

**Validity and reliability of the Frontotemporal Dementia Rating Scale (FTD-FRS)  
for the progression and staging of dementia in Brazilian patients.**

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## ABSTRACT

**Introduction:** Few studies on instruments for staging FTD have been conducted. **Objective:** To analyze the factor structure, internal consistency, reliability and convergent validity of the Brazilian version of the Frontotemporal Dementia Rating Scale (FTD-FRS). **Methods:** 97 individuals aged  $\geq 40$  years with  $> 2$  years' education took part in the study, 31 patients diagnosed with behavioral variant FTD (bvFTD), 8 patients with primary progressive aphasia (PPA), 28 with AD, 8 with mild cognitive impairment (MCI), and a control group of 22 healthy subjects. The FTD-FRS was completed by family members or caregivers and Neurologists completed the 8-item CDR-FTLD scale (six original domains plus Language and Behavior). The AD and FTD patients had equivalent disease severity level. **Results:** The internal consistency of the FTD-FRS, estimated by Cronbach's alpha, was 0.975 while test-retest reliability was 0.977. Scree plot and exploratory factor (Varimax rotation) analyses revealed the existence of four factors, with eigenvalues  $>1$ , which together explained 77.13% of the total variance with values of 1.28 to 17.52. The domains of the Brazilian version of the FTD-FRS scale correlated with the domains of the CDR-FTLD. **Conclusions:** The present study is the first to document the factorial structure of the FTD-FRS and its convergent validity with the CDR-FTLD. These tools are key to determine dementia severity in FTD. The Brazilian FTD-FRS demonstrated adequate psychometric properties for use in Brazil. This instrument may contribute to disease staging in FTD and may help to document intervention-related changes.

*Key words:* staging, dementia progression, frontotemporal dementia, behavioral variant frontotemporal dementia, primary progressive aphasia.

## Introduction

Staging of dementia allows better management of the clinical condition and can help reduce caregiver dependency and burden<sup>1,2</sup>. Dementia severity assessment scales can be more suitable for monitoring the course of symptoms of neurodegenerative diseases than brief cognitive assessment measures, such as the MMSE, or neuropsychological assessment<sup>3</sup>. However, scales for staging dementia were developed based on symptoms of Alzheimer's Disease (AD) and are potentially less sensitive to the progression observed in other dementias<sup>4</sup>.

Currently, the most widely used dementia staging scale worldwide is the Clinical Dementia Rating (CDR)<sup>5,6</sup>. This is a semi-structured interview performed with both patient and their caregiver that collects information on six functional domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Each domain is rated as 0, 0.5, 1, 2 and 3, where higher scores indicate worse functioning in the domain. All the domains taken together yield a global CDR score also ranging from 0 to 3<sup>5</sup>, with 0 indicating no impairment, 0.5 questionable impairment, 1.0 mild impairment, 2.0 moderate impairment and 3.0 severe impairment.

More recently, a CDR version was devised that includes two additional domains which are often impaired in frontotemporal dementia (FTD), namely, language and behavior, forming the Clinical Dementia Rating Scale for FTLD (CDR-FTLD)<sup>7</sup>. These new domains provide information on the specific symptoms of the variants of FTD, i.e. the primary progressive aphasia (PPA) and behavioral variant frontotemporal dementia (bvFTD), which can significantly impact severity assessment of these conditions<sup>8</sup>. In other words, individuals with FTD may be defined as having questionable or mild impairment on the CDR in the absence of assessment of these additional domains.

Given the need to develop specific instruments for staging typical symptoms of FTD variants, Mioshi et al.<sup>4</sup> developed the Frontotemporal Dementia Rating Scale (FTD-FRS). The FTD-FRS was structured based on the questions from the Disability Assessment For Dementia (DAD) functional scale<sup>9</sup> and the Cambridge Behavioral Inventory (CBI)<sup>10,11</sup>, producing a 75-item questionnaire covering behavioral disorders and functional disability. The new instrument was applied in a sample of 77 FTD patients (behavioral variant=29; semantic variant=28; non-fluent variant=20), matched for age and length of symptoms. After analysis of the psychometric characteristics and

construct validity for staging the dementia condition, the scale was shortened to 30 items.

In the study by Mioshi et al.<sup>4</sup>, six stages of severity were identified by the scale (very mild, mild, moderate, severe, very severe and advanced/profound). The FTD-FRS was capable of detecting functional deterioration in the three clinical variants of FTD over 12 months. The decline in FTD-FRS over this period was found to differ across the FTD subtypes, where bvFTD progressed the most rapidly. Lastly, the scale was useful for assessing progression given that length of behavioral symptoms and global cognitive assessments, alone, do not reflect severity in FTD. The internal consistency with Cronbach's alpha was 0.93 and stability on the test-retest was 0.994, suggesting good psychometric characteristics.

Turró-Garriga et al.<sup>12</sup> carried out the translation and adaptation of the FTD-FRS into Spanish. The authors recruited 82 patients, comprising 60 with bvFTD and 22 with AD. The Spanish-language version of the FTD-FRS displayed good internal consistency ( $\alpha = 0.897$ ) and strong correlation with the MMSE, DAD and CDR. The severity of dementia was rated as more severe by the FTD-FRS than by the CDR.

The FTD-FRS has been translated and adapted into Portuguese for use in Brazil. After back-translation, pilot application and assessment by specialist judges, the final version of the scale was produced<sup>13</sup>. Application of this version of the FTD-FRS in a pilot study suggested the scale is adequate for use in Brazil. However, no studies assessing the validity of the Brazilian version of the scale have been conducted. Therefore, the objective of the present study was to examine the factor structure, internal consistency, temporal stability and convergent validity with the MMSE and CDR-FTLD.

## **Methods**

This is a cross-sectional analysis based on the initial dataset of a clinical study including healthy controls (HC), bvFTD, AD, PPA and mild cognitive impairment (MCI) patients.

## **Participants**

Databases from university-based neurology outpatient services were consulted and patients and their caregivers were invited to take part in the study, at the following institutions: Cognitive and Behavioral Neurology Group (GNCC-SP) and Program for

the Elderly (PROTER) at the University of São Paulo; Cognitive and Behavioral Neurology Group (GNCC-MG) at the Federal University of Minas Gerais and the Department of Neurology at the State University of Campinas (UNICAMP). HC participants were recruited from an Open University for the Third Age.

The diagnosis of dementia patient was performed by neurologists, geriatricians and psychiatrists, based on clinical and cognitive assessments along with laboratory and neuroimaging exams. Dementia was diagnosed based on the criteria from the Diagnostic and Statistical Manual 5<sup>th</sup> Edition (DSM-V)<sup>14</sup>. International diagnostic criteria were employed for diagnosing probable bvFTD<sup>1</sup>. The National Institute on Aging- Alzheimer's Association- NIA/AA criteria were used for AD diagnosis<sup>16, 17</sup>. Patients at mild and moderate stages (CDR 0.5-2.0) of bvFTD<sup>1</sup> and AD<sup>5,6</sup> were selected. The criteria recommended by Gorno-Tempini et al. were used for diagnosing semantic and non-fluent variants of FTD<sup>18</sup>. MCI (amnesic and non-amnesic) were diagnosed based on the criteria of Albert et al.<sup>19</sup>.

Inclusion criteria for patients were age >40 years, education >2 years and presence of an informant who was involved in the daily routine of the patient (formal or informal caregiver, spending at least 8 hours/day with the patient). Individuals presenting with visual, auditory or motor deficits preventing them from understanding instructions or performing cognitive tasks; individuals with other uncontrolled clinical diseases (such as hypertension and diabetes); serious and debilitating psychiatric disorders such as major depression, schizophrenia, bipolar disorder; clinical evidence or neuroimaging exam findings suggestive of vascular problems; dementias or etiologies other than FTD or AD, were excluded.

For the control group, participants that were illiterate, scored > 5 on the Geriatric Depression Scale (GDS)<sup>20</sup> or whose performance on the MMSE was below the cut-off point for dementia<sup>21</sup> were excluded. The following cut-off points were adapted for educational level: 1-4 years' education, 22 points; 5-8 years, 24 points; > 8 years, 26 points. These cut-off scores were adapted from Brucki et al.<sup>21</sup> based on the mean for each educational band minus one standard deviation. Additionally, subjects exhibiting functional changes suggestive of dementia on the Functional Activities Questionnaire (FAQ>2)<sup>22,23</sup> were also excluded.

Caregivers included in the study were mostly women, with mean age of 54.1 (SD ± 15.4) and mean educational level of 12.9 (SD ± 3.8).

## **Instruments**

### **Patient protocol**

A questionnaire collecting sociodemographic and clinical data including age, income, years of education, marital status, general health status, presence of other clinical disease and use of medications was applied. This block of the protocol was applied to controls and caregivers of dementia patients.

### Cognitive assessment

The Addenbrooke's Cognitive Examination-Revised ACE-R<sup>24,25</sup> was used and provided scores for the MMSE. The maximum score is 100 points, distributed among the domains: attention and orientation (18), memory (35), verbal fluency (14), language (28) and visual-spatial ability (5). The cut-off point for dementia on the battery is 78 points (Brazilian version)<sup>25</sup>.

### **Family member/companion protocol**

#### Functional Assessment

The FAQ is based on an indirect assessment of patient functioning. The scale comprises ten items that investigate the degree of independence for performing activities of daily living. The minimum score is zero and maximum 30 points where higher scores indicate greater degree of dependency of the patient<sup>22,23</sup>.

#### Dementia staging scales

The CDR-FTLD version adapted by Knopman et al.<sup>1</sup> was used. This version of the scale includes the assessment of the domains memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care from the original, plus the domains of language and behavior. Part of the assessment is performed with the patient while a complementary semi-structured interview is conducted with their companion. Based on the data collected, the clinician rates each domain with scores of 0, 0.5, 1, 2 and 3, and finally provides a global rating of the patient's cognitive status using this same rating scale for total score. The CDR-FTLD sum of boxes scores was also employed in this study.

The FTD-FRS assesses the domains: Behavior, Outing and Shopping, Household chores (use of Telephone, Finances, Medications, Meal Preparation), Self-care and Mobility. Response options for each question are: All the time=0;

Sometimes=0 and Never=1. The “Never” answers are tallied and divided by the number of questions (ranging from 0-30) answered by the interviewee, multiplied by 100 (number of “Never” responses/number of questions answered x 100) to give a score in percent which using a logarithm Table indicates the disease stage of the patient<sup>4,13</sup>. A total raw score of 30 is obtained, which is then converted into a logit score that ranges from 5.39 normal to -6.66 advanced/profound impairment. The score indicates six stages of severity: very mild, mild, moderate, severe, very severe and advanced/profound.

The Brazilian version of FTD-FRS was generated after a translation and cross-cultural adaptation processes which consisted of the following steps: translation, back-translation (prepared by independent translators), evaluation of the back-translated version against the original version, discussion of the Portuguese version of the FTD-FRS with specialists, development of a final version after minor adjustments, and pilot application in patients with a diagnosis of bvFTD and AD. This procedure has been described in detail in a previous study<sup>13</sup>.

## **Procedures**

Data collection took place at the research centers involved in a room reserved for this purpose offering suitable lighting and acoustic conditions. Application of the protocol took around 60 minutes for patients and 45 minutes for healthy subjects. The interview with informants took around 45 minutes. The protocol was applied by previously trained examiners.

## **Ethical aspects**

This study was approved by the Ethics Committee for Analysis of Research Projects (CAPPesq) of the Medical Board of the Clínicas Hospital and of the University of São Paulo School of Medicine, permit 311.601. All participants and their caregivers signed the Free and Informed Consent Form (TCLE) and were given explanations on the study procedures. The study was conducted in compliance with International ethics standards (Declaration of Helsinki).

## Statistical analyses

The Kolmogorov-Smirnov test confirmed that cognitive, functional and dementia staging variables did not have a normal distribution and non-parametric tests were therefore used for these variables. The Chi-square test was employed to compare the categorical variables among diagnostic groups. Kruskal-Wallis tests were used to make dementia subgroup comparisons in regards to age, years of education, and clinical variables such as ACE-R, MMSE, PFAQ and staging tools. Mann-Whitney tests were used for post hoc analyses. When the Kruskal-Wallis test was significant, means were compared with the Bonferroni multiple comparisons test. Spearman's correlations were used to analyze the relationship among the variables.

The data from the 97 participants for the 30 items of the FTD-FRS were submitted to Exploratory Factor Analysis using the common factor model. This model holds that the variance observed in each measurement can be attributed to a relatively small number of common factors (i.e. common characteristics not observable in two or more variables) and to a single specific factor (not related with any other underlying factor from the model). Thus, the aim of exploratory factor analysis, with a common factor model, is to identify the common factors (separate from specific factors) and explain their relationship with the data observed. Varimax rotation was chosen in order to maximize the power of discrimination among the factors.

Additionally, Cronbach's  $\alpha$  coefficient was calculated to analyze the internal consistency of the FTD-FRS and its domains. In a subsample of 22 healthy control subjects, temporal stability was tested by comparing FTD-FRS scores obtained in two applications (test and retest) with an interval of approximately two months ( $M=7.2$  weeks,  $SD=1.8$ ), using two-way mixed intraclass correlation coefficient with absolute agreement.

The data were keyed into Version 3.1 of the Epidata Program. All statistical analyses were performed using the SPSS v.17.0 and Statistica v.7.0 software packages. The level of significance adopted for the statistical tests was 5%, (i.e. a  $p\text{-value}<0.05$ ).



## Results

### Sociodemographic and clinical data of the studied sample

A total of 97 individuals, comprising 31 diagnosed with bvFTD, 8 with PPA (semantic variant n=3 and non-fluent variant n=5), 28 with AD, and 8 with MCI, and a control group of 22 healthy subjects. Family members or caregivers who had frequent contact with the patient also took part. The patients with bvFTD and with AD had equivalent disease severity on the CDR-FTLD. The sociodemographic and clinical characteristics of the sample are given in Table 1. Patients with AD and PPA had worse performance on the MMSE and ACE-R relative to participants of the other groups.

### Insert Table 1

Scores on the CDR-FTLD and FTD-FRS for the groups are given in Table 2. A significant difference was found among the groups on the CDR-FTLD and FTD-FRS, indicating greater severity in patients diagnosed with bvFTD.

### Insert Table 2

### Indicators of construct validity

In order to achieve one of the objectives of the study, Bartlett's test of Sphericity and the Kaiser-Meyer-Olkin (KMO) test were performed. The results indicated correlation among the items assessed on the FTD-FRS ( $\chi^2$ [df=435]= 2261.91;  $p < 0.001$ ) and sampling adequacy (KMO=0.715), respectively, for performing the exploratory factor analysis below.

The exploratory factor analysis (with Varimax rotation) of the FTD-FRS revealed the existence of four factors, with *eigenvalues* >1, which together explained 77.13% of the total variance with values from 1.28 to 17.52 (see Table 3).

### Insert Table 3

The factor loadings matrix (i.e. the matrix whose values are the correlations among the original variables and common factors) for the four-factor solution is given

in Appendix A. The criteria for belonging to the factor was having a loading  $\geq 0.50$ <sup>26-27</sup>. Factor 1 is associated with behavior, Factor 2 self-care and mobility, Factor 3 meal preparation, and Factor 4 to outings and shopping, household chores, finances and medications.

The results of the analysis of the internal consistency of the factors found are given in Table 4. The overall instrument and each factor exhibited high consistency ( $> 0.90$ ) and the removal of items with lower factor loadings was not beneficial since it reduced the coefficients. The analysis of temporal stability yielded a Kappa index of 0.97 (p value  $< 0.001$ ) suggesting high stability<sup>26,27</sup>.

#### **Insert Table 4**

#### **Convergent validity of the FTD-FRS with the CDR-FTLD**

Correlations of the factors of the FTD-FRS with the subdomains of the CDR-FTLD scale are given in Table 5. The four proposed domains of the FTD-FRS showed significant correlations with the subdomains of the CDR-FTLD scale.

#### **Insert Table 5**

#### **Discussion**

The objective of the present study was to examine the factor structure, internal consistency, temporal stability and convergent validity of the Brazilian version of the FTD-FRS. This is the first study that carried out an exploratory factorial analysis of the items composing the FTD-FRS. It is also the first to perform a convergent validation analysis with the CDR-FTLD and another scale specific for dementia staging for the DFT spectrum.

#### **Clinical findings**

Descriptive analyses suggested the CDR-FTLD appeared to underestimate the severity of dementia in bvFTD, as a substantial proportion of the patients rated as mild on the scale (CDR=1.0) had moderate or severe impairment according to the FTD-FRS. This finding supports recent evidence that the FTD-FRS may capture subtle changes associated with disease progression<sup>4</sup> that may not be observed when the original CDR

is used<sup>4, 13</sup>. However, in a more recent study<sup>8</sup>, the CDR-FTLD, which includes language and behavior domains, was also shown to be sensitive for documenting decline in patients with FTD but a direct comparison between the FTD-FRS and the CDR-FTLD is yet to be conducted.

In a previous imaging study<sup>28</sup>, where the CDR-FTLD and FTD-FRS were correlated with brain perfusion in patients diagnosed with FTD, both scales were predictors of frontal lobe perfusion in the bvFTD patient group and predictors of temporal hypoperfusion in the PPA group. In the study, the authors considered the scales adequate for documenting severity in FTD.

### **Psychometric characteristics of the FTD-FRS**

In the original FTD-FRS design and validation study<sup>4</sup>, the authors aimed to divide the questions by domains to facilitate their application in clinical practice. The scale in its original form contains 30 items organized into seven domains. The current exploratory factor analysis of the FTD-FRS identified the possibility to reduce the number of domains to four. In this new format, the first domain or Factor 1, with 6 items (factor loadings of 0.67-0.81) is associated with behavior changes. The second domain or Factor 2, with 4 items (factor loadings of 0.81-0.85), is related to self-care and mobility. The third domain or Factor 3, comprising 8 items (factor loadings of 0.60-0.87), is linked to meal preparation. Lastly, the fourth domain or Factor 4, comprising 12 items (factor loadings of 0.50-0.81), relates to outings and shopping, household chores, finances and medications. The high eigenvalues observed in the scale domains may reflect the behavioral changes of the sample which impact the basic and instrumental activities of daily living<sup>26-27</sup>, contemplated in FTD-FRS items<sup>4, 12, 13</sup>.

The four observed domains of the FTD-FRS correlated with the domains of the CDR-FTLD, consistent with a previous study<sup>12</sup>. These results indicate the convergent validity of the Brazilian version of the scale, according to the present exploratory factor analysis.

The results for the internal consistency and reliability on the test-retest analyses suggested construct validity and temporal stability, congruent with the previous findings<sup>4, 12</sup>. The FTD-FRS is a recent scale and hence there are few studies investigating its psychometric characteristics. The present study is the first to document the factorial structure of the FTD-FRS and its convergent validity with the CDR-FTLD. These tools are key to determine dementia severity in FTD variants.

Determining disease severity in dementia, and especially in less prevalent subtypes, is still a controversial issue. There is currently a lack of consensus regarding the definition of severity in dementia and its ideal staging tools<sup>29</sup>. Cognitive-based staging strategies are limited, since they are heavily dependent on language skills, which might overestimate disease severity, as observed in primary progressive aphasia<sup>30</sup>. Additionally, in developing countries, cutoff scores in cognitive tests are unsuitable for dementia staging because of great variability in educational background. The FTD-FRS may provide a better understanding of disease progression in FTD, by showing which abilities are lost early and late in the disease, as it relies on collateral information<sup>12</sup>.

The present study has some limitations, including the fact that the sample studied was derived from a specialized outpatient clinic for cognitive disorders in adults and elderly and may possibly have contained a high proportion of individuals with specific needs or more severe symptoms. This might have introduced biases that could reduce the generalizability of results to other populations.

In summary, the results suggest that the Brazilian FTD-FRS has satisfactory psychometric properties for clinical use. This instrument may aid in characterizing clinical symptoms relevant for diagnosis and disease staging. It may also document intervention-related outcomes. This study provides clinicians and researchers with a valid instrument with which to classify and follow up on patients diagnosed with FTD. The drafting of a severity scale adapted to the symptoms typical of FTD may facilitate early identification of these conditions and reduce delays between symptom onset and diagnosis. It would also aid in the selection and use of drug treatments, and implementing care. The FTD-FRS is a tool able to improve clinical attention to patients (and their family members), whether in the initial or terminal stages of FTD.

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