools

Neuropsychological assessment is challenging in many ethnocultural contexts, due to the substantial influence of culture, language, education, institutional, and economic factors on neuropsychological testing, as illustrated in the ECLECTIC framework[62]. These influences are particularly evident in the cognitive domains most relevant to bvFTD and PPA: social cognition, executive functioning, and language. Unfortunately, most assessment tools have been designed in Western Europe and North America and cannot be applied directly in other regions and countries, such as in Latin America[63]. This section will focus on screening tools, behavioral scales, functional impairment scales, and these three cognitive domains.

Although FTD manifests with decline of multiple cognitive domains, including memory[64], we focus on social cognition, executive functions and language, particularly as tests of memory have been widely studied in diverse populations (for example, in AD, see Franzen et al.[65]).

3.1 Cognitive screening tests

Some widely used cognitive screening tests like the Mini-Mental State Examination[66] have low sensitivity in the early symptoms of bvFTD and PPA, as they fail to detect impairment in executive dysfunction, social cognition and language. Several exceptions should be noted, however. The Addenbrookse's Cognitive Examination (ACE) was developed to assess and differentiate cognitive impairment in AD from that in the different FTD syndromes. The ACE-Revised (ACE-R) and ACE-III have been translated and culturally adapted into many languages and are used in research and clinical settings worldwide[67–69]. Most studies report fair sensitivity and specificity of all ACE versions for FTD[70,71] and these tests may also be useful in PPA[72] because of the inclusion of items to screen for language deficits.

The Frontal Assessment Battery (FAB) is another example of a test that has been examined in different populations and translated/adapted to several languages[73]. Although most items of the FAB can be translated with relative ease, the letter fluency subtest poses more challenges, particularly as languages that adopt a logographic script (e.g. Chinese languages, Japanese-Kanji) do not possess sublexical form graphemes with phonemic information, leading to adaption and interpretation challenges for phonographic dependent tests such as letter fluency[74]. For example, two different versions of the FAB are available for different Chinese populations: a Traditional Chinese FAB in which letter fluency has been substituted with orthographic fluency[75] where patients are asked to name words that begin with a given Chinese orthographical structure (e.g. a word with left-right orthographical pattern) and the FAB-phonemic[76] which requires patients to generate words starting with a specific phoneme (fā, **发)**. In other languages, the letter used in letter fluency may have to be changed to ensure equivalent difficulty, such as in the Chilean version of the FAB[77]. An instrument that captures several elements of the abovementioned tests (verbal fluency, ACE-III and other tests) is the INECO Frontal Screening, originally developed in Argentina[78], now also used in several other Latin American countries. This instrument was found to be more useful for discriminating AD from FTD than the FAB in Peru[79].

The Montreal Cognitive Assessment (MoCA) is a screening tool designed to evaluate individuals with mild cognitive impairment[80]. While the test has been translated widely into more than 60 languages, many are merely direct translations; there is then a need to adapt the instrument for cross-cultural use to ensure validity[81]. The test has also been used as a global cognitive measure in FTD, including a few case-control studies conducted in diverse populations[82,83]. In these studies, the MoCA was essentially used to characterize the overall cognitive profile of the participants, without specific analysis of its diagnostic purposes. The Clinical Dementia Rating (CDR)[84] has been extensively used for almost three decades to stage cognitive and functional impairment in AD. However, the CDR does not contemplate clinical domains that are impaired in FTD, such as behavior and language. These domains have been incorporated in a modified version of the instrument, the CDR®

plus NACC FTLD rating scale, which has proven to be an effective staging tool in FTD[85]. These scales have been used in two Latin American studies assessing bvFTD and PPA patients[86,87]. While the CDR did not display good sensitivity in severe disease stages in one study[87], the CDR® plus NACC FTLD rating scale proved to be a valuable staging measure.

Although these instruments may be promising screening tools for FTD, more research is needed. It is also important to emphasize that FTD diagnosis cannot be made on the basis of scores on any bedside or field screening tests. Accurate diagnosis requires a comprehensive clinical assessment. Screening tests are more valuable for facilitating case detection in population studies and monitoring illness severity.

3.2 Behavioral rating scales

The Frontal Behavioral Inventory (FBI) was designed to operationalize and quantify personality and behavior changes in FTD[88]. The FBI is a study partner-based questionnaire which assesses the severity and frequency of negative and positive behaviors. Blair et al.[89] demonstrated that the original English version of FBI was better than the Neuropsychiatric Inventory (NPI) for discriminating FTD from AD patients. Kertesz et al.[90] administered the FBI in patients with FTD, nfvPPA, AD, vascular dementia and depressive disorder and demonstrated that the scale correctly classified 92.7% of the patients with FTD with a high internal consistency and inter-rater reliability[90]. The FBI has been validated for the diagnosis of bvFTD or FTD with ALS in several languages in Europe and Asia[91–99] and the different versions have generally shown good interrater and test-retest reliability, internal consistency, convergent validity, and diagnostic accuracy (when reported).

Portuguese and Spanish language adaptations of the Frontotemporal Dementia Rating Scale (FTD-FRS)[100] have been shown to have good utility for assessing and monitoring illness severity[101,102]. The Frontal Systems Behavior Scale (FrSBE), developed for measuring behavioral disturbances related to frontal lobe functions, with subscales for apathy, executive dysfunction, and disinhibition[103] has been shown useful for discriminating AD from FTD. A translated version has been created and used in the linguistically diverse FTD patient population in India[104].

3.3 Functional impairment scales

Functional impairment is a key dimension in neurodegenerative disease, as it determines the threshold between the early stages of cognitive impairment and dementia[105]. Assessment of functional impairment is generally accomplished with self-report, informant-report, and performance-based measures. In bvFTD, self-report measures tend to have little use due to loss of insight early in the disease. Performance-based measures of functional impairment are time consuming and administered under artificial conditions, potentially leading to results that differ significantly from the individual’s performance in real environments[106]. Informant-rated questionnaires have proven to be a practical and valid measure of everyday functioning in dementia. Current evidence suggests that patients with FTD show a differential pattern of functional impairment compared to patients with Alzheimer’s disease dementia; patients with FTD show greater functional impairment than patients with Alzheimer’s disease dementia and tend to experience both impairment in

instrumental and basic activities of daily living at an early stage[107]. Cultural factors are critical to take into considerations in the assessment of functional impairment. For example, in certain cultures, it may be customary for younger members of the family to manage the household and take care of financial matters, while elders play a more social role within the community as they are aging[108]. Similarly, older individuals who are illiterate or low educated may always have been dependent on others to support them in administrative and financial matters. Studies are now increasingly conducted on this topic in non-European and non-North American countries (for example see Musa Salech et al.[109]). Emerging evidence shows that gender, age, education, and culture influence scores on commonly used instruments of functional impairment in many parts of the world[110].

3.4 Social cognition

Social cognition refers to the ability to attend to, interpret and respond to social cues, and normal performance is essential for successful interactions with others[111,112]. While definitions vary, the term encompasses three domains: 1) emotion reactivity and recognition, 2) mentalizing (empathy and theory of mind), and 3) regulation, including moral reasoning and knowledge of social norms[113]. Impaired social cognition is increasingly recognized as a core clinical feature of FTD and has been shown to be associated with abnormal social behaviors[1,2,11,104,114]. Culture can impact all aspects of social cognition, such as 1) how emotions are perceived and categorized, e.g., the perception of emotion intensity[115]; 2) how social cues are responded to and how empathy is demonstrated[116,117]; and 3) which behaviors are considered appropriate according to local social rules and norms[118]. Multiple studies have shown different neuroanatomical activation patterns between participants of East Asian and ‘Western’ cultures when engaged in similar social tasks, suggesting that the neural networks underlying social cognition and affective processes may vary across cultures[119–123].

Relatively few tests of social cognition have been validated in FTD in general[124]. Unsurprisingly, even less research is available in underrepresented populations with FTD[125]. The adaptation or development of novel tests of social cognition has been identified as a research priority by European experts on cross-cultural neuropsychological assessment[126]. The Global Social Cognition Study in cognitively healthy adults demonstrated that cultural background, education, gender, and age impact performance on tests of emotion recognition and theory of mind[127]. Cultural differences explained almost 21% of the variance on an emotion recognition task and 25% of the variance on a *faux pas* test[127]. Similar cross-cultural differences were found in theory of mind using the Reading the Mind in the Eyes test[128]. Such differences do not necessarily limit the tests’ utility for discriminating patients with FTD from other patients or control subjects (e.g.[129]), provided normative data are available for the target population. Cultural differences can, however, impact the construct validity of these tests across cultural contexts; that is, instead of measuring a specific aspect of the construct social cognition, the test may actually measure general FTD severity or aspects of language related to the format of the test. Newly designed or adapted tests may be needed for a more valid assessment of specific cognitive domains.

Not all studies of emotion recognition report differences across different cultural groups[130]. However, tests of emotion recognition and theory of mind using faces as stimuli, such as the Ekman 60 Faces Test or Reading the Mind in the Eyes test, may need to include photographs of individuals sharing physical features with the target population (e.g. Chinese faces in the assessment of Chinese participants), given the differences in performance depending on whether the individuals portrayed have similar or different physical features[128,131–133]. Tests of mentalizing such as theory of mind and tests of social reasoning, such as *faux pas* detection and humor interpretation, are likely to be particularly influenced by culture[127,134,135]. Such tasks therefore need to be adapted to suit local contexts. Furthermore, the use of more objective measures (e.g., physiological responses) is also receiving increasing attention[136–138], as it may be less susceptible to sociocultural bias.

3.5 Executive functioning

Executive functioning encompasses the capacity to form a goal, plan, and carry out goal-directed actions effectively, making use of abilities such as cognitive flexibility, concept formation, inhibition, and reasoning[139]. A twofold challenge exists in the assessment of this complex set of functions. First, large cross-cultural differences in executive test performance (e.g., Trail Making Test) have been reported even across 'Western' countries[140]. While causes of these differences are varied, linguistic diversity plays an important role in test performance on certain executive measures. A recent study has examined alternating category verbal fluency as an alternative to letter fluency tests in multicultural settings (e.g.[141]); researchers found that alternating fluency is a suitable measure of cognitive flexibility in diverse populations, but may not be able to discriminate patients with AD from patients with 'frontal' neurodegenerative disease. Second, adequate assessment of low educated or illiterate individuals may be particularly challenging due to a lack of suitable tests[65]. Common tests of executive functioning, such as the Trail Making Test, Stroop test, and phonemic fluency, are generally not appropriate in these populations; such tests often require a certain level of literacy and abstract reasoning skills acquired through formal education. Alternative tests of executive functioning have therefore been developed, such as the Color Trails Test[142], Five Digit Test[143] and Sun-Moon test[144]. However, the majority of these novel or adapted tests have not yet been studied in bvFTD and PPA.

3.6 Language

Changes in language are the hallmark of PPA and frequently occur in bvFTD[145]. The Boston Naming Test (BNT) is the most widely used test to assess naming impairment in North America and Europe[146,147]. However, its items – such as a pretzel, beaver, and asparagus – are culture-specific and not suitable for use in many parts of the world. Additionally, items such as the noose (BNT) are explicitly criticized for their offensive nature due to associations with traumatic historical and political events[148–152]. In addition, several studies suggest that the two-dimensional black-and-white line drawings included in most confrontation naming tasks may not be appropriate for evaluation of individuals with low educational attainment or illiterate populations[153,154]. The Multilingual Naming Test[155] was developed to assess bilingual individuals in several languages; while the test is useful in some contexts, the stimuli (presented as black-and-white line drawings) may not be recognized equally across cultures[156]. Several initiatives have therefore focused on

the development of widely applicable naming tests using colored photographs, such as the Cross-Linguistic Naming Test[157] and the Naming Assessment in Multicultural Europe (NAME[158]). However, these tests have not yet been studied in patients with FTD or PPA specifically.

In addition to naming tests, category fluency tests are relatively widely used and studied in diverse populations, although not specifically in diverse individuals with FTD[65]. It is known that category fluency can be substantially influenced by education[159] – animal fluency tests more so than foods and supermarket fluency[160,161]. Linguistic effects can also occur; for example, Spanish speakers produce relatively few words in animal fluency due to animal names being relatively long in comparison to other languages, such as Vietnamese[162].

To differentiate between different types of PPA, neuropsychological tests are needed that take into account other aspects of language, such as syntax and phonology. Given the unique characteristics of languages across the globe, mere translation of existing tests will not be sufficient. For example, to address deficits relating to tone in individuals with PPA speaking tonal languages, researchers have used a ‘one-syllable tongue twister’ test to measure tonal errors in the Chinese Language Assessment for PPA (CLAP)[41]. In Spanish-speakers, surface dyslexia may be hard to study because of the transparent spelling to sound matching[163]; a reading test using words in which stress marks have been left out has been proposed as a valid alternative[164]. These examples highlight the challenges in this area and the need for language-specific test development. To this end, the Mini-Linguistic State Examination has been proposed as a brief assessment tool for the diagnosis and classification of PPA, with several language versions available, such as Spanish, Farsi, and Japanese[165,166]. In addition, language specific tests of semantic memory, which is culture and context dependent, have been developed to aid in the assessment of bvFTD and svPPA (e.g., in China[167] and India[168]).

Additional challenges may arise in cross-linguistic assessments of bilingual and multilingual patients. Before such an assessment can begin, it is important to examine the level of proficiency in each language to determine which language the assessment should be conducted in and how to subsequently interpret the findings. As stated by Mendis et al.[169], however, bilingualism is dynamic, meaning proficiency can vary based on exposure to other language users, as well as opportunity and frequency of use. In addition, appropriate, short screening tests to determine language proficiency across languages are lacking. The assessment becomes even more complex when patients are assessed in their second or even third language (as is often the case for immigrant and/or refugee patients), when patients switch between languages during the assessment, or when they use different languages in speaking versus writing[170]. Even with the use of an interpreter, the validity and reliability of such assessments can quickly become compromised (for a more in-depth illustration, see Plejert et al.[171]).

4. Treatment

4.1 Clinical trials

Clinical trials of pharmacologic and non-pharmacologic interventions for patients with FTD have largely been conducted in North America, Western Europe, and Australia. Ethnoracial, sex, gender, and socioeconomic data for participants enrolled in FTD clinical trials are limited but are likely similar to trends observed in AD research studies, particularly clinical trials. Participants in AD studies are consistently predominantly non-Hispanic white, with <5% of participants being ethnoracially diverse, as noted in the ISTAART perspective paper for Diversity in AD research[172]. Diversity of participants with FTD enrolled in clinical trials is limited by numerous factors that have the potential to reduce the generalizability and applicability of the study findings.

Restricted geographic accessibility is a common limitation as most interventional trials are conducted in academic centers, usually in urban settings, that have small catchment areas and require long travel times of rural participants. Strict inclusion and exclusion criteria typically prohibit participation of patients with medical comorbidities and patients who are not proficient in the dominant language in a country. In a recent randomized controlled trial investigating a monoclonal antibody infusion for AD, screen failure rates were higher for traditionally underrepresented groups than for non-Hispanic white participants[173]. Frequent in-person visits and limited flexible scheduling present high opportunity costs which limit access for those whose caregiver or study partner is lacking adequate transportation, are working or need childcare. In our experience, enrollment of symptomatic women with FTD is more challenging than enrolling men, which delays trial completion and increases costs for studies targeting balanced enrollment.

Additional barriers need to be overcome to conduct clinical trials in LMICs. Funding (private and public) for research development has been limited in many countries outside North America, Western Europe, Australia and Japan. For example, in Latin America less than 2% of national public health budgets (the minimal percentage recommended by the Council on Health Research for Development) has been invested in research[174]. Difficulties with regulatory processes and SES represent additional barriers. Approximately 10% of the Latin American population is indigenous and the vast majority of this population lives in poverty, and sometimes in isolation, complicating their access to education and health programs[175]. Similar circumstances exist in parts of Asia and Africa.

4.2 Speech and language interventions.

Most of the extant literature has focused on *linguistic* diversity (i.e., speakers of the nonmainstream language or bilingual speakers), specifically in those presenting with PPA. Although a systematic review is beyond the scope of the current paper (see instead[176,177]), an assessment of the literature shows bias in PPA treatment research wherein English and Western European contexts and languages are over-represented compared to other language families (as has been well documented in post-stroke aphasia[178]). A notable exception is a recent study from Brazil examining a case-based intervention to promote different aspects

of language functioning in 18 Brazilian Portuguese speaking patients with PPA that found significant improvement in 13 of the subjects[179].

There is a very limited body of research investigating bilingual effects in the context of PPA treatment. A study in the United States[180] investigated the effects of a lexical retrieval intervention in a group of bilingual speakers with logopenic variant PPA and svPPA. All participants were bilingual and were treated in both English and a second language (i.e., Spanish, Portuguese, Farsi or French). The intervention was designed to engage residual orthographic, phonological and semantic knowledge and to encourage self-cueing. After treatment, participants showed improved performance in both dominant and nondominant languages. In addition, cross-linguistic transfer for words that share meaning and form across languages, e.g., telephone and *téléfono*, was observed for most participants. In sum, there is promising evidence that dual-language speech and language intervention results in immediate and long-term naming improvements in bilingual individuals with PPA. Further research is needed to investigate additional language families, and to optimize approaches such that the unique linguistic characteristics of each language are incorporated into the treatment designs. Furthermore, future studies might indicate whether such approaches can be applied in unbalanced bilinguals, i.e., individuals more proficient in one language than the other, such as immigrant populations who learned a second language later in life. Importantly, cultural factors must be considered in the future development of novel interventions in diverse populations. In the current era of globalization, it will be incumbent upon researchers and clinical training programs[181] to advance knowledge regarding assessment and treatment in bilingual FTD, as these individuals are often underserved due to low referral rates[182,183].

5. Care needs

5.1 Caregivers – cultural differences

Caregiver burden is a complex and multifaceted construct mediated by several variables and their interactions[184]. Examining variables that contribute to caregiver burden in FTD is important given the particularly high level of caregiver burden in FTD compared to AD[185–188]. Mioshi et al. showed in 2009 that caregiver variables such as depression were relevant and, in 2013, that FTD disease severity was the main factor contributing to high levels of caregiver burden[189,190]. However, most studies of caregiver burden in FTD have been conducted in North America, Europe, and Australia and primarily in non-Hispanic white populations. A 2013 study by Mekala et al.[20], was the first to compare caregiver burden in FTD in two countries with different cultures, India and Australia. They found that both groups experienced similar levels of stress and depression, despite the Indian caregivers caring for a more impaired group of patients and delivering a greater number of hours of care; however, the Indian caregivers did report higher levels of anxiety. The authors suggest that perhaps some Indian caregivers perceived their loved one’s symptoms as part of ‘normal’ aging, making it difficult to address their worries and to obtain the right coping skills. Differences in reporting of anxiety and depression may also originate from cultural variations, such as differences in the willingness and comfort discussing such topics as part

of research. The authors concluded that addressing FTD caregiver coping skills with Indian caregivers may have a greater impact than those targeting dementia specific symptoms.

5.2 Shame and stigma affecting diagnosis and care in FTD

Shame and stigma are important cultural factors that can impact caregiver burden and quality of life (QoL), and also affect the recognition of symptoms and whether patients obtain a diagnosis. In the following paragraphs, several illustrative examples are provided of shame and stigma affecting diagnosis and care in FTD in different global contexts. Furthermore, an example from one of the author's clinical practice is described in Box 1.

In Colombia, caregivers felt stigmatized by their role, in that they thought they were less worthy, which predicted increased caregiver burden, greater depression and reduced QoL[191]. In China, Chao et al.[15] reported that there was often confusion and disagreement about various symptoms, e.g., motor or cognitive symptoms being attributed to "normal aging", thereby delaying the seeking of medical attention. Given the stigma surrounding mental illness in China, psychiatric or behavioral symptoms are generally not openly discussed and may not be disclosed on direct questioning. Disclosure is even less likely if the specialist is of a different race or culture. "Dementia" has the meaning of "crazy and catatonic disorder", and stigma may thus be amplified for FTD given the concurrence of cognitive dysfunctions and behavioral changes. Delayed diagnosis is very common, and the disease is often advanced before being brought to the attention of a medical professional[15]. Both in China and in Latin America, there is a culture of looking after the person at home which also relates to difficulties in finding appropriate aged care facilities when the decision is made to eventually transition the person into a formal care facility. There are also feelings of guilt that influence the willingness to pursue placement in care facilities.

In Latin America, care is predominantly provided by women with low education living in multigenerational households[9]. As unconditional respect for the patriarch is considered very important in some Latin American cultures, women and younger family members who are caregivers for an older male are uncomfortable and have difficulty managing dysfunctional behaviors. Secondly, there is shame in seeking help for these behaviors, such as sexualized behavior, disinhibition and excessive alcohol drinking. Furthermore, caregivers may perceive these behaviors as deliberate, not recognizing them as symptoms of FTD, which delays evaluation, diagnosis and treatment—with adverse impacts on the levels of caregiver burden. For PPA specifically, the loss of communications pertaining to traditions and heritage can contribute to frustration and guilt[9].

Emerging evidence from Sub-Saharan Africa pertaining to all-cause dementia has shown that people may simultaneously hold a number of different beliefs about dementia and its causes[192]. For example, a study in South Africa found that participants, on the one hand, often believed that dementia was related to witchcraft or punishments from ancestors or God, while on the other they also believed dementia to be a medical condition[193]. Help was therefore often sought from multiple different sources simultaneously, typically faith healers and traditional medicine practitioners, and to a lesser degree allopathic medicine providers[194]. It is also to be noted that access to psychiatrists and neurologists is very low in much of Africa. In cases of suspected witchcraft, caregivers may be shunned by

community, and even family, due to fear[192]. It is not hard to imagine that the 'strange' behavior displayed by individuals with bvFTD may be misconstrued as caused by such forces in environments where religio-magical explanatory models are commonly used. In much of Africa, there is a culturally entrenched reliance on informal care from younger relatives—and residential programs are uncommon[4].

5.3 Caregiver support and interventions

There is very little information on caring and how to care for people with FTD in an international context. In Peru, the majority (76%) of 145 medical professionals (neurologists, psychiatrists, residents in neurology or psychiatry) who completed a survey about knowledge and attitudes for the management of bvFTD indicated that they do not provide education, information, and support to the caregiver of the bvFTD patient. The survey respondents reported that 88% of patients with advanced bvFTD were not followed by a palliative care team[195].

An appraisal of the current literature indicates large gaps with respect to intervention studies aimed at caregivers of individuals with FTD from ethnoculturally diverse populations. Nevertheless, a body of research has examined the effects of interventions administered to caregivers with AD and related disorders, some of which included those presenting with FTD. A subset of these studies purposefully included individuals from diverse backgrounds. Outcomes demonstrate that tailored caregiver interventions result in improved caregiver quality of life and increased strategy and skill usage[196–199]. Future interventions specifically tailored to the different variants of FTD will need to be developed specially for diverse populations. In addition, it is vital that such interventions take into consideration the ethnocultural differences in clinical presentations and the related differences in caregiver perceptions of FTD. In many contexts, raising dementia awareness will be a crucial first step[200].

6. Gaps and next steps.

As the preceding sections emphasize, a substantial amount of research is needed to cover the gaps in FTD research and clinical practice. In the following paragraphs, we outline the workgroup's recommendations for next steps.

6.1 Recognition of bvFTD and PPA in diverse populations

Awareness of bvFTD and PPA is often limited and requires targeted efforts and awareness campaigns. For example, in a study of 14 countries, the level of public awareness of the general concept of aphasia varied from 1% in Argentina to 66% in Sweden[201]. Given the influence of cultural diversity in clinical presentations, and of dementia literacy, explanatory models, and modes of help-seeking, public awareness campaigns need to be tailored to the specific ethnocultural contexts, and target audiences must be mindfully defined. In addition to awareness campaigns in the general population, investments should be made to disseminate expert knowledge on FTD and PPA to clinicians working in the field. For example, a study in New Zealand found that only 21% of healthcare professionals surveyed had basic knowledge about the general concept of aphasia[202]. This knowledge dissemination

can take different forms. One option is through remote or in-person clinician training for general practitioners, neurologists, and psychiatrists, to improve recognition of early and later presentations and to differentiate different subtypes. Another possibility is the development of a best practice manual for the diagnosis of FTD—as was recently done for dementia in Latin America[203]. Additionally, this topic should be included in the curriculum of undergraduate studies from health sciences.

From a systems perspective, the development of formal partnerships and exchange programs between established centers in North America, Western Europe, Australia and Japan, and clinical programs in LMICs will foster knowledge transfer and the development of local expertise. A global effort to map the definitions and delineations of normal and abnormal behavior in FTD and language symptoms (via table or concept map) may be helpful to gain a better understanding of the variation in presentation across cultures. To this end, researchers in LMICs may contribute valuable knowledge about the influence of culture on behavioral symptoms of FTD, as well as the role of language typology and the different linguistic features characteristic of PPA in different languages. Consensus criteria could then be developed to diagnose PPA in diverse populations, moving away from the current over-reliance on aspects such as surface dyslexia. Such advances are hindered, however, by a lack of funding for FTD-research in LMICs. For example, of the 613 FTD-related grants ($432,167,275) awarded between 1998–2008, the majority (89%) was from the United States and the remainder largely from Europe[204]. In addition to more funding, open access publication should be the standard requirement to improve access to scientific knowledge for researchers working in low-resource settings. Open access publications will facilitate access to scientific knowledge.

6.2 Cognitive assessment and diagnosis of FTD in diverse populations

Researchers should be aware that mere translation of existing cognitive tests developed in North America and Europe is insufficient to make such tests appropriate for other populations. Test development should follow international guidelines for cross-cultural translation and adaptation procedures, such as those currently being formulated in a neuropsychological addendum to the existing International Test Commission Guidelines by the Cultural Special Interest Group of the International Neuropsychological Society[205]. They should also take into consideration the cultural and linguistic appropriateness of the stimuli and test procedures. Ideally, individuals possessing relevant cultural expertise are involved early on in the development and/or adaptation of the target measure and during pilot-testing. Regrettably, few researchers use these guidelines for test development in FTD research.

To enhance the diagnosis of PPA, language-specific tests are likely needed; however, as there are over 6000 living languages worldwide, it may not be feasible to develop unique sets of speech and language batteries for all these languages. Instead, the demands for linguistically tailored tests in each language should be evaluated by comparing the linguistic differences of each PPA relevant language features with that of the English language that are relatively well studied in the PPA research field. For instance, the reading and writing presentations between languages with different writing systems would be expected to vary

more than between languages using the same writing system. Since most research has been dedicated to the reading and writing symptomatologies of alphabetic language users with PPA, the demands for studying dyslexia and dysgraphia in non-alphabetical languages may be more clinically imperative. Culture is to be taken into account as well; studies relying on the Boston Naming test have demonstrated that speakers of the same language may have regional differences in their item responses[206,207]. This is likely related to the local variations in a language and differences in cultural background. Thus, it is also important to consider validating the speech and language tools of the same language in a population specific manner.

Researchers in the domain of social cognition face similar questions about whether to develop culture-specific tests or try to design tests applicable to individuals with a wider variety of backgrounds. One interesting example from schizophrenia research is the development of the SOCRATIS battery[208], in which researchers tailored a commonly used false belief task to reflect the local context in India by changing stories, characters, and images to reflect culture-specific settings (e.g. temple instead of a church).

Using novel digital technologies such as virtual reality and automatic speech processing may provide promising ways of obtaining neuropsychological data that closely resembles everyday life, which may be particularly important for individuals who are not familiar with being formally tested due to a lack of formal education or relevant exposure, and who may not understand the need to complete more abstract tests[170,209].

6.3 Addressing diversity in FTD treatment and care

Much work remains to be done to improve FTD treatment and care across the globe. A crucial first step is to improve equity in access to a timely and accurate diagnosis of FTD. In addition to this being a priority on ethical grounds, a delayed or incorrect diagnosis will also impede access to care and participation in research. It is also to be noted that lower levels of case recognition also impede FTD treatment development, by reducing the pool of potential participants in the relevant research. In the context of clinical trials, in 2020, the US Food and Drug Administration issued non-binding guidance recommendations for industry for enhancing the diversity of clinical trial populations. The guidance highlights two key steps—broadening eligibility while limiting exclusion criteria and improving recruitment so that participants involved in the trial reflect those most likely to use the drug[210]. For clinical trials in FTD, purposeful study design and support for participants will be needed to ensure sufficient enrollment of women, residents from rural settings, and participants from underrepresented ethnic and racial groups. Potential strategies to accomplish broader participation and more diverse enrollment and retention in FTD clinical trials and other studies include:

1. Limiting in-person study visits and using remote data collection to reduce participant burden and opportunity costs, with increased reliance on remote data collection either directly from the patient’s home or from digital assessment tools or standardized sample collection deployed with local clinical sites. Such decentralized trial design would also enable broader catchment areas for

established sites within countries and expansion to a larger set of international sites.

2. Active collaboration with physicians and health providers serving rural and underrepresented racial and ethnic communities, alongside international collaborations, in long term relationships that foster education and clinical support and extend research opportunities. Partnerships between leading clinical trials centers and those in developing countries has been implemented successfully for decades in infectious disease clinical trials[211].

3. Adaptation, translation, and validation of study materials to a broader range of languages and cultures to facilitate inclusion of countries outside of North America, Western Europe and Australia in FTD clinical trials, leveraging existing local expertise and growing international FTD consortia. This would also include the development of measures less reliant on reports from a single caregiver, for patients in alternate living and care situations. Language and cultural similarities have motivated the organization of research networks that will facilitate clinical research and trials across international networks, such as the ReDLat group, an FTD consortium spanning Latin American and Caribbean countries[212]. Similar consortia have been developed in Japan and South Korea, and are developing in China and South East Asia.

4. Providing under-resourced centers with technical assistance for navigating regulatory processes, study start-up, and other infrastructure necessary for the implementation of clinical trials (e.g., modern brain imaging methods, sophisticated genetic and biochemical assays). The use of direct-to-patient registries like the FTD Disorders Registry may also help identify which under-resourced clinical sites are likely to have a substantial cohort of potential participants for FTD clinical trials.

5. Assurance of adequate enrollment of men and women, and consideration of sex/gender effects on behavioral and other psychometric measures, and caregiver and quality of life outcomes.

6. Application of the social marketing model of recruitment to maximize the diversity of participant enrollment. The social marketing model is an effective means to increase research participation of underrepresented populations[213]. The recruitment method involves six principles: product, price, place, promotion, participants and partners.

7. Involvement of people with FTD and caregivers from diverse backgrounds in the design of interventions to maximize fit with needs and expectations. Similar input should be incorporated on clinical trial design and outcome measures, to maximize participation, minimize attrition, and ensure that the trial tools accurately capture what matters.

8. Involvement of researchers from diverse backgrounds in the design and implementation of interventions.

It is fundamental that caregivers of patients with FTD are provided with a tailored, interdisciplinary approach to care, including training on complex medical symptoms, psychosocial issues, spiritual well-being, and planning for the future. However, improvement in health literacy, such as what is considered “normal aging” is required to increase the profile of dementia, including FTD. This should not be targeted just to caregivers, but also needs to be recognized as a social issue by government and health bodies. Using social media might be one method to provide relevant information to large populations[214]. This might improve help-seeking, access to care and decrease stigma. Furthermore, high quality online resources and remote caregiver programs may improve access to people living in remote areas by reducing financial and logistical barriers. For PPA, multidisciplinary teams with speech pathologists and other language experts need to collaborate to design language-specific interventions that can be delivered by non-specialists available in community settings.

7. Conclusions

This work has focused on priorities pertaining to a multicultural and international perspective of FTD care and research, highlighting gaps in our understanding of the ethnocultural factors that shape how illness is manifested, experienced and articulated, as well as what happens for diagnosis, treatment and research, and for the psychosocial adaptation of patients and families. Questions regarding FTD epidemiology, genetics, biofluid and neuroimaging biomarkers, are also crucial—they are tackled in a subsequent paper[215]. From the foregoing, it will be clear to the reader that examination of these cross-cultural aspects of FTD is in its infancy—and disparities exist worldwide with respect to the expertise, knowledge and resources required to provide the care and to bridge gaps in our knowledge.

Recognition of the need for global and ethnocultural perspectives for FTD research is timely and growing. The multicentric research collaborations developed in North America (ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration[216]) and Europe (Genetic FTD Initiative[217]) have yielded invaluable insights regarding the natural history of FTD, with respect to symptom progression, brain atrophy and physicochemical change. However, it is recognized that these findings, valuable as they are, derive from a study population that lacks diversity. As such, it would be premature to take the findings as representative of all FTD cases in the various ethnocultural contexts around the world. This limitation, and its recognition, is one of the motivations for the formation of the Frontotemporal Prevention Initiative (FPI[218]). The FPI is working actively to coalesce the regional international consortia (currently those from North America, Europe, Latin America and the Caribbean, Australian and New Zealand, South East Asia, Japan, South Korea, and China) into a global initiative to foster harmonization of methods and sharing of resources, and bring a timely diversity in the populations and contexts in which FTD is investigated. This is a work in progress, with recognized gaps that include incomplete worldwide reach (e.g., no presence in Africa and Eurasia), need for knowledge transfer and capacity building programs, and the necessity of adaptations of research methods for the cross-cultural work that is to be done.

Alongside this international development within the field, there is recognition at the policy level, embodied in the 2022 United States National Institutes of Health draft recommendations for FTD research, of the urgency for major investments in research to advance our understanding how ethnocultural and socioeconomic factors correlate with risk factors and pathophysiology, and influence FTD clinical expression, illness progression, treatment response, psychosocial adaptation, and research participation, advocacy and other sociocultural aspects.

Ultimately, we hope that the increasing recognition of the importance of diversity in FTD, together with the recommendations presented in this perspective paper, will encourage global discussion of diversity in FTD research and practice, and result in the formation of one or more workgroups or multi-stakeholder expert panels that can determine which goals to prioritize, formulate action plans, and generate the road map and activities to these challenges.

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Box 1:

Amir's story

Amir had always been a generous, compassionate, and devoted Muslim. He and his family were respected and valued members of the Muslim community and particularly well-regarded at their local mosque.

In his late 50's, Amir's behavior began to change; he would breach etiquette when visiting the mosque (e.g., speaking loudly and wearing shoes) and he would flirt with other women. He also stopped observing Ramadan and showed indifference to other people's feelings and beliefs. This behavior is different to common societal perceptions of dementia (e.g., forgetfulness and disorientation) which led others to perceive Amir as a bad Muslim, someone who had "turned away the Prophet and the Qur'an". Amir's behavior created embarrassment and high levels of concern and distress to Amir's wife and daughters, who also had to deal with great social rejection and stigma. To avoid conflicts in the mosque, Amir's family drastically reduced their activities outside their home. As a result, Amir's family became more isolated, Amir's behaviors became more agitated and the whole family's mental health suffered.

When Amir received a diagnosis of bvFTD, his wife was able to explain his symptoms to their religious community leaders. Amir's dementia was acknowledged and consequently, he was exempted from performing religious duties. Moreover, the understanding of Amir's symptoms also served to repair the bonds between his family and their religious community and partially restored their social and spiritual activities.

Research in context

Systematic review:

The authors reviewed the literature on diversity and disparities in behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) research using traditional sources (e.g., PubMed).

Interpretation:

Experts from the Diversity and Disparities and the Frontotemporal Dementia Professional Interest Areas of the International Society to Advance Alzheimer's Disease and Treatment (ISTAART) outline critical gaps in knowledge how diversity in culture, language, education, and socioeconomic factors among others, impacts clinical presentation, recognition, and diagnosis of bvFTD and PPA, as well as subsequent treatment and care.

Future directions:

Future research should be aimed at 1) increasing global awareness and recognition of bvFTD and PPA; 2) modifying current diagnostic criteria and diagnostic procedures; 3) developing more/sensitive cognitive tests to diagnose bvFTD and PPA in diverse populations; 4) increasing enrollment of patients from underrepresented groups in FTD clinical trials; 5) conducting more research into inclusive caregiver interventions.

Table 1.

Individual and clinical barriers to FTD diagnosis in diverse populations

Individual and Family Barriers to Diagnosis	Medical and Health System Barriers to Diagnosis
Lack of awareness in the population[a] 15,17,20,219,220	Lack of awareness in clinicians[a] 7,195,220–222
Poor education[a,b] 223,224	Disregard for expressed concerns[a] 219
Attributing dementia to normal aging[a,b] 20,219	Misinterpretation of behavioral symptoms by clinicians[17]
Associating dementia with amnesia[15,219]	Lack of social cognition assessment tools based on local cultural norms[24]
Stigma against mental illness[a]15,225–227	MMSE limited cognitive assessment and lack of validation of detailed cognitive tests[a] 228
Tendency to talk to religious leaders instead of doctors[a]219	Limited time for patient assessment and lack of trained neuropsychologists[a] 221,228
Considering symptoms not important enough to address in clinical settings[a] 15,17,219	Difficulties in accessing high-cost diagnostic tools such as biomarkers, genetic screening, or PET scans[a] 13,228
Focusing on cognitive/motor symptoms or considering behavioral changes less important or secondary features[15,17]	Barriers in research; poor support from the governments, fewer funding opportunities for research, and negative beliefs/attitudes towards brain (organ) donation[a] 229
Lack of medical insurance or knowledge for the utilization of services[a] 15,219,230	Diagnostic criteria that do not reflect global diversity[40,231]

[a]This barrier also applies to dementia in general

[b]This barrier can also be present in medical and health systems