Portuguese version of the CDR plus NACC FTLD: Validation studies

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Abstract

Introduction: The CDR Dementia Staging Instrument PLUS National Alzheimer’s Coordinating Center (CDR plus NACC FTLD) was developed by adding to the standard CDR two extra domains focused on the main features of frontotemporal lobar degeneration (FTLD): language and behavior/personality. We intended to perform the validation studies for the European-Portuguese population.

Methods: A total of 105 participants matched for age, education, and disease staging (35 bvFTD, 35 AD, and 35 controls) were included. A translated-version of the CDR and the two added domains was administered by a neuropsychologist who was blinded to the diagnosis.

Results: The bvFTD group had higher baseline CDR plus NACC FTLD scores compared to the AD and controls. Only the sum-of-boxes (SB) score, the behavior/personality, and language domains were able to distinguish between clinical groups. Logistic regression analyses showed that adding the behavior/personality domain with or without language significantly enhanced the discriminating ability.

Discussion: Results show that the CDR plus NACC FTLD is a reliable tool in the diagnostic process of bvFTD patients and has an added value in distinguishing them from patients with AD.

KEYWORDS
Alzheimer’s disease, CDR plus NACC FTLD, disease staging, frontotemporal dementia, FTLD-CDR

1 | BACKGROUND

Frontotemporal lobar degeneration (FTLD) is the second most frequent cause of early-onset degenerative dementia and is, so far, an incurable disease.1 Classic FTLD syndromes are characterized by a personality/behavioral and/or language decline anchored in clinical variants: the behavioral-variant FTD (bvFTD) and language variants known as primary progressive aphasia.2,3 bvFTD is responsible for 60% of all cases but its clinical assessment and diagnosis are particularly complex due to heterogeneity in presentation and lack of biomarkers. The ability to detect clinical variations and changes in the dementia spectrum is of utmost relevance in classification and prognosis and for a patient-tailored intervention.4 The Clinical Dementia Rating (CDR) scale5 is a broadly used instrument in Alzheimer’s disease (AD) and sometimes in FTLD for rating disease staging and severity, being a primary end point in the majority of clinical trials and research...
studies of AD. Specific staging instruments in FTLD have not achieved the same kind of agreement. The Frontotemporal Dementia Rating Scale (FTD-FRS), first published in 2010, displayed a good capacity for detecting differences between FTLD subtypes and changes during the disease course. However, due to their specificity, neither the CDR nor the FTD-FRS, can be reliably used in both AD and FTLD. The CDR Dementia Staging Instrument PLUS National Alzheimer’s Coordinating Center (NACC) (CDR plus NACC FTLD) solves this limitation with the addition of two extra domains, typical of FTD phenomenology: language and behavior/personality. Previous validation studies show that this new scale, allowing a more comprehensive description of disease, enhances sensitivity to FTLD and improves the distinction between FTD and AD. Furthermore, the CDR plus NACC FTLD shows a good correlation with the regional frontotemporal Cerebral Blood Flow (CBF)-hypoperfusion typical of FTLD. As a result, the CDR plus NACC FTLD was selected as the primary end point in FTD clinical trials recently launched. In this study, we aimed to validate the CDR plus NACC FTLD for our clinical setting and language (European-Portuguese) and further evaluate its potential to distinguish between AD and bvFTD patients.

2 | METHODS

2.1 | Participants and procedures

The validation study of the FTLD-CDR is included in a broader Portuguese financed project (SFRH/BD/144001/2019) entitled: “Frontotemporal dementia: new tools of diagnosis and predictors of progression.” A cross-sectional study was conducted using a convenience sample of consecutive patients followed at the Memory Clinic of the Centro Hospitalar e Universitário de Coimbra (CHUC) between August 2019 and August 2021. From the initial sample of 122 participants, 12 (9.8%) were excluded due to cognitive impairment (severe dementia stages) and 5 participants (4%) were excluded due to the absence of an available caregiver/informant. Our final sample included 105 participants (35 bvFTD, 35 AD dementia, and 35 community-dwelling subjects), matched for age, education, and disease staging. All the patients (n = 70) were thoroughly studied, with most of them being evaluated with magnetic resonance imaging (MRI) and either cerebrospinal fluid (CSF) biomarkers or amyloid-PET (positron emission tomography) imaging. For inclusion, both bvFTD and AD dementia patients had a diagnosis established by a multidisciplinary team according to the most recent international criteria. As part of the exclusion criteria, patients with a diagnosis of primary progressive aphasia (PPA; 3) and with severe forms of dementia were excluded from this study, since they are no longer able to perform comprehensive neuropsychological assessment at baseline. Disease stage was based on clinical assessment and on the accepted Mini-Mental State Examination (MMSE) staging scores (mild 21–26, moderate 11–20, and severe ≤10). The following exclusion criteria adapted from Knopman et al. were also further considered: (1) native language other than European-Portuguese, whenever patients were too severely impaired or presented major expressive language deficits to allow testing at baseline; significant motor, visual or auditory deficits with a possible negative impact in cognition; (2) unequivocal presence of other neurological condition besides FTLD or AD dementia, like neurodegenerative or cerebrovascular disease; prior history of psychiatric disease, including a past history of alcoholism or drug abuse or traumatic brain injury; and (3) lack of a caregiver/informant was also an exclusion criteria because the CDR interview is administered both to the patient and the caregiver.

The control group (CG) was composed of cognitively healthy community-dwelling participants. For exclusion criteria we

**RESEARCH IN CONTEXT**

1. **Systematic review**: The authors reviewed the literature using traditional sources such as PubMed, and meeting abstracts regarding CDR plus NACC FTLD. Because there are no validated disease-staging instruments for use in frontotemporal lobar degeneration (FTLD) adapted for the European-Portuguese population, we intended to validate the CDR plus NACC FTLD for our language and clinical setting. As so, we conducted an exploratory analysis on its psychometric properties, analyzed the performance of the study groups and further evaluated its ability to distinguish between patients with Alzheimer’s disease (AD) and patients with behavioral variant frontotemporal dementia (bvFTD). Several recent publications have described the clinical utility of this rating scale in improving patients’ evaluations. These relevant citations are appropriately cited.

2. **Interpretation**: Our findings showed that the CDR plus NACC FTLD is a psychometrically valid instrument in bvFTD. In addition to this, we found that when taken together, CDR plus NACC FTLD sum-of-boxes, sex, behavior/personality, and language domains achieved the highest model fit in distinguishing between AD and bvFTD. These results are in agreement with previous findings currently published.

3. **Future directions**: The manuscript proposes a framework for the conduct of additional studies with the CDR plus NACC FTLD, namely with patients with primary progressive aphasia variants who deserve a specific characterization. Our findings confirm the good capacity of the FTLD-CDR to identify cognitive impairment in patients with bvFTD and AD dementia as well as its added value in distinguishing between them in our cultural context. Future directions include longitudinal studies in order to confirm the ability to detect clinical decline or improvement as well as the correlation with cerebrospinal fluid and neuroimaging biomarkers.
considered: (1) abnormal scores according to the normative values defined for the Portuguese population on MMSE14 and the Montreal Cognitive Assessment (MoCA15); (2) functional or sensory deficits with a recognized influence on daily living autonomy and testing; (3) clinically significant depressive symptomatology (determined by a Geriatric Depression Scale (GDS) – 30 items, score ≥11 points).16

Previously all participants underwent a baseline NP evaluation, composed of the following instruments: MMSE, MoCA, a comprehensive neuropsychological tool, the Battery of Lisbon for the Assessment of Dementia (BLAD17), and the Disability Assessment for Dementia (DAD) scale.18

The CDR plus NACC FTLD was then administered by a trained neuropsychologist blinded for the diagnosis.

The study was approved by the ethics committee (CE-029/2019) on June 24, 2019; and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was given by all study participants or their legal next of kin.

2.2 Instruments

Clinical Dementia Rating scale (CDR)—The CDR (Morris, 1993).5 is a semi-structured global-functioning measure developed to characterize six domains (memory, orientation, judgment and problem solving, home and hobbies, community affairs, and personal care) of cognition and daily function and also to stage and track the severity/progression of dementia in patients in the AD spectrum. It provides information related to the staging of the disease (CDR global score [CRD-GS]) and also regarding the extent to which the domain is currently impaired, seeming to be a more precise indicator of interindividual and intraindividual changes (CDR sum-of-boxes [CDR-SB]).19

Frontotemporal lobar degeneration-CDR (FTLD-CDR)—An extended version of the standard CDR, which encompasses two additional domains: language and behavior/personality.20 The terminology “FTLD-CDR” has now the updated name of “CDR Dementia Staging Instrument PLUS National Alzheimer’s Coordinating Center (NACC) Behavior and Language Domains (CDR plus NACC FTLD).” Because the standard CDR is now trademarked, this updated terminology for the 8-domain version was proposed by the developers of CDR and the NACC FTLD Module. However, to facilitate comprehension, all references to this 8-domain version will be referred to as the older terminology “FTLD-CDR” hereafter in this article. The behavior/personality and language domains are similar to the standard CDR domains, with each one being rated on a 5-point scale from 0 to 3 [0 = absence of impairment; 0.5 = possible/questionable impairment; 1 = mild impairment; 2 = moderate impairment; and 3 = severe impairment]. We translated and applied the published scoring procedures for both the FTLD-CDR global score (GS) and the sum-of-boxes (SB) score, as they were created among a group of FTLD experts in the ARTFL/LEFFTDS Consortium10;

1. If all domains are 0, the FTLD-CDR GS is 0.
2. If the maximum domain score is 0.5, the FTLD-CDR GS is 0.5.
3. If the maximum domain score is above 0.5 in any domain, then the following applies:
   a. If the maximum domain score is 1 and all the other domains are 0, the FTLD-CDR GS is 0.5.
   b. If the maximum domain score is 2 or 3 and all the other domains are 0, the FTLD-CDR GS is 1.
   c. If the maximum domain score occurs only once, and there is another rating besides zero, the FTLD-CDR GS is one level lower than the level corresponding to maximum impairment.
   d. If the maximum domain score occurs more than once, then the FTLD-CDR GS is that maximum domain score.

2.3 Statistical analysis

Statistical analyses were developed using the SPSS, version 22.0, for Windows. Normal data distribution was assessed through the Shapiro-Wilk normality test. One-way analysis of variance (ANOVA) or Kruskal-Wallis was applied depending on the result of normality testing. For baseline comparison of demographic data between groups, ANOVA, and Pearson’s chi-square test were used, for numerical and nominal data, respectively. The influence of sociodemographic characteristics, as gender, in FTLD-CDR GS and SB scores was addressed with multiple linear regression (MLR) analysis. To investigate FTLD-CDR psychometric properties, namely, internal consistency and unidimensionality, a number of metrics were generated through Rasch analysis (FTD group only) using Winsteps 7; we estimated consistency and dimensionality by a variance analysis (specifically, through item reliability and the standardized residual loading for item). Convergent and construct validity were assessed using Spearman correlation coefficients. Group differences were examined using ANOVA or Kruskal-Wallis test analysis. Multinomial logistic regression analyses were conducted to identify the best contributors in distinguishing between AD dementia and bvFTD. Variables with a regression coefficient associated with P < .05 were considered to be contributing significantly to the prediction of the outcome variable. Receiver-operating characteristic (ROC) curve analysis were performed based on the predicted probabilities derived from the logistic regression models used to distinguish AD dementia and bvFTD. The ROC curves were compared according to the area under the curve (AUC) comparison method of Hanley and McNeil using MedCalc (version 11.6) (MedCalc Software, Mariakerke). Supervised learning models using generalized linear model (binary classification) were applied with a cross-validation method of 5 and reported accuracy and P-value as performance metrics. The predictive models were built under R version 4.1.3.

3 RESULTS

3.1 Sample characterization

Demographic data as well as neuropsychological and clinical features of study participants are given in Table 1. As expected, there were no
TABLE 1  Demographic, neuropsychological, and clinical characterization of the study sample

|                    | CG         | AD dementia | bvFTD      | Differences between groups (P-value) |
|--------------------|------------|-------------|------------|-------------------------------------|
| n                  | 35         | 35          | 35         |                                     |
| Education          | 7.20 ± 3.57| 8.29 ± 4.41 | 7.60 ± 4.07| P = .545                            |
| Age                | 65.54 ± 8.02| 65.26 ± 8.03| 64.55 ± 7.32| P = .884                            |
| Sex (% female)     | 57.1       | 57.1        | 22.6       | P = .005                            |
| Family history (% positive) | 28.6 | 30.3 | 54.8 | P = .039 |
| MMSE score         | 29.11 ± 1.05| 19.77 ± 4.85| 20.97 ± 7.27| P < .001                           |
| MoCA score         | 23.91 ± 3.09| 13.21 ± 3.85| 13.96 ± 4.19| P < .001                           |
| Aβ42 levels        | –          | 510.87 ± 170.35| 822.49 ± 269.70| P < .001 |
| Tau levels         | –          | 652.75 ± 368.09| 377.14 ± 179.58| P = .003                           |
| p-Tau levels       | –          | 109.68 ± 65.63| 44.54 ± 18.31| P < .001                           |

Note: Data are presented as mean ± standard deviation with the exception of gender and family history. Statistically significant differences between the groups are presented in bold.

Abbreviations: CG = Control group; AD dementia = Alzheimer’s disease dementia; bvFTD = behavioral variant Frontotemporal Dementia.

statistically significant differences between the three groups in mean age (65.14 ± 7.75 – results are presented as mean age ± standard deviation, ranging from 51 to 79 years) and mean educational level (7.70 ± 4.01, ranging from 3 to 17 years). According to a post hoc Bonferroni test analysis, we obtained the same pattern for each comparison (mean age: control = AD dementia = bvFTD; mean education level: control = AD dementia = bvFTD). Statistically significant differences were found for gender and family history. Post hoc Bonferroni test analysis showed that the bvFTD group had the smallest percentage of female participants, as well as the highest percentage of participants with a positive family history of dementia. Regarding cognitive screening measures, as expected, statistically significant differences were found in both MMSE and MoCA. Post hoc Bonferroni test analysis showed that the CG had a better performance than both clinical groups on cognitive tests, with equivalent results between bvFTD and AD dementia.

To characterize the influence of age, education, sex and familial history in the results, we correlated the FTLD-CDR GS and SB scores with the above-mentioned sociodemographic and clinical variables. There were no statistically significant correlations between the total scores and the SB scores and age, education, and family history (all p > .05). However, we found that sex was significantly positively correlated with the FTLD-CDR GS (s = .204, P = .042) and SB scores (s = .232, P = .020). These results were confirmed by an MLR analysis (enter method), showing that sex is a significant contributor to the prediction of both scale scores (Table 2). Regarding the total scores, the adjusted R2 value was .048, which means that 4.8% of the variance on the FTLD-CDR GS was explained by sex. The same was observed for FTLD-CDR SB scores, with an adjusted R2 value of .057 (5.7%).

3.2 Psychometric properties

Rasch analysis confirmed that FTLD-CDR fulfills all criteria for a valid scale. Test consistency was excellent (0.99), even higher than Cronbach’s alpha of 0.95. Unidimensionality was low (34%; desired raw variance would be 50%). This was expected because FTLD-CDR is inherently not unidimensional, containing eight different domains. The convergent validity was determined through Spearman correlations between the GS and SB scores of the FTLD-CDR and the DAD, MMSE, and MoCA. We found significant negative correlations (P < .001) between the FTLD-CDR GS and MMSE (s = −0.817) and MoCA (s = −0.834), as well between FTLD-CDR SB and MMSE (s = −0.780) and MoCA (s = −0.790). These results indicate an inverse relationship, that is, the higher the scores on the global staging tool, the lowest performances on the cognitive measures. The same analysis using the DAD total score revealed significant positive correlations (P < .001) for FTLD-CDR GS (s = 0.921) and SB scores (s = 0.915). For construct validity, we explored correlations between the eight domains and the GS of the FTLD-CDR. In the total sample, the coefficients ranged between s = 0.951 (Memory) and s = 0.686 (language), all P’s < .001. In the AD dementia group, these correlations ranged between s = 0.814 (P < .001; Memory) and s = 0.335 (P = .049; behavior/personality). In the bvFTD group, the coefficients ranged between s = 0.747

TABLE 2  MLR analysis for sex

| Variable           | Unstandardized coefficients | Standardized coefficients |
|--------------------|------------------------------|---------------------------|
| FTLD-CDR GS*       | .297                         | .219                      |
| Sex                | .134                         | .187                      |
| FTLD-CDR SB*       | .215                         | .239                      |
| Sex                | .882                         | .221                      |

Abbreviations: B, unstandardized coefficient; Std. Error, standard error of B; β, beta.

*R² = .048; F(2, 103) = 4.918, P = .029.
†R² = .057; F(2, 103) = 5.939, P = .017.
The variables were retained in Model 2 (Akaike Information Criterion (AIC) = 79.3), we included the behavior/personality domain to the first model, and all variables were retained in Model 2 (AIC = 52.0): FTLD-CDR SB (P = .001), sex (P = .004), and behavior/personality (P < .001). Because language was the only other domain that allowed the distinguishing between AD dementia and bvFTD, we created Model 3 (AIC = 76.7), encompassing FTLD-CDR SB, sex, and language, with the three variables being retained (P = .001; P = .004; P < .001, respectively). Model 4 (AIC = 47.7) was then created including the FTLD-CDR SB, sex, behavior/personality, and language. All variables were retained in the model (P = .001 and P = .004, respectively and P < .001 for the last two), showing a significantly better fit than the remaining three models (74.2 for Model 1, 86.4 for Model 2, 77.3 for Model 3, and 92.4 for Model 4), as the 2 log-likelihood or deviance (a measure for unexplained variance) was lower.

We then compared the ROC curves of the predicted probabilities derived from the four logistic regression models (Figure 1). Statistically significant differences of 0.143 were seen between the AUC of Model 1 and Model 3 (P = .001), which means that adding the behavior domain increases the ability to differentiate the two groups. Conversely, a significant difference of 0.166 between the AUC of the Model 1 and Model 4 (P = .0016) shows that both behavior and language add diagnostic accuracy to the model. The difference between Model 3 and Model 4 was 0.0959 (P = .0249), pointing out that even when language is already included in the models the further addition of behavior still has added value. No differences were found between the AUC of Model 1 and Model 3 (P = .0587) and Model 2 and Model 4 (P = .2406), implying that adding the language domain does not improve the discrimination ability alone or when behavior is already included in the models.

A cross-validation study showed that the best classification models was Model 2 (Accuracy = 0.78, P = .003), and in Model 4 there was a perfect separation between AD and FTD.

### 3.3 Group differences

We conducted an ANOVA to analyze the differences between diagnostic groups on CDR-GS/CDR-SB and FTLD-CDR-GS/SB scores as well as with each one of the eight domains. As expected, we observed statistically significant differences between the three groups in both CDR, CDR-SB, FTLD-CDR-GS, and SB scores, as well as in the respective eight domains (see Table 3). According to post hoc analysis, the CG obtained the lower total scores in all measures and the bvFTD group obtained the highest total scores in all measures, except in the Orientation domain, where the AD dementia group attained the higher total scores.

All the eight domains were able to distinguish controls from bvFTD and from AD dementia as well as from the Dementia-combined group. However, only the FTLD-CDR SB, the behavior/personality, and the language domains allowed distinguishing between clinical groups.

As so, logistic regression models were employed to identify the best contributors in distinguishing between AD dementia and bvFTD. In Model 1 (Akaike Information Criterion (AIC) = 79.3), we included FTLD-CDR SB and sex, and we verified that both variables significantly contribute to the model (P = .001 and P = .004, respectively). We then added the behavior/personality domain to the first model, and all the variables were retained in Model 2 (AIC = 52.0): FTLD-CDR SB (P = .001), sex (P = .004), and behavior/personality (P < .001). Therefore, statistically significant differences were found between the AUC of Model 1 and Model 3 (P = .0249), implying that adding the behavior domain increases the ability to differentiate the two groups. Conversely, a significant difference of 0.166 between the AUC of the Model 1 and Model 4 (P = .0016) shows that both behavior and language add diagnostic accuracy to the model. The difference between Model 3 and Model 4 was 0.0959 (P = .0249), pointing out that even when language is already included in the models the further addition of behavior still has added value. No differences were found between the AUC of Model 1 and Model 3 (P = .0587) and Model 2 and Model 4 (P = .2406), implying that adding the language domain does not improve the discrimination ability alone or when behavior is already included in the models.

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### Table 3 Characterization of the groups on CDR and FTLD-CDR

|               | CG          | AD dementia + bvFTD | AD dementia | bvFTD | Differences between groups (P-value) |
|---------------|-------------|---------------------|-------------|-------|-------------------------------------|
| n             | 35          | 70                  | 35          | 35    |                                     |
| CDR           | 0 ± 0.00    | 1.01 ± 0.40         | 0.91 ± 0.35 | 1.12 ± 0.43 | **P < .001; P < .001; P = .659; P < .001** |
| CDR-SB        | 0 ± 0.00    | 5.43 ± 2.84         | 4.86 ± 2.28 | 6.10 ± 3.29 | **P < .001; P < .001; P = .375; P < .001** |
| FTLD-CDR GS   | 0 ± 0.00    | 1.08 ± 0.55         | 0.94 ± 0.40 | 1.23 ± 0.67 | **P < .001; P < .001; P = .590; P < .001** |
| FTLD-CDR SB   | 0 ± 0.00    | 7.15 ± 3.65         | 5.80 ± 2.72 | 8.73 ± 3.98 | **P < .001; P < .001; P = .042; P < .001** |
| Memory        | 0 ± 0.00    | 1.05 ± 0.46         | 0.96 ± 0.33 | 1.17 ± 0.56 | **P < .001; P < .001; P = 1.000; P < .001** |
| Orientation   | 0 ± 0.00    | 0.75 ± 0.55         | 0.79 ± 0.49 | 0.72 ± 0.61 | **P < .001; P < .001; P = 1.000; P < .001** |
| Judgement and problem solving | 0 ± 0.00 | 1.15 ± 0.78         | 0.99 ± 0.43 | 1.35 ± 0.67 | **P < .001; P < .001; P = .422; P < .001** |
| Community affairs | 0 ± 0.00 | 0.82 ± 0.51         | 0.76 ± 0.49 | 0.88 ± 0.52 | **P < .001; P < .001; P = 1.000; P < .001** |
| Home and Hobbies | 0 ± 0.00 | 0.97 ± 0.63         | 0.81 ± 0.50 | 1.15 ± 0.72 | **P < .001; P < .001; P = .470; P < .001** |
| Personal Care  | 0 ± 0.00    | 0.67 ± 0.73         | 0.54 ± 0.66 | 0.80 ± 0.81 | **P < .001; P < .001; P = .544; P < .001** |
| Behavior/personality | 0 ± 0.00 | 1.07 ± 0.76         | 0.56 ± 0.47 | 1.68 ± 0.59 | **P < .001; P < .001; P < .001; P < .001** |
| Language      | 0 ± 0.00    | 0.68 ± 0.69         | 0.39 ± 0.61 | 1.02 ± 0.62 | **P < .001; P < .001; P < .001; P < .001** |

Note: Data is presented as mean ± standard deviation. Statistically significant differences between the groups are presented in bold.

*CG vs AD dementia.
*CG vs AD dementia + bvFTD.
*AD dementia vs bvFTD.
*CG vs bvFTD.
There is a growing interest in the identification of persons at risk for FTLD as well as for the predictors of progression from prodromal stages to FTLD dementia, since innovative mutation-target treatments are already available. The FTLD-CDR is currently being used as the primary outcome measure in clinical trials in FTLD.

The aim of the present study was to validate the European-Portuguese version of the FTLD-CDR. We conducted an exploratory analysis on its psychometric properties, analyzed the performance of the study groups, and further evaluated its ability to distinguish between AD dementia and bvFTD patients compared to the standard CDR. Patients with PPA were excluded due to application limitations and also because, in our opinion, these variants deserve a specific evaluation comparing progressive non-fluent aphasia (PNFA) and semantic dementia related to FTD with logopenic aphasia related to AD, which is beyond the scope of this study.

The exploration of the psychometric properties is critical to guarantee that the results are fully adequate for the aims of the study and to ensure that the instrument will provide with appropriate values of diagnostic acuity, allowing its optimal use in both clinical and research contexts. Our results showed that the FTLD-CDR is a psychometrically valid instrument in bvFTD. It presents excellent values of test consistency (0.99), which would not improve with the exclusion of any domain, settling the adequacy of this global staging instrument to examine European-Portuguese patients. Concurrent validity should be ideally explored with another global staging tool, so we used the DAD scale and as expected significant positive correlations were found for both GS and SB scores (all \(P < .001\)). In addition to this, we explored the correlation between the FTLD-CDR and the most used cognitive screening measures, the MMSE and the MoCA, confirming significant negative correlations between them (\(P < .001\)). Construct validity was also assessed through the correlation between the FTLD-CDR GS and SB and each one of the eight domains. With the exception of language in the AD dementia group, all the correlations were significant and positive, emphasizing that each domain had a statistically significant contribution for the structure of the scale. This comprehensive evaluation of psychometric proprieties of the FTLD-CDR shows that it is a reliable tool in the diagnostic process of bvFTD.

Previous studies with the European-Portuguese population have already highlighted the influence of sociodemographic and clinical variables on NP results. According to our findings, age and education were not significant predictors of FTLD-CDR scores. We believe that the main reason for this discrepancy was the patients’ matching according to age and educational level. Besides, CDR, contrary to neuropsychological instruments, was developed as a global staging scale and is largely dependent on caregivers/informants’ judgment. Moreover, MLR analysis showed that sex was the only significant predictor of the results, explaining 4.8% of the variance on the FTLD-CDR GS and 5.7% on the SB. This may suggest that the performance on the FTLD-CDR is influenced by gender asymmetries regarding the performance of core daily activities. We speculate that the female advantage is caused by gender-specific cultural and life circumstances/activities that are manifest in this generation of elderly Portuguese persons and further transposed for functional scales.

Regarding the differences between groups, only the FTLD-CDR SB, behavior/personality, and language domains could differentiate the clinical groups. These results corroborate and extend the findings of Miyagawa et al. since they presented a Kruskal-Wallis analysis for only the two newly added domains. Then, we included these three
variables in multinomial logistic regression models to identify the best contributors in the distinguishing between AD dementia and bvFTD. Our results showed that Model 4, which includes FTLD-CDR SB, sex, behavior/personality, and language, achieved the highest Model fit of 92.4%. These results are in agreement with Knopman et al.,26 who also performed a logistic regression compared to the behavior/personality. Our results are fully in agreement, since our sample did not include FTLD-related aphasic variants. The comparison between the AUCs (and AICs) of Models 1 (FTLD-CDR SB + sex + behavior) and Model 3 (FTLD-CDR SB + sex + language) show that the behavior/personality domain is a better isolated disease classifier between AD dementia and bvFTD when compared to the language domain. This was not completely surprising, since our sample did not include FTLD-related aphasic variants. The comparison between the AUCs (and AICs) of Models 2 (FTLD-CDR SB + sex + behavior) and Model 4 (FTLD-CDR SB + sex + language + behavior) show that adding the behavior/personality domain always improves the model fit. The same pattern was not observed with the addition of the language domain, since the comparison between Models 2 and 4 is not significant, possibly suggesting that the language domain is composed of more heterogeneous data when compared to the behavior/personality. Our results are fully in agreement with Miyagawa et al.,26 who also performed a logistic regression analysis encompassing the above-described domains, concluding that the CDR SB alone was not a good instrument in discriminating the two clinical groups, and that adding the behavior/personality domain with or without language significantly enhanced its discriminative ability.

The main limitation of our study is the cross-sectional design, without longitudinal follow-up evaluating sensitivity to disease progression. However, previous studies with the FTLD-CDR already showed that the newly added behavior/personality and language domains are able to detect changes over 1 year in patients with bvFTD and PPA.13,20,26 In addition, we did not perform interrater agreement for FTLD-CDR administration. This study was developed in the context of a memory clinic, so additional studies are needed to confirm the added value of FTLD-CDR in other clinical settings. The same applies to the sub-group of primary progressive aphasia, which deserves a specific characterization. We point out the important strengths: (1) it is a homogeneous group and diagnosis was made by consensus according to the most recent international criteria2,11; (2) the clinical groups were studied extensively and fully characterized with neuropsychological, neuroimaging, and available disease biomarkers.27 (3) the groups were equivalent in mean age and educational level, reducing the possible biases in inter-individual and inter-group variability; and also (4) the differential diagnosis between FTD and AD dementia was always supported by CSF biomarkers or amyloid-PET imaging.28

Our findings confirm the good capacity of the FTLD-CDR to identify cognitive impairment in patients with bvFTD and AD dementia as well as its added value in distinguishing between them in our cultural context. Future directions include longitudinal studies in order to confirm the ability to detect clinical decline or improvement as well as the correlation with CSF and/or neuroimaging biomarkers.

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CONFLICTS OF INTEREST

Dr. Knopman serves on a Data Safety Monitoring Board for the DIAN study. He served on a Data Safety Monitoring Board for a tau therapeutic for Biogen but received no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Magellan Health, and Alzecca Biosciences but receives no personal compensation. He receives funding from the National Institutes of Health (NIH). The remaining authors have nothing to disclose.

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

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