

FRONTIER Executive Screen: A brief executive battery to differentiate frontotemporal dementia and Alzheimer's disease

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ABSTRACT

Background and Objective: Executive dysfunctions are a key clinical feature of behavioural-variant frontotemporal dementia (bvFTD). Such deficits are also found in Alzheimer's disease (AD), making the differentiation between these two diseases difficult at times, particularly in the absence of extensive cognitive assessments. To address this issue, we developed the FRONTIER Executive Screen (FES), which combines three abbreviated measures of verbal fluency, inhibitory control and working memory.

Methods: We administered the FES to 28 dementia patients (14 bvFTD, 14 AD) matched for disease severity and 33 age- and education-matched healthy controls. We also administered traditional tests of executive function to establish the concurrent validity of the FES.

Results: Both patient groups obtained lower FES scores (total and subscores) compared to controls. Correct classification into patient or control groups was reached in over 90% of study participants based on the FES total score. Only two bvFTD patients obtained FES scores within 2 standard deviations of the control group. ROC analyses on the patient groups showed that a cut-off FES total score of 7/15 achieved 71% sensitivity and 73% specificity for a diagnosis of bvFTD. In addition, the FES showed high correlations with traditional measures of executive function.

Conclusions: The FES is a brief (5-10 min) bedside screening measure which is simple to administer and score, and demonstrates good discriminative validity to differentiate bvFTD from AD. It is a useful addendum to general cognitive screening measures and can help with the differential diagnosis of dementia.

INTRODUCTION

Differentiation between behavioural-variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) remains challenging in clinical settings, given the heterogeneity of clinical presentations[1, 2] and overlapping cognitive profiles[3]. Accurate diagnosis is important given the implications for prognosis[4], heritability[5], and available interventions[6].

Executive dysfunction is characteristic of bvFTD and is one of the earliest cognitive features to arise, secondary to frontal lobe atrophy[7]. While executive impairments tend to be a later manifestation in AD[8], they are also found at presentation in a subset of AD patients[9]. Evidence suggests, however, that executive dysfunctions in AD may be dissociable from those observed in bvFTD[10-13]. Tasks eliciting inhibitory control, verbal working memory and verbal fluency have demonstrated diagnostic potential[10].

Neuropsychological assessment of executive functions remains problematic, given that long test batteries can be unrealistic and disadvantageous within a clinical setting. Whilst brief executive screening tests have been developed to address this issue, many existing tools were not specifically designed for use within dementia populations[14], show limited discrimination between bvFTD and AD[15], include items that are vulnerable to misinterpretation[16] or items which fail to exclusively tap executive functions[17]. Tools focusing on executive function to assist with differential dementia diagnosis already exist (e.g., INECO Frontal Screen[18]; Frontal Assessment Battery[19]), but these are not without limitations, which include inconsistent patient differentiation across subtests[20], need for training in scoring responses and inclusion of items vulnerable to educational achievement[21]. While the Addenbrooke's Cognitive Examination[22], a broad cognitive screening tool, is also often thought to assist with differential diagnosis, this was not its

intended design and an acknowledged caveat of the test is its limited capacity to assess executive functions.

This study examines the capacity of a novel test, the FRONTIER Executive Screen (FES) to differentiate between bvFTD and AD. The FES is a brief, easily administered and sensitive bedside screening test of executive functions. It combines items analogous to existing executive tasks which have previously demonstrated diagnostic potential in differentiating bvFTD from AD.

METHODS

Participants

Fourteen bvFTD and 14 AD patients were recruited from the multidisciplinary FRONTIER Dementia Clinic between January 2013 and July 2014. BvFTD patients met current clinical consensus criteria[23] and showed progressive deterioration in behaviour, functional decline and presence of frontal lobe atrophy on brain MRI. Patients diagnosed with AD met diagnostic criteria for probable AD[24] and presented predominantly with progressive anterograde episodic memory impairment on neuropsychological testing. Thirty-three age- and education-matched healthy control participants were selected from a panel of healthy volunteers recruited from the community. Exclusion criteria included history of prior mental illness, significant head injury, movement disorders, other neurological conditions and substance abuse.

Instruments

The FRONTIER Executive Screen (FES)

The FES was devised by combining measures of verbal fluency, inhibitory control and working memory (Supplemental Appendix 1). The novel Fluency, Inhibition and Working Memory subtests each generates a score between 0 and 5, which are summed to produce a total score (max of 15), with higher scores indicative of better executive functioning.

The Fluency test, akin to the Controlled Oral Word Association Test[25], comprises the total number of unique words produced in two 1-minute trials for the letters F and P. Word generation rules are explained (that no word can be a proper noun). Scaled scores range from 0 to 5 depending on the number of correct words produced as follows: <12 words = 0; 13–16 words = 1; 17–20 words = 2; 21–25 words = 3; 26–30 words = 4; >30 words = 5). Scaled scores were determined based on frequencies and cumulative percentages of raw P and F combined scores, to provide optimal discriminative ability. Concurrent validity was established by comparing scaled Fluency scores with P and F raw scores ($r = 0.925$; $p < 0.001$).

The Inhibition subtest is akin to the Hayling Sentence Completion Test[26]. It comprises 5 practice items and 5 test items. Participants listen to sentences where the last word of the sentence is missing and have to provide a word that will complete the sentence either correctly (practice sentences) or incorrectly (test sentences). Providing an incorrect or unconnected word, for the test sentences, necessitates inhibiting an automatic response. Responses to sentences items are scored 1 if deemed correct and completely unconnected to the sentence in every way or 0 if incorrect. The task is untimed and responses to practice sentences are not included in the FES Inhibition score. Participants were firstly administered 10 test sentences which were then ranked according to discriminative ability. The 5 test sentences with the highest discriminability between bvFTD and AD were included in the FES. Concurrent validity was established by comparing the novel Inhibition score with the original overall score (out of 10), which showed very high relationship ($r = .915$; $p < .0001$).

The Working Memory subtest, akin to the Digit Span Backward test[27], comprises 2 practice and 7 test items of sequences of letters ranging between 2 and 5 letters. This task evaluates short-term memory for auditorily presented letter strings of increasing length. Participants are required to repeat strings of letters they hear in reverse order. One point is awarded for each level of difficulty with an additional point given when all trials are performed successfully across 3 consecutive items, providing a score ranging between 0 and 5. Participants were originally administered items evaluating the integrity of up to 8 letters backwards. This selected range of 2 to 5 letters was based on mean performance of healthy controls, where 73.9% scored 4 or above. In contrast, 100% of bvFTD and 92.2% AD patients scored less than 5. Administration procedure and scoring instructions for the FES are detailed in the Supplementary file or can be freely downloaded from our website (<http://www.neura.edu.au/frontier>).

Functional abilities

Behavioural symptoms were also assessed using the Cambridge Behavioural Inventory (CBI)[28]. The CBI is a questionnaire with 81 items evaluating behaviour, mood, personality, activities of everyday living and memory/orientation. An increased CBI score indicated impaired daily functioning.

Cognitive assessment

General cognitive functioning was assessed using the Addenbrooke's Cognitive Examination – III[22]. The ACE-III evaluates five cognitive domains including orientation and attention, memory, verbal fluency, language and visuospatial abilities. It provides a score out of 100, with a score of 88 or higher denoting intact cognitive performance.

The concurrent validity of the FES was established against three traditional measures of executive function targeting different components of executive function: set shifting, inhibitory control and short-term working memory. Set shifting was measured with the Trail Making Test Part B (TMT B)[29]. This test requires participants to join a series of randomly positioned numbers and letters alternately in respective sequence (i.e., 1-A-2-B). Inhibitory control was measured using the Hayling Sentence Completion Test[26]. Participants must provide a word to complete an auditorily presented sentence correctly (Part A) or incorrectly (Part B) as quickly as possible. Finally short-term working memory was investigated with Digit Span Backward[27]. This test requires participants to repeat strings of digits of increasing length they hear in reverse order.

Statistical Analyses

Data were analysed using SPSS Statistics (Version 21.0). All variables were checked for normality of distribution using Kolmogorov-Smirnov tests. Non-parametric data were first analysed using the Kruskal-Wallis Test to assess the group effect, followed by Mann-Whitney U tests for posthoc pairwise comparisons where appropriate. Similarly, one-way analyses of variance (ANOVA) followed by posthoc Tukey tests were used for parametric data. Associations between the FES and other cognitive measures were examined using Pearson's correlation coefficients for normally distributed data, or Spearman's correlation for non-parametric data. Logistic regression analyses using the Enter method were performed, first on all participant groups to establish the ability of the FES total score to differentiate patients from controls and, in a second step, on the two patient groups to differentiate between bvFTD and AD. We then calculated the receiver operating characteristic (ROC) curve to determine the best sensitivity and specificity indices of the FES.

RESULTS

Demographic and clinical profiles

All groups were matched for age and education and patient groups were matched for disease duration (Table 1). In contrast, groups differed on the general cognitive measure ACE-III, with lower scores found in the AD and bvFTD groups compared to controls (all p values $< .001$). No difference, however, was present between the two patient groups on this measure, reflecting similar disease severity. Patient groups also performed below controls on all executive measures (all p values $< .001$). The bvFTD group performed worse than the AD group on the Hayling Sentence Completion Test. The patient groups, however, did not differ on Digit Span Backward and TMT B. Finally, the bvFTD group experienced higher behavioural disturbance than the AD group on the CBI.

Table 1: Demographic Variables and Clinical Profiles of Patient (bvFTD, AD) and Control Groups ($M \pm SD$).

	bvFTD (n = 14)	AD (n = 14)	Controls (n = 33)	H/χ^2 value
Sex (M:F)	10:4	5:9	12:21	NS
Age	62.7 ± 8.9	64.9 ± 8.1	67.5 ± 8	NS ^b
Education	$12.2 \pm .4$	11.8 ± 3.4	14.3 ± 2.9	NS ^b
Disease Duration (months)	57.8 ± 37.7	53.5 ± 26.3	N/A	NS
CBI	40.8 ± 18.2	16.7 ± 8.8	5.4 ± 5.0	*** ^{c,d}
ACE-III (/100)	68.2 ± 9	70.7 ± 9	96.4 ± 2.7	*** ^c
Hayling Test	2.3 ± 1.9	4.4 ± 1.7	$6.1 \pm .8$	*** ^{c,d}
Digit Span (B)	4.3 ± 1.9	4.4 ± 1.4	8.4 ± 2.9	** ^c
TMT B	141.8 ± 73.9	177 ± 92.6	74.1 ± 27.7	*** ^c
FES Total	5.07 ± 3.1	8.9 ± 2	12.4 ± 1.1	*** ^{c,d}
Fluency	1.5 ± 1.7	3.6 ± 1.2	4.6 ± 0.7	*** ^{c,d}
Inhibition	1.3 ± 1.4	2.7 ± 1.3	4.3 ± 0.7	*** ^{c,d}
Working Memory	2.3 ± 0.9	2.8 ± 0.9	3.8 ± 1.0	*** ^c

Abbreviations: bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease; CBI = Cambridge Behavioural Inventory; ACE-III = Addenbrooke's Cognitive Examination-III; Hayling Test = Hayling Sentence Completion Test; Digit Span (B) = Digit Span Backward; TMT B = Trail Making Test Part B; FES Total = FRONTIER Executive Screen Total score.

^b = ANOVA F test; NS = not significant; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$
Significant Tukey post hoc tests ($p < .05$): ^cControls vs patient groups (bvFTD, AD), ^dbvFTD vs AD

FRONTIER Executive Screen performance and patient classification

Both patient groups performed below controls on the FES total score and each individual subtest ($p < .001$ for all comparisons) (Table 1 and Figure 1). In addition, the bvFTD group obtained lower scores than the AD group on the FES total, Fluency and Inhibition subtests ($p < .007$ for all comparisons), but not on the Working Memory subtest (Table 1).

*****Insert Figure 1 about here*****

Discriminative ability of the FES was determined by calculating the overlap in performance between controls and patient groups, defined as falling within 2 SDs of the mean of the control group. Better discriminative ability of each patient group from controls is indicated by a smaller percentage overlap. On the whole, better discriminability was found for the FES total score than for the individual subscores (Table 2). In addition, the bvFTD group showed lower overlaps with controls (ranging between 7% and 43%) on all FES measures compared to the AD group (ranging between 29% and 65%). Difference scores were also derived to determine the discriminability between AD and bvFTD on these measures, with larger scores indicative of better discrimination (Table 2). All FES measures demonstrated effective discrimination between the two patient groups with the exception of the Working Memory subscore.

Table 2: Score overlap (%) between patient groups (bvFTD, AD) and Controls and discriminability between patient groups.

	bvFTD (n = 14)	AD (n = 14)	Difference Score (AD vs bvFTD)
FES Total	7	29	22
Fluency	14	50	36
Inhibition	14	65	51
Working Memory	43	57	14

Note: bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease; FES = FRONTIER Executive Screen.

Hierarchical logistic regression analyses, with disease (AD, bvFTD vs Control) as the dependent variable, revealed that the total FES was able to classify 91.7% of patients correctly (i.e., patients: 23/28 [82.1%], Controls 32/32 [100%]). Similar analyses with diagnosis (AD vs bvFTD) as the dependent variable revealed that the total FES was able to classify 71.4% of patients correctly (i.e., AD: 10/14 [71.4%], bvFTD: 10/14 [71.4%]). The ROC analysis revealed an area under the curve of .842 (95% CI 688-996; $p = .002$). Cut-off scores derived from this analysis indicated that a total FES score of 8 or less identified bvFTD with 86% sensitivity and 50% specificity, while a total FES score of 7 or below achieved 71% sensitivity and 73% specificity.

Relations between FES and existing executive function measures

The FES total score and subscores were compared to independent and established measures of executive functioning. Associations were observed between the total FES and TMT B ($r = -.501, p = .002$), Digit Span Backward ($r = .661, p < .001$), and Hayling ($r = .729, p < .001$).

With regards to subscores, the Fluency subscore correlated with TMT B ($r = -.336, p = .045$), Digit Span Backward ($r = .469, p < .001$) and Hayling ($r = .601, p < .001$). The Inhibition subscore was associated with TMT B ($r = -.447, p = .006$), Digit Span Backward ($r = .507, p < .001$) and Hayling ($r = .721, p < .001$). Finally, the Working Memory score was associated with Digit Span Backward ($r = .669, p < .001$) and Hayling ($r = .564, p < .001$), but not TMT B ($r = -.300, p = .075$).

DISCUSSION

This study addresses the challenges of screening assessment of executive functions in dementia clinics and of the differentiation between AD and bvFTD. Here, we demonstrated that a novel screening instrument, the FRONTIER Executive Screen (FES), provides an important contribution towards establishing a differential diagnosis of dementia. A combination of short executive function tests that measure verbal fluency, verbal inhibitory control and working memory cognitive processes demonstrated excellent discriminative validity in distinguishing healthy controls from dementia patients and bvFTD from AD patients. Based on its global score, the FES correctly classified over 90% of study participants into healthy controls or dementia patients (bvFTD and AD). Within patient groups, almost three quarters of dementia patients were correctly classified into bvFTD and AD based on the total FES score.

These findings highlight the need for multiple measures of executive function, as opposed to a single test, during diagnostic workup. Executive function encompasses a range of cognitive processes supported predominantly by the prefrontal cortex[13, 30], a brain region undergoing early pathological changes in bvFTD[31, 32]. The superior specificity of the FES total score over its individual subtests is evidenced by the lowest score overlap with healthy controls for the total score compared to each individual subtest. Indeed, only two bvFTD

patients performed within two standard deviations of the range of healthy controls. Both patients presented with significant behavioural disturbances, scoring in the top quartile on the CBI, and exhibited marked frontal atrophy on coronal MR images at presentation which worsened over time. Interestingly, neither patient was positive for the *C9ORF72* gene expansion, which has been identified in slowly progressing bvFTD patients with mild neuropsychological deficits[33]. Preserved performance on executive function tests has been reported in some bvFTD patients despite marked behavioural changes early in the disease process[34]. Overall, however, the bvFTD group performed the worst across all FES subtests, and demonstrated the lowest overlap with control performance. Similarly, a marked difference on these measures was present between bvFTD and AD. Importantly, this distinction occurred in the context of comparable performance on a broad cognitive index (ACE-III)[22]. This finding indicates that the FES is tapping into cognitive processes distinct from the ACE-III and highlights the importance of executive function tests as part of cognitive screening for dementia. This result further indicates that administration of the FES, in conjunction with the ACE-III, will enhance sensitivity towards a differential dementia diagnosis.

While sensitive to executive dysfunction, the ability of the FES Working Memory subtest to differentiate between patient groups was limited, in contrast to previous reports[10]. This apparent discrepancy may be explained in two ways: First, this reduced discriminative ability may reflect the vulnerability of working memory to co-existing non-frontal cognitive impairments, as is often observed in patients with AD[11, 35]. Second, working memory integrity was examined using a letter span task, unlike previous studies which used a digit span task. Evidence suggests that working memory may be sensitive to modality effects with recall of digits being above that of letters in healthy controls[36]. As such, the use of a letter span task may have reduced the potential magnitude of discrepancy between patient groups.

The fact that the average letter span in the healthy control group was the lowest of all FES subscores (each out of 5) provides support for this position.

The development of the FES was empirically-based and comprised tasks known to recruit cognitive processes mediated predominantly by prefrontal brain regions and with diagnostic potential within a dementia population[10, 37]. The FES was designed to be brief (5-10 minutes administration time), simple to administer and score (e.g., by removing the need to time responses) and requiring no particular equipment to assist clinical or bedside screening assessment. The correlations with similar established tests of executive function indicate that these simplifications did not reduce the validity of these novel measures. To facilitate scoring, the FES only contains cognitive measures, unlike other test batteries such as the Frontal Assessment Battery (FAB), which can be difficult to administer and interpret without training and experience[19].

Despite the advantages the FES offers, clinicians need to be aware of some of its limitations. First, the FES was developed to differentiate bvFTD from AD patients, and its utility for assessing executive dysfunction in other clinical populations will need to be explored. Second, it is important to emphasise that the FES was not designed to replace a comprehensive cognitive assessment. Certainly, a diagnosis of dementia should not rely on the presence of impaired performance on this instrument alone. Finally, recruitment into the study was based on clinical grounds. As such, we do not have pathological confirmation of dementia diagnoses for our study participants. Importantly, however, all patients recruited into the study were assessed on multiple occasions and demonstrated progressive decline over time accompanied by characteristic patterns of brain atrophy on neuroimaging, mitigating the risk of including individuals with unrelated disorders.

Our findings indicate that the combination of the FES with the ACE-III will improve discriminative ability between dementia syndromes; however, this result will need to be demonstrated in prospective studies. Future research will also benefit from exploring the utility of administering the FES, in conjunction with social cognition measures, with evidence that such measures can also assist with differentiating bvFTD from AD[38], and bvFTD from psychiatric conditions[39].

In summary, neuropsychological measures eliciting verbal fluency, inhibition and working memory can assist in differentiating dementia diagnoses. The FES is a novel brief executive screening tool, which elicits such abilities, and has demonstrated good concurrent validity and discriminative validity to differentiate bvFTD from AD patients. The FES is also conducive for use within a clinical setting or for a bedside assessment, requiring limited equipment, brief administration time and simple scoring.

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CONTRIBUTORS

FVCL and OP contributed to the design and conceptualisation of the study, analysis and interpretation of data, drafting and revising the manuscript. ND, DF and EF contributed to drafting and revising the manuscript. JRH contributed to the interpretation of data and manuscript revision.

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COMPETING INTERESTS

None.

ETHICS APPROVAL

Human Research Ethics Committee of South Eastern Sydney Local District and the University of New South Wales.

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DATA SHARING STATEMENT

We will consider sharing our data on request.

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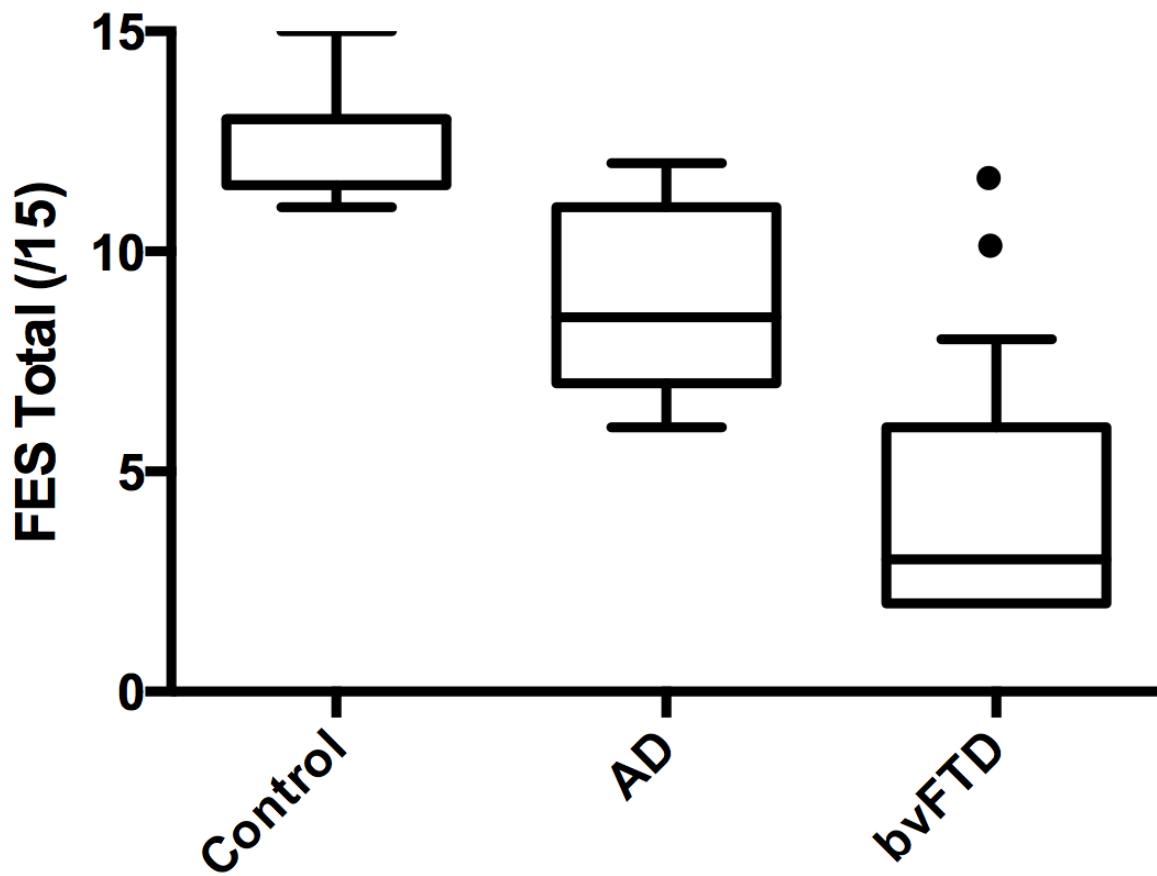


Figure 1: FRONTIER Executive Screen total scores in healthy controls, AD and bvFTD patients. AD = Alzheimer's disease; bvFTD = behavioural variant frontotemporal dementia. Boxes indicate interquartiles and whiskers at the 95% intervals. Dots represent individual scores.