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Research Article

Psychometric Validation of the Frontal Systems Behaviour Scale in Greek patients with Neurodegenerative Diseases

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Abstract

Background: The Frontal Systems Behaviour Scale (FrSBe) is a widely used tool for the assessment of behavioural problems in neurodegenerative disorders with frontal- system dysfunctions, including apathy, disinhibtionsinhibition and executive problems. Nevertheless, evidence of the scale for the Greek clinical population remains limited. The current study aimed to investigate the known-groups validity of the FrSBe by examining its ability to differentiate among patients with Alzheimer's disease (AD), behavioural variant frontotemporal dementia (bvFTD), semantic variant frontotemporal dementia (svFTD), and healthy groups. Another aim was to examine the validity of the FrSBe through its association with the Neuropsychiatric Inventory (NPI).

Methods: A total of 226 participants (N=226) were included. FrSBe subscales and total scores were compared across diagnostic groups and healthy controls. Receiver Operating Characteristic (ROC) analyses were conducted to assess the discriminative ability of the scale, and correlations between FrSBe and NPI scores were also examined.

Results: Patients with AD, svFTD, and bvFTD demonstrated significantly higher FrSBe scores than healthy controls. Compared with the FTD groups, patients with AD exhibited significantly lower levels of apathy, disinhibtionsinhibition, executive dysfunction, and total behavioural disturbance. Associations were also observed between FrSBe scores and multiple NPI domains (such as apathy, disinhibtionsinhibition, irritability, agitation, aberrant motor behaviour, and total NPI scores). ROC analyses demonstrated satisfactory ability of the FrSBe to discriminate between patients with neurodegenerative diseases and healthy controls.

Conclusions: The findings are in accordance with the literature. FrSBe demonstrated satisfactory ability to distinguish healthy groups from patients with neurodegenerative diseases. The FrSBe is a useful tool for assessing behavioural disturbances in neurodegenerative diseases and distinguishing clinical from healthy controls. Further research is needed to establish its diagnostic accuracy across neurodegenerative disorders.

Keywords: FrSBe; NPI; Apathy; Disinhibition; Dysexecutive; Dementia

Introduction

Neurodegenerative disorders are characterised by progressive loss of neurons and neuronal function. The neurons have limited capacity for regeneration and replacement, leading to multiple and severe cognitive, behavioural and motor problems [1]. They can be classified based on clinical manifestations, including cognitive disorders, extrapyramidal disorders, frontotemporal degenerations, or motor neuron disease. The most common neurodegenerative diseases from a neuropathological perspective are amyloidopathies, α- synucleinopathies, TDP-43 proteinopathies and tauopathies [1]. They are a heterogeneous group of disorders, which affect the quality of life of the patients and their caregivers globally. Nowadays, 57 million patients worldwide are affected by dementia and other neurodegenerative diseases and due to increasing life expectancy, the number is estimated to exceed 115.4 million by 2050 [2].

Dysfunction of the frontal lobes has been associated with a broad spectrum of behavioural symptoms, such as apathy, disinhibtionsinhibition and executive dysfunction [3]. These symptoms are often reported in patients with neurodegenerative diseases, including Alzheimer's disease (AD), Frontotemporal Dementia (FTD) and Parkinson's dementia (PDD) [3]. Specifically, apathy is characterised by diminished motivation, reduced activity and lack of emotional engagement [4]. Disinhibtionsinhibition is characterised by impaired social skills and impulsivity [5]. Executive dysfunction refers to cognitive and behavioural deficits in domains such as planning, cognitive flexibility, response inhibition, self- monitoring, sequencing and goal- directed behaviour [6].

However, a crucial point is that behavioural symptoms vary across neurodegenerative diseases. Specifically, patients with behavioural variant frontotemporal dementia (bvFTD) typically suffer from disinhibtionsinhibition, apathy and executive deficits. On the other hand, patients with Alzheimer's disease (AD) typically have less severe behavioural problems, during the early stages of the disease. Patients with Semantic variant frontotemporal dementia (svFTD) often experience behavioural changes, such as loss of empathy, strict routines and dietary changes, that differ from those observed in AD and bvFTD [7]. Thus, tools assessing frontal- system behavioural symptoms are critical to differential diagnosis across neurodegenerative disorders. The ability of a scale to distinguish between groups that are expected to differ is referred to as known-groups validity (or discriminative validity). It represents an important aspect of construct validity. This is relevant in neurodegenerative disorders, where behavioural profiles differ across diagnostic groups and may facilitate differential diagnosis.

Nevertheless, the lack of reliable tools for assessing behavioural symptoms in neurodegenerative disorders presents significant challenges for both clinical practice and research. The Frontal Systems Behaviour Scale (FrSBe), formerly known as the Frontal

Lobe Personality Scale (FLOPS), was developed by Grace and Malloy in 2001 and published by Psychological Assessment Resources. The scale was designed in order to assess behavioural disturbances associated with frontal-system dysfunction, particularly apathy, disinhibtionsinhibition, and executive dysfunction [8]. Previous studies have demonstrated good reliability and validity of the FrSBe across a variety of neurological populations [9-11]. Moreover, the scale has shown promising results in distinguishing between neurodegenerative diseases. However, despite the fact that the scale is considered reliable, little is known about its discriminant validity in the Greek clinical population.

Therefore, the primary aim of the current study was to investigate the known-groups validity of the FrSBe by examining the ability of its subscales and total score to distinguish among patients with Alzheimer's disease (AD), semantic variant frontotemporal dementia (svFTD), and behavioural variant frontotemporal dementia (bvFTD). Another aim was to examine the validity through the association between FrSBe and NPI scores.

Methods

226 participants were recruited from the Center of Third Age "Iasis" and provided written informed consent prior to assessment. Diagnoses were established by psychiatrists, neurologists and clinical psychologists according to international diagnostic criteria. For the purposes of the current study, the reduced version of the Frontal Systems Behaviour Scale (FrSBe) was used, because it is easier to use and more time-efficient than the original one, while maintaining discriminative ability comparable to the original version [12-14]. The reduced model differs from the original version by the exclusion of eight items. Specifically, three items were removed from the Apathy subscale ("Has difficulty starting an activity, lacks initiative, motivation"; "Neglects personal hygiene"; "Starts things but fails to finish them, 'peters out'"), three items from the Executive Dysfunction subscale ("Apologizes for misbehaviour"; "Uses strategies to remember important things"; "Benefits from feedback, accepts constructive criticism from others"), and two items from the Disinhibtionsinhibition subscale ("Laughs or cries too easily"; "Is sensitive to the needs of other people") [12]. In addition, the Neuropsychiatric Inventory (NPI) was administered to all participants in order to assess behavioural disturbances and to examine its association with FrSBe scores [15].

Statistical analysis

Quantitative variables were expressed as means and standard deviations (SDs), while qualitative variables were expressed as absolute and relative frequencies. For the comparison of proportions chi-square test was used. Analysis of variance (ANOVA) was used for the comparison of mean values. Bonferroni correction was used to control for Type I error. Spearman correlation coefficients were used to explore the association of two continuous variables. Correlation coefficient between 0.1 and 0.3 was considered low, between 0.31 and 0.5 moderate and those over 0.5 were considered high. Partial correlation coefficients were computed after adjustment for group, age, gender, years of education, and ACE-R. Simple and multiple linear regression analyses were used with dependent the FrSBe scores. The regression equation included terms for group, age, gender, years of education and ACE-R. Adjusted regression coefficients (β) with standard errors (SE) were computed from the results of the linear regression analyses. ROC curves (Receiver operating characteristic curves) were used in order to estimate the discriminative ability of FrSBe scores. Sensitivity and specificity were calculated for optimal cut-offs. The area under the curve (AUC) was also calculated. All reported p values are two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (version 22.0).

Results

The sample consisted of 226 participants, including 168 patients and 58 healthy controls, with mean age 66.9 years (SD=9.8). Demographics and clinical characteristics in total sample and by group are presented in Table 1. The study groups were similar in terms of age, education and sex. ACE-R and MMSE were significantly higher in the control group compared to all other 3 groups ($p<0.001$ for all comparisons). Furthermore, AD group had significantly greater ACE-R score compared to svFTD and bvFTD group ($p<0.001$ and $p=0.031$ respectively). Similarly, MMSE scores were significantly higher in the AD group than in the svFTD and bvFTD groups ($p=0.002$ and $p=0.045$ respectively).

Table 2 shows comparison of FrSBe subscales between study groups. Total FrSBe by group is shown in Figure 1. Both unadjusted and adjusted for age, sex, years of education and ACE-R comparisons

	Total sample (N=226; 100%)	Controls (N=58; 25.7%)	svFTD (N=45; 19.9%)	AD (N=78; 34.5%)	bvFTD (N=45; 19.9%)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P+
Gender, N (%)						
Males	75 (33.2)	19 (32.8)	19 (42.2)	27 (34.6)	10 (22,2)	.243++
Females	151 (66.8)	39 (67.2)	26 (57.8)	51 (65.4)	35 (77,8)	
Age	66.9 (9.8)	65.5 (9.7)	68.0 (7.3)	69.2 (9.7)	65.4 (9.9)	.211
Years of education	10.4 (4.6)	11.0 (3.0)	9.7 (4.5)	10.6 (4.8)	10.0 (4.4)	.301
ACE-R	65.4 (24.0)	94.0 (3.1)	47.0 (21.0)	61.8 (16.1)	53.1 (21.0)	<.001
MMSE	22.4 (7.0)	29.4 (0.8)	18.0 (7.8)	21.7 (4.9)	19.0 (6.9)	<.001
Apathy	30.9 (10.5)	21.9 (7.1)	35.0 (10.8)	30.6 (8.0)	39.4 (8.5)	<.001
Disinhibition	25 (8.2)	21.4 (5.0)	28.6 (9.7)	23.3 (5.4)	29.0 (10.6)	<.001
Dysexecutive syndrome	40.3 (13.8)	26.3 (9.2)	46.3 (11.3)	40.5 (10.7)	52.1 (10.4)	<.001
Total FrSBe score	96.2 (28.1)	69.4 (18.8)	110.6 (22.5)	94.0 (20.2)	120.5 (24)	<.001

Table 1: Sample characteristics and FrSBe scores, in total sample and by group.

+ANOVA; ++Pearson's chi-square test.

showed significantly greater scores for Apathy, Disinhibition, Dysexecutive syndrome and total FrSBe score in svFTD, AD and bvFTD group as compared to controls. Only Disinhibition was not greater in AD patients as compared to controls in unadjusted comparison but the association turned to be significant after adjustment for age, gender, years of education and ACE-R. Also, AD group had significantly lower Apathy score (compared to bvFTD group [β(SE)=-8.12(1.64); p<0.001] adjusted for age, gender, years of education and ACE-R. AD group had significantly lower Disinhibition score compared to svFTD [β(SE)=-5.64(1.48); p<0.001] and bvFTD groups [β(SE)=-5.70(1.46); p<0.001] after adjustment for age, gender, years of education and ACE-R. Similarly, AD group had significantly lower Dysexecutive syndrome score compared to svFTD [β(SE)=-5.34(2.06); p=0 .010] and bvFTD groups [β(SE)=-11.17(2.03); p<0.001] as well as lower total score compared to svFTD [β(SE)=-14.84(4.18); p<0.001] and bvFTD groups [β(SE)=-25.24(4.12); p<0.001]. No significant differences were found between svFTD and bvFTD groups, in any of the scores.

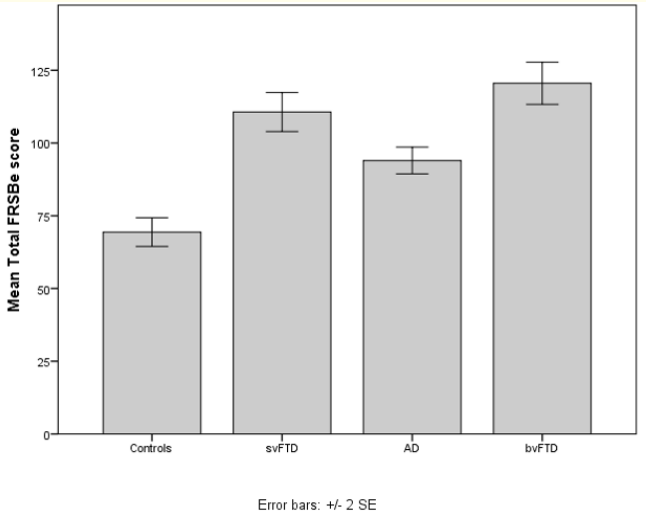

Figure 1: Mean total FrSBe score, by group.

Note. Raw mean scores are depicted in the figure.

		β (SE)+	β (SE)++
Apathy	svFTD vs Controls	13.12 (1.69)***	8.73 (2.37)***
	AD vs Controls	8.70 (1.48)***	5.81 (1.90)**
	bvFTD vs Controls	17.50 (1.70)***	13.93 (2.22)***
	AD vs bvFTD	-8.80 (1.60)***	-8.12 (1.64)***
	AD vs svFTD	-4.41 (1.59)**	-2.92 (1.66)
	bvFTD vs svFTD	2.39 (1.80)	2.20 (1.82)
Disinhibition	svFTD	7.25 (1.50)***	9.61 (2.11)***
	AD	1.86 (1.31)	3.98 (1.69)**
	bvFTD	7.60 (1.51)***	9.67 (1.98)***
	AD vs bvFTD	-5.74 (1.43)***	-5.70 (1.46)***
	AD vs svFTD	-5.39 (1.42)***	-5.64 (1.48)***
	bvFTD vs svFTD	0.36 (1.60)	0.06 (1.62)
Dysexecutive syndrome	svFTD	19.92 (2.06)***	19.30 (2.94)***
	AD	14.12 (1.80)***	13.95 (2.35)***
	bvFTD	25.77 (2.07)***	25.12 (2.76)***
	AD vs bvFTD	-11.65 (1.96)***	-11.17 (2.03)***
	AD vs svFTD	-5.81 (1.94)**	-5.34 (2.06)*
	bvFTD vs svFTD	3.85 (2.20)	3.82 (2.25)
Total FrSBe score	svFTD	41.25 (4.20)***	38.10 (5.96)***
	AD	24.59 (3.67)***	23.26 (4.78)***
	bvFTD	51.13 (4.23)***	48.50 (5.59)***
	AD vs bvFTD	-26.54 (3.99)***	-25.24 (4.12)***
	AD vs svFTD	-16.66 (3.96)***	-14.84 (4.18)***
	bvFTD vs svFTD	8.88 (4.49)	9.40 (4.57)

Table 2: Comparisons of FrSBe subscales among all study groups.

+unadjusted regression coefficient (Standard Error); ++regression coefficient (Standard Error) adjusted for age, gender, years of education and ACE-R, *p<.05; **p<.01; ***p<.001.

Correlations between NPI items and FrSBe subscales (see Table 3) indicated significant association of NPI 1 (delusions), NPI 3 (agitation/aggression), NPI 6 (euphoria/elation), NPI 7 (apathy/indifference), NPI 8 (disinhibtionsinhibition), NPI 9 (irritability/lability), NPI 10 (aberrant motor), NPI 11 (night-time behaviour), NPI 12 (appetite/eating) and NPI TOTAL with Apathy, Disinhibition, Dysexecutive syndrome and total FrSBe score. NPI 4 (dysphoria/depression) and NPI 5 (anxiety) were positively correlated with Disinhibition, while hallucinations were not correlated with any of the FrSBe subscales.

		Apathy	Disinhibition	Dysexecutive syndrome	Total FrSBe score
NPI 1	r+	.22**	.28***	.28***	.32***
Delusions	r++	.16*	.33***	.21**	.28***

NPI 2 Hallucinations	r+	.10	.13	.11	.12
	r++	.05	.03	.00	.03
NPI 3 Agitation/aggression	r+	.21**	.35***	.34***	.36***
	r++	.26***	.31***	.33***	.36***
NPI 4 Depression	r+	.09	.15*	.12	.13
	r++	.06	.17*	.11	.13
NPI 5 Anxiety	r+	.08	.16*	.08	.12
	r++	.10	.15*	.10	.14
NPI 6 Euphoria	r+	.29***	.23**	.41***	.38***
	r++	.16*	.18*	.26***	.25**
NPI 7 Apathy	r+	.53***	.23**	.45***	.48***
	r++	.29***	.21**	.20**	.23**
NPI 8 Disinhibtionsinhibition	r+	.23**	.31***	.37***	.36***
	r++	.21**	.30***	.33***	.34***
NPI 9 Irritability	r+	.12	.25***	.23**	.25**
	r++	.19**	.31***	.30***	.32***
NPI 10 Abnormal motor Behaviour	r+	.36***	.28***	.38***	.43***
	r++	.29***	.23**	.26***	.32***
NPI 11 Sleep disorders	r+	.30***	.29***	.28***	.34***
	r++	.19**	.28***	.20**	.26***
NPI 12 Eating disorders	r+	.43***	.30***	.35***	.44***
	r++	.28***	.25**	.16*	.27***
NPI TOTAL	r+	.57***	.50***	.59***	.66***
	r++	.39***	.44***	.41***	.50***

Table 3: Correlation between NPI and FrSBe subscales.

+Spearman correlation coefficient; ++Partial correlation coefficient adjusted for study group, age, gender, years of education and ACE-R.

*p<.05; **p<.01; ***p<.001.

When ROC analysis was conducted (see Table 4) to evaluate the discriminative ability of FrSBe subscales between patient and controls in males, it was found that Apathy, Dysexecutive syndrome and Total FrSBe score could discriminate well with optimal cut-off points equal to 32.5, 30 and 83.5, respectively. In females the optimal cut-off points for the discrimination between patient and controls were 26.5 for Apathy, 23.5 for Disinhibition, 35.5 for Dysexecutive syndrome and 83.5 for Total FrSBe score and the AUCs ranged from 0.71 to 0.90. All FrSBe subscales had significant discriminative ability in those aged less than 65 years with

sensitivities ranging from 63.5% to 80.8% and specificities ranging from 82.4% to 94.1%. Among participants aged 65 years or older, Disinhibition had no significant discriminative ability (p=0.090).

		AUC (95% CI)	P	Optimal cut-off	Sensitivity (%)	Specificity (%)
Males (Controls/Patients: 19/56)	Apathy	0.80 (0.70 — 0.90)	<.001	32.5	66.1	89.5
	Disinhibition	0.60 (0.47 — 0.74)	.184	-	-	-
	Dysexecutive syndrome	0.86 (0.77 — 0.95)	<.001	30.0	85.7	78.9
	Total FrSBe score	0.83 (0.73 — 0.93)	<.001	83.5	80.4	78.9
Females (Controls/Patients: 39/112)	Apathy	0.86 (0.8 — 0.93)	<.001	26.5	81.1	76.9
	Disinhibition	0.71 (0.62 — 0.79)	<.001	23.5	61.3	79.5
	Dysexecutive syndrome	0.90 (0.84 — 0.96)	<.001	35.5	82.0	87.2
	Total FrSBe score	0.90 (0.85 — 0.95)	<.001	83.5	84.7	89.7
Age <65 years (Controls/ Patients: 34/52)	Apathy	0.87 (0.79 — 0.94)	<.001	29.5	69.2	91.2
	Disinhibition	0.74 (0.64 — 0.85)	<.001	24.5	63.5	82.4
	Dysexecutive syndrome	0.94 (0.90 — 0.99)	<.001	36.5	80.8	94.1
	Total FrSBe score	0.92 (0.87 — 0.97)	<.001	83.5	80.8	91.2
Age >=65 years (Controls/ Patients: 24/116)	Apathy	0.81 (0.73 — 0.90)	<.001	32.5	56.5	95.8
	Disinhibition	0.61 (0.50 — 0.72)	.090	-	-	-
	Dysexecutive syndrome	0.83 (0.73 — 0.92)	<.001	29.5	88.7	75.0
	Total FrSBe score	0.83 (0.74 — 0.91)	<.001	83.5	84.3	79.2

Table 4: ROC analysis results for the discrimination between patient and controls from FrSBe subscales, in specific groups of patients.

Discussion

The current study demonstrates the known-groups validity and validity of the FrSBe in a Greek clinical population with neurodegenerative diseases. According to the results, FrSBe subscales and total scores demonstrated significant ability to distinguish patients from healthy control groups. Moreover, FrSBe identified behavioural profiles across the groups, but its diagnostic accuracy in neurodegenerative diseases was not examined. FrSBe was designed to measure behavioural/ executive changes associated with damage to the frontal-subcortical brain circuits [16] and has been administered to a wide range of neurological and medical patient populations [10]. In line with the study of Malloy., *et al*. [17], FrSBe subscales as well as total FrSBe scores displayed sufficient discriminatory ability to correctly classify AD or FTD patients versus controls; albeit the current study utilized a much larger sample size (168 patients vs 58 controls) [17]. Stratification of the participants by gender showed that in females the discriminatory power of all FrSBe subscale scores was significant, with sensitivity and specificity ranging between 61.3%-84.7% and 76.9%-89.7%, respectively. Similar results were observed in males, with sensitivity to be around 66.1–85.7% for all FrSBe scores except for that of Disinhibition. The Disinhibition subscale failed to reach sufficient discriminatory power, which may have been due to the relatively small number of male participants compared with female participants (56 vs 112). On the other hand, age was not associated with differences in the discriminative performance of the total FrSBe score. To our knowledge, this is among the first studies to propose optimal FrSBe cutoff scores stratified by age

and sex in a large neurodegenerative cohort. As expected, patients with FTD and AD displayed significant increases in non-cognitive behaviour disturbances compared to controls but the pattern of these changes was considerably different between the two groups of patients. In particular, AD patients exhibited less dramatic changes in apathy and Disinhibition compared to bvFTD and svFTD groups, respectively. FTD is strictly correlated with greater executive dysfunction, because of the involvement of frontal neural networks, including the dorsolateral and orbitofrontal cortices and their white matter connections, therefore causing executive problems. Moreover, the score for dysexecutive syndrome , as well as the total FrSBe score was significantly lower in the AD group compared to both FTD groups. These results are in accordance with previous studies; albeit of smaller sample size, suggesting that behaviours of apathy and disinhibtionsinhibition as well as dysexecutive syndrome are more prevalent in patients with FTD than in those with AD [18].

Although differences in behavioural profiles were identified across the diagnostic groups, the ROC analyses assessed discrimination between the patients and healthy controls and did not establish diagnostic accuracy across neurodegenerative diseases. One crucial finding was the absence of significant differences between the svFTD and bvFTD groups across all FrSBe subscales and the total score. Although svFTD is primarily characterized by progressive language decline, behavioural symptoms often emerge as the disease progresses. This may result in an overlap with those observed in bvFTD. Therefore, the lack of significant differences may reflect convergence of behavioural phenotypes in the sample. Moreover, another concern is that the reduced version of the FrSBe may have been less sensitive to subtle behavioural differences between these FTD subtypes. Finally, the relatively modest sample size within each subgroup may have limited statistical power to detect smaller between-group differences.

Despite the fact that the aforementioned non-cognitive behaviour disturbances are well recognized in FTD and AD patients by physicians, little research has been conducted until now regarding specific neuropsychiatric problems, as captured by the NPI scale [15,19] that are associated with them. Our results demonstrated that patients who present with apathy, disinhibtionsinhibition or dysexecutive syndrome also experience behavioural difficulties, which may be difficult for caregivers and clinicians to manage, such as irritability, lability, agitation and aggression. Furthermore, it seems that this group of patients is more likely to exhibit aberrant motor activity, appetite/eating disorders as well as sleep disturbances. Interestingly, the FrSBe measures of apathy, disinhibtionsinhibition and dysexecutive syndrome were significantly associated with the NPI apathy and NPI disinhibtionsinhibition rating as well as with the total NPI score. Similarly, the FrSBe total score correlated highly with the NPI total score. These findings are in accordance with the small-scale study of Norton., *et al*. [20], that included 30 patients with dementia and reported a fair correlation between NPI and FrSBe scale.

Additionally, there is an absence of association between the FrSBe Apathy sub scale and the NPI Depression domain. The absence may provide evidence of discriminant validity. However, apathy and depression may often overlap, they represent different behavioural philosophy. Patients with apathy may have reduced motivation and goal- directed behaviour, without experiencing negative feelings and/ or sadness and anhedonia as depressive patients do. This distinction is critical, because apathy and depression may require different therapeutic approaches.

Several limitations of the current study should be acknowledged. First of all, participants were recruited from just one clinical centre. The sample consisted exclusively of Greek participants, which may limit the generalisability of the findings. Secondly, although the reduced version of the FrSBe is more time-efficient and has demonstrated satisfactory discriminative ability, the exclusion of eight items may have affected its sensitivity, particularly regarding differences between the bvFTD and svFTD groups. Thirdly, the ROC analyses evaluated discrimination between patients and healthy controls rather than diagnostic accuracy across specific neurodegenerative diseases. Therefore, future studies should include larger and more diverse cohorts and examine the psychometric properties of the FrSBe and its diagnostic accuracy across specific neurodegenerative disorders.

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Compliance with Ethical Standards

The study was approved by the Ethics Committee of the [blind for review]. The study was performed in accordance with the

ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Informed Consent

All participants provided written informed consent prior to assessment.

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