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Cambridge University Press
2023-10-06

Heikkinen, A-L, Tikkanen, V, Hänninen, T, Hublin, C, Koivisto, A M, Saari, T T, Remes, A M, Paajanen, T I & Kruger, J 2023, 'Utility of the INECO Frontal Screening and the Frontal Assessment Battery in detecting executive dysfunction in early-onset cognitive impairment and dementia', Journal of the International Neuropsychological Society. https://doi.org/10.1017/S135561772300061

http://hdl.handle.net/10138/571650
10.1017/S1355617723000619

Journal of the International Neuropsychological Society (2023), 1–11
doi:10.1017/S1355617723000619

Research Article

Utility of the INECO Frontal Screening and the Frontal Assessment Battery in detecting executive dysfunction in early-onset cognitive impairment and dementia

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Abstract

Objective: The INECO Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) are executive dysfunction (ED) screening tools that can distinguish patients with neurodegenerative disorders from healthy controls and, to some extent, between dementia subtypes. This paper aims to examine the suitability of these tests in assessing early-onset cognitive impairment and dementia patients. **Method:** In a memory clinic patient cohort (age mean = 57.4 years) with symptom onset at ≤65 years, we analyzed the IFS and the FAB results of four groups: early-onset dementia (EOD, $n = 49$), mild cognitive impairment due to neurological causes (MCI-n, $n = 34$), MCI due to other causes such as depression (MCI-o, $n = 99$) and subjective cognitive decline (SCD, $n = 14$). Data were gathered at baseline and at 6 and 12 months. We also studied the tests' accuracy in distinguishing EOD from SCD patients and ED patients from those with intact executive functioning. Correlations with neuropsychological measures were also studied. **Results:** The EOD group had significantly ($p < .05$) lower IFS and FAB total scores than the MCI-o and SCD groups. Compared with the FAB, the IFS showed more statistically significant ($p < .05$) differences between diagnostic groups, greater accuracy (IFS AUC = .80, FAB AUC = .75, $p = .036$) in detecting ED and marginally stronger correlations with neuropsychological measures. We found no statistically significant differences in the EOD group scores from baseline up to 6- or 12-months follow-up. **Conclusions:** While both tests can detect EOD among memory clinic patients, the IFS may be more reliable in detecting ED than the FAB.

Keywords: neurodegenerative diseases; mild cognitive impairment; executive functions; neuropsychology; neuropsychological assessment; cognitive screening

(Received 28 February 2023; final revision 11 July 2023; accepted 12 September 2023)

Introduction

Early-onset dementia (EOD), the onset of the disease at the age of 65 years or younger, is a diagnostic challenge. As there is a wider range of possible etiologies to consider in EOD than in late-onset dementia (LOD; Masellis et al., 2013), EOD patients are more likely to end up being misdiagnosed than LOD patients (van Vliet et al., 2013; Woolley et al., 2011). One characteristic of EOD is early and prominent executive dysfunction (ED), which refers to the impairment of cognitive functions essential to fluent performance and goal-directed behaviors, such as in working memory operations, inhibition, and task-switching (Diamond, 2013; Miyake et al., 2000). ED is more prominent in both early-onset Alzheimer's disease (AD) and early-onset vascular dementia (VaD) than in later-onset forms of such diseases (Jang et al., 2016; Mendez, 2019; Smits et al., 2012). The core feature of the behavioral variant frontotemporal dementia (bvFTD) is ED, which is more common in EOD than in LOD (Rascovsky et al., 2011). ED is also often present in other common and potentially treatable conditions underlying cognitive impairment in younger patients, including depression, sleeping disorders, pain problems, and drug abuse (Alves et al., 2014; Brownlow et al., 2020; Bunk et al., 2019; Lautenbacher et al., 2021; Smith et al., 2014). Detecting ED also has clinical value in identifying mild cognitive impairment (MCI) patients who either remain stable (Ganguli et al., 2019) or progress to dementia (Kim et al., 2016; Kirova et al., 2015; Reinvang et al., 2012).

Given the emphasis on ED in early-onset cognitive impairment, it is important to include the assessment of executive functions in cognitive evaluations conducted at an early stage. Typically, ED is

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Cite this article: Heikkinen A.-L., Tikkanen V., Hänninen T., Hublin C., Koivisto A.M., Saari T.T., Remes A.M., Paajanen T.I., & Krüger J. Utility of the INECO Frontal Screening and the Frontal Assessment Battery in detecting executive dysfunction in early-onset cognitive impairment and dementia. *Journal of the International Neuropsychological Society*, 1–11, https://doi.org/10.1017/S1355617723000619

assessed by standard neuropsychological tests, such as the Trail Making Test-Part B (TMT-B) (Reitan, 1958) and the Stroop test (Golden, 1978), to measure working memory, set shifting, and inhibition. Considering the multifaceted nature of the executive functions, a normal performance on a single task is not sufficient evidence of intact executive functions (Burgess & Stuss, 2017). As evidence of ED, clinical neuropsychologists often observe also qualitative aspects of performance that may not be presented on any test scores (Andrewes, 2016). A comprehensive neuropsychological assessment is highly recommended but time-consuming (Sitek et al., 2015). Cognitive screening tests can be useful in initial assessments and aid primary and occupational healthcare in identifying patients who need more detailed assessments. However, widely used screening tests for dementia, such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989) or the Mini-Mental State Examination (MMSE; Folstein et al., 1975), are designed for evaluating features typical of late-onset Alzheimer's disease, including memory impairment and global cognitive performance deficits (O'Malley et al., 2019; Sitek et al., 2015). Some screening tests include tasks that assess aspects of executive functioning, e.g., the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) or the Addenbrooke's Cognitive Examination-Revised (Mioshi et al., 2006).

To identify neuropsychological profiles with a prominent ED, it may be relevant to measure executive functions in more detail, as evidence has shown that a method specifically designed for detecting ED can better identify patients with dysexecutive profiles than general screening methods (Broche-Pérez et al., 2019; Fiorentino et al., 2013). Related to this, the Frontal Assessment Battery (FAB; Dubois et al., 2000) and the Institute of Cognitive Neurology (INECO) Frontal Screening (IFS; Torralva et al., 2009) are tools designed to assess executive functions and may be particularly useful in the early detection of EOD, especially considering the prominence of ED in EOD. The FAB and the IFS have good psychometric properties in terms of internal consistency and concurrent validity (Bahia et al., 2018; Dubois et al., 2000; Torralva et al., 2009). The clinical utilities of both tests have been evaluated mostly in older study populations, and both tests have shown the ability to distinguish healthy controls from patients with neurodegenerative diseases (Bahia et al., 2018; Ihnen et al., 2013; Moreira et al., 2014; Oguro et al., 2006; Torralva et al., 2009) or MCI (Goh et al., 2019; Moreira et al., 2019; Yamao et al., 2011). Furthermore, these tests can effectively distinguish AD from other dementia subtypes (Custodio et al., 2016; Iavarone et al., 2004; Nakaaki et al., 2007; Slachevsky et al., 2004; Torralva et al., 2009). However, conflicting results have also been reported (Bahia et al., 2018; Boban et al., 2012; Castiglioni et al., 2006; Lipton et al., 2005).

When comparing the two tests, the IFS seems more accurate in differentiating AD from bvFTD (Custodio et al., 2017; Gleichgerrcht et al., 2011), as well as AD or FTD from healthy controls (Custodio et al., 2016; Moreira et al., 2014). Furthermore, the IFS has been reported to identify MCI more accurately than the FAB (Fernández-Fleites et al., 2021) and to have stronger correlations with standard neuropsychological executive tests (Gleichgerrcht et al., 2011). Dementia diagnosis often requires clinical follow-up; therefore, the ability of a method to detect possible changes in executive functions is essential. There are only a few follow-up studies on the respective performances of the IFS and the FAB and they have shown partly contradictory results (Custodio et al., 2017; da Silva et al., 2021).

Despite the diagnostic challenges of EOD, there is limited literature about the utility of the IFS and the FAB in initial-level diagnostics with patients under 65 years of age. Thus, the current study aimed to extend previous studies by evaluating these tests for detecting ED in a younger clinical population, including multiple subgroups with different levels of cognitive impairment. We compared the performances of EOD, MCI due to neurological causes (MCI-n), MCI due to other causes such as depression or sleep disturbances (MCI-o) and subjective cognitive decline (SCD) groups. The MCI-n and MCI-o groups were analyzed separately because distinguishing between potentially reversible and nonreversible conditions is highly relevant in clinical settings. Given that ED is a prominent symptom in many EOD subtypes, we expected other patient groups to outperform EOD patients in both tests. Furthermore, considering previous studies, we hypothesized that the IFS has better discriminatory properties than the FAB in distinguishing patient groups (EOD/MCI-n vs others and EOD vs SCD) and detecting ED, as well as stronger correlations with standard neuropsychological tests. We also studied the test scores in a longitudinal setting and hypothesized that EOD patients would show a greater decline in performance on both tests than other groups, even though the results are not fully consistent in previous studies.

Materials and methods

Participants

Participants ($n = 210$) of the *Cognitive Impairment and Work Ability* study were recruited between 1.3.2019 and 31.3.2021 from among patients referred to the specialized memory outpatient clinics of Oulu or Kuopio University hospitals in Finland. These clinics are responsible for diagnosing neurodegenerative diseases in catchment areas in patients with symptom onset at the ages of 65 years or younger. All participants were native Finnish speakers. The specific inclusion criteria and patient groups are shown in Figure 1.

Experienced neurologists specializing in dementia and memory disorders diagnosed the patients in accordance with current diagnostic guidelines (Gorno-Tempini et al., 2011; McKhann et al., 2011; Mckeith et al., 2017; O'Brien et al., 2003; Rascovsky et al., 2011; Winblad et al., 2004) based on a comprehensive diagnostic workup that included medical history, neuropsychological assessment, magnetic resonance imaging of the brain, laboratory tests, and neurological examinations. The cerebrospinal fluid markers of $A\beta_{42}$, tau and phosphotau ($n = 77$), or FDG-PET ($n = 12$) from a subset of patients were analyzed. When diagnostics required evidence of symptom progression, the patients' conditions up to two years before receiving the diagnosis were assessed. All patients received oral and written information on the study and provided written informed consent in accordance with the Declaration of Helsinki. The ethics committees of the Northern Ostrobothnia and Northern Savo Hospital districts approved the study.

Diagnostic outcomes

The EOD, MCI-n, MCI-o, and SCD groups were formed based on the final diagnoses made at the memory clinic (Figure 1). The EOD group ($n = 49$) included patients diagnosed with neurodegenerative disorders, VaD or alcohol-related dementia. The MCI-n ($n = 34$) patients had vascular cognitive impairment or MCI due to a suspected neurodegenerative disease. The MCI-o group ($n = 99$) included individuals diagnosed with a cognitive impairment

https://doi.org/10.1017/S1355617723000619 Published online by Cambridge University Press

Table 1. The neuropsychological tests used for the assessment of cognitive domains

Cognitive domain[a]	The neuropsychological tests used in the assessment	References
Verbal memory	WMS III Logical Memory I & II, Word List I and II and recognition task	(Wechsler, 2008)
Visual memory	WMS III Visual Reproduction I & II, ROCFT immediate and delayed recall	(Lezak et al., 2012; Wechsler, 2008)
Working memory	WAIS-IV Digit Span and Letter–Number Sequencing	(Wechsler, 2012)
Attention and vigilance	247 Cancelation Test	(Lezak et al., 2012)
Executive functions	TMT-B, Stroop test, Serial alternating S, dual task (phonemic fluency and serial alternating S)	(Allison, 1966; Golden, 1978; Lezak et al., 2012; Reitan, 1958)
Processing speed	TMT-A, WAIS-IV Digit Symbol Coding and Symbol Search	(Lezak et al., 2012; Reitan, 1958)
Language skills	WAIS-IV Similarities and Comprehension, semantic and phonemic fluency, 15-Item version of the Boston Naming Test	(Lezak et al., 2012; Morris et al., 1989; Wechsler, 2012)
Visuospatial skills	WAIS-IV Block Design and Visual Puzzles, copying tasks (flag, cube and Greek cross), clock hands, ROCFT copy	(Lezak et al., 2012; Morris et al., 1989; Wechsler, 2012)

Abbreviations: WMS, Wechsler Memory Scale; ROCFT, Rey-Osterrieth Complex Figure Test; WAIS, Wechsler Adult Intelligence Scale; TMT-B, Trail Making Test Part B; TMT-A, Trail Making Test Part A.
[a]The scale on each cognitive domain was as follows: 0 = normal cognition, 1 = subtle impairment, 2 = mild impairment, 3 = moderate impairment, and 4 = severe impairment.

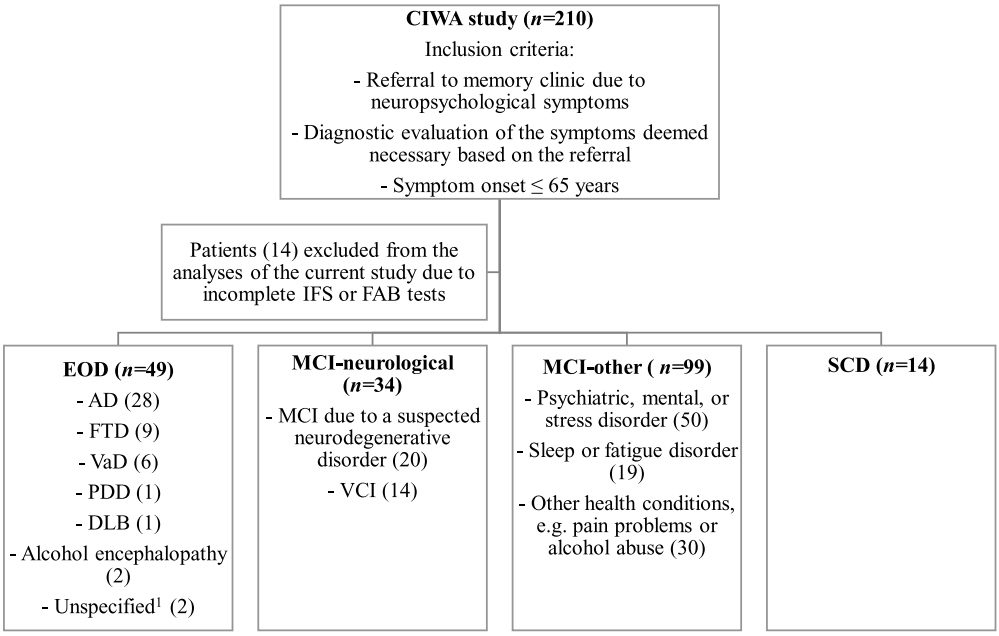

Figure 1. The Cognitive Impairment and Work Ability (CIWA) study participants. Abbreviations: AD, Alzheimer's disease; FTD, Frontotemporal dementia; VaD, Vascular dementia; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; VCI, vascular cognitive impairment; SCD, subjective cognitive decline. [1] Two patients were diagnosed with dementia due to a neurodegenerative disorder; however, the specific subtype could not yet be specified by the time of the last visit of this study.

related to conditions other than a degenerative or vascular condition. In accordance with the research guidelines and recent findings (Jessen et al., 2020; Molinuevo et al., 2017; Wolfsgruber et al., 2020), SCD ($n = 14$) patients reported subjective cognitive symptoms with a rather sudden or insidious onset and a concern associated with the symptoms. Their performances in the neuropsychological assessment were within a normal or subtle impairment range (i.e. not meeting the criteria of MCI). All the SCD patients were evaluated by the neurologists as not expressing any signs of an incipient neurodegenerative disease.

Neuropsychological assessment and classification of cognitive impairment levels

As part of the diagnostic workup for the participants, neuropsychological assessment was conducted by experienced psychologists specializing in assessing patients with memory disorders. Table 1 summarizes the neuropsychological tests used and the cognitive functions assessed by these tests. As with an advanced level neuropsychological assessment, the impairment level on each cognitive domain was determined based on clinical evaluations (i.e., integrative interpretation of the cognitive test results considering normative data, premorbid intelligence level, and qualitative and quantitative test performance) (Jacova et al., 2007; Weintraub, 2022). The scoring was as follows: normal cognitive functioning (0), subtle (1), mild (2), moderate (3) or severe (4) cognitive impairment. The general impairment level was calculated as the mean of all cognitive domains.

The IFS and the FAB

The participants attended another session for a more specific assessment of executive functions, including novel computer-based tests and the IFS and FAB tests. The assessment was conducted at baseline (average of 25 days after the neuropsychological assessment), 6 months and 12 months.

The FAB includes six subtests: Conceptualization, Verbal Fluency, Motor Programming, Conflicting Instructions, Motor Inhibitory Control, and Prehension Behavior (Dubois et al., 2000). The score range for all the subtests is 0–3 points, resulting in a maximum score of 18 points. The IFS consists of eight subtests (Torralva et al., 2009), including three identical subtests with the

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Table 2. Patient demographics

	Total sample $n = 196$	Diagnostic outcome				p-value
		EOD $n = 49$	MCI-n $n = 34$	MCI-o $n = 99$	SCD $n = 14$	
Age (mean, *SD*)	57.4 (6.1)	59.8 (4.7)[a,b]	60.7 (5.2)[c,d]	55.3 (6.3)[a,c]	55.5 (5.1)[b,d]	**<.001**
Gender (female, %)	56.6	55.1	55.9	56.6	64.3	.943
Education (%):						
≤9 years	17.4	20.4	15.2	18.2	7.1	.455
10–12 years	51.8	53.1	63.6	48.5	42.9	
>12 years	30.8	26.5	21.2	33.3	50.0	
Working (%)	39.8	20.4[a]	32.4	46.5[a]	78.6*	**<.001**

Abbreviations: EOD = Early-onset dementia; MCI-n = Mild cognitive impairment-neurological; MCI-o = Mild cognitive impairment-other; SCD = Subjective cognitive decline; *SD*, standard deviation. Statistically significant ($p < .05$) p-values are highlighted. [a,b,c,d]Letter-pair (e.g., a–a) denotes a statistically significant pairwise group comparison ($p < .05$, after correction with the Bonferroni method). *All pairwise comparisons to the other diagnostic group are significant ($p < .05$, after correction with the Bonferroni method).

FAB (Motor Programming, Conflicting Instructions, Motor Inhibitory Control), along with Verbal Inhibitory Control (0–6 points), Abstraction Capacity (0–3 points), Backward Digit Span (0–6 points), Verbal Working Memory (0–2 points), and the Spatial Working Memory (0–4 points). The maximum score for the IFS is 30 points, and a higher score reflects better functioning in both tests. Officially translated (Finnish) versions of the original tests were used in the study. The tests were administered in the same order to all participants: first the shared subtests, followed by the FAB only and then the IFS subtests only.

Data analysis

Group differences for gender, education, and work status were identified using the chi-square test, while those for age and the IFS and FAB scores were examined using the non-parametric Kruskal-Wallis test. The IFS and the FAB results were also analyzed using the quantile regression, with age and diagnostic group as the explanatory variables. The eta-squared (η^2) was calculated as an effect size measure and interpreted as small (.01–.059), medium (.06–.139) or large (≥.14) (Fritz et al., 2012). For correlation analyses, the Spearman's correlation coefficient (r) was used, and the results were interpreted as very weak (≤.19), weak (.20–.39), moderate (.40–.59), strong (.60–.79) or very strong (≥.80) (Evans, 1996). For comparing the IFS and the FAB follow-up data, the Wilcoxon signed-rank test and r-values as effect size measures were calculated (Tomczak & Tomczak, 2014). Receiver operating characteristic (ROC) analysis with area under the curve (AUC) values was used for evaluating the IFS and the FAB and distinguishing the following groups: (a) EOD and MCI-n patients from other patient groups, (b) EOD from SCD subjects, and (c) patients exhibiting at least a mild impairment in the executive function and/or working memory domains from those who perform within a normal range. The discriminatory accuracies of the IFS and the FAB were compared following the method described by DeLong et al. (1988).

A p-value < .05 was considered statistically significant. The Bonferroni correction was used to adjust the significance values in pairwise comparisons. All statistical analyses were performed using the IBM SPSS version 27.0 software.

Results

Demographics

The demographics for the total study population and the diagnostic groups are summarized in Table 2. The results showed that the EOD, MCI-n, MCI-o, and the SCD groups did not differ in terms of gender ($p = .943$) or education level ($p = .455$). However, significant ($p < .001$) differences in age were observed: the EOD and MCI-n patients were older than the MCI-o and SCD subjects. Moreover, the proportion of SCD subjects currently working was significantly higher than in any of the other patient groups ($p < .001$). Thus, patients diagnosed with a cognitive impairment, irrespective of its etiology, were likelier to be outside of working life.

Group differences in the IFS and the FAB performance

The IFS and the FAB results of the total sample and diagnostic groups are summarized in Table 3. The EOD and MCI-n groups had significantly lower scores on the IFS than the MCI-o and SCD groups. The SCD group also performed at a higher level than the MCI-o patients; therefore, the SCD group outperformed all other groups in the IFS total score. The FAB score results followed a similar pattern; however, the difference between the SCD and MCI-o groups was not significant.

Age ($p < .05$) and diagnostic group ($p < .01$) contributed significantly to the IFS and the FAB regression models. The diagnostic group had a stronger relative contribution than the age in the IFS and FAB regression models, as the model fit decreased by 11% and 12% for the IFS and FAB, respectively, after removing the diagnostic group, and by 3% and 0.3%, respectively, after removing age.

Shared subtests of the IFS and the FAB

In the Motor Programming subtest, the SCD group performed better than the other groups (Figure 2). In Conflicting Instructions, the EOD group performed at a lower level than the MCI-n and MCI-o groups. Significant group differences were also observed in Motor Inhibitory Control, where the MCI-o and SCD groups performed better than the EOD and MCI-n groups.

Subtests included only in the IFS

Statistically significant group differences were observed in all the subtests included only in the IFS. The SCD group performed better than the EOD and MCI-n groups in Backward Digit Span, whereas the EOD group scored significantly lower than the MCI-o and SCD groups in Verbal Working Memory. The SCD group outperformed all other groups in Spatial Working Memory. There were also statistically significant group differences in Abstraction Capacity, in which the EOD group had weaker results than the SCD group. Finally, the MCI-n group had a lower score on Verbal Inhibitory Control than the MCI-o and SCD groups.

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Table 3. The INECO Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) results for the total sample and the diagnostic groups

		Mean score (standard deviation), 95% confidence interval for mean					
	Total, $n = 196$	EOD, $n = 49$	MCI-n, $n = 34$	MCI-o, $n = 99$	SCD, $n = 14$	p-value	η^2
IFS Total Score	19.5 (4.8) 18.8, 20.1	16.7 (5.7)[a] 15.1, 18.4	18.0 (3.2)[b] 16.9, 19.1	20.6 (3.9)[a,b] 19.8, 21.3	24.7 (2.3)* 23.4, 26.0	**<.001**	.214
FAB Total Score	14.7 (2.5) 14.3, 15.0	13.2 (2.7)[a,b] 12.4, 14.0	13.9 (2.1)[c,d] 13.2, 14.6	15.4 (2.1)[a,c] 15.0, 15.8	16.9 (1.1)[b,d] 16.3, 17.6	**<.001**	.200
Shared subtests							
Motor Programming	1.7 (1.1) 1.5, 1.8	1.4 (1.1) 1.1, 1.7	1.4 (1.0) 1.0, 1.7	1.8 (1.0) 1.6, 2.0	2.7 (0.5)* 2.4, 3.0	**<.001**	.094
Conflicting Instructions	2.6 (0.8) 2.5, 2.7	2.2 (1.1)[a,b] 1.8, 2.5	2.7 (0.7)[a] 2.5, 3.0	2.8 (0.6)[b] 2.7, 2.9	2.9 (0.4) 2.6, 3.0	**<.001**	.082
Motor Inhibitory Control	1.9 (1.1) 1.7, 2.0	1.4 (1.0)[a,b] 1.1, 1.6	1.4 (0.9)[c,d] 1.1, 1.8	2.2 (1.0)[a,c] 2.0, 2.4	2.5 (0.9)[b,d] 2.0, 3.0	**<.001**	.146
Only IFS							
Backward Digit Span	3.2 (1.0) 3.0, 3.3	3.0 (1.2)[a] 2.6, 3.3	3.0 (0.9)[b] 2.7, 3.3	3.2 (1.0) 3.0, 3.4	3.9 (0.8)[a,b] 3.5, 4.4	**.012**	.042
Verbal Working Memory	1.7 (0.6) 1.6, 1.8	1.3 (0.9)[a,b] 1.1, 1.6	1.8 (0.4) 1.7, 1.9	1.8 (0.5)[a] 1.7, 1.9	2.0 (0.0)[b] 2.0, 2.0	**<.001**	.092
Spatial Working Memory	2.6 (1.1) 2.5, 2.8	2.4 (1.1) 2.1, 2.7	2.4 (1.0) 2.1, 2.8	2.7 (1.1) 2.5, 2.9	3.5 (0.7)* 3.1, 3.9	**.002**	.060
Abstraction Capacity	1.6 (0.9) 1.5, 1.7	1.4 (0.9)[a] 1.2, 1.7	1.5 (0.9) 1.2, 1.8	1.6 (0.9) 1.5, 1.8	2.2 (0.6)[a] 1.8, 2.6	**.025**	.033
Verbal Inhibitory Control	4.2 (1.7) 3.9, 4.4	3.7 (2.0) 3.2, 4.3	3.7 (1.5)[a,b] 3.2, 4.2	4.4 (1.5)[a] 4.1, 4.7	5.0 (1.0)[b] 4.4, 5.6	**.007**	.047
Only FAB							
Conceptualization	2.9 (0.3) 2.9, 3.0	2.8 (0.5)[a] 2.7, 2.9	2.9 (0.4) 2.7, 3.0	3.0 (0.2)[a] 2.9, 3.0	2.9 (0.3) 2.8, 3.0	**.007**	.047
Prehension Behavior	3.0 (0.0) 3.0, 3.0	3.0 (0.0) 3.0, 3.0	3.0 (0.0) 3.0, 3.0	3.0 (0.0) 3.0, 3.0	3.0 (0.0) 3.0, 3.0	1.00	.031
Verbal Fluency	2.6 (0.6) 2.5, 2.7	2.5 (0.8) 2.2, 2.7	2.5 (0.7) 2.3, 2.7	2.7 (0.6) 2.6, 2.8	2.9 (0.3) 2.8, 3.0	.054	.016

Abbreviations: EOD = Early-onset dementia; MCI-n = Mild cognitive impairment-neurological; MCI-o = Mild cognitive impairment-other; SCD = Subjective cognitive decline; η^2 = eta-squared estimate of an effect size. Statistically significant ($p < .05$) p-values are highlighted. [a,b,c,d]Letter-pair (e.g., a–a) denotes a statistically significant pairwise group comparison ($p < .05$, after correction with the Bonferroni method). *All pairwise comparisons to the other diagnostic groups are significant ($p < .05$, after correction with the Bonferroni method).

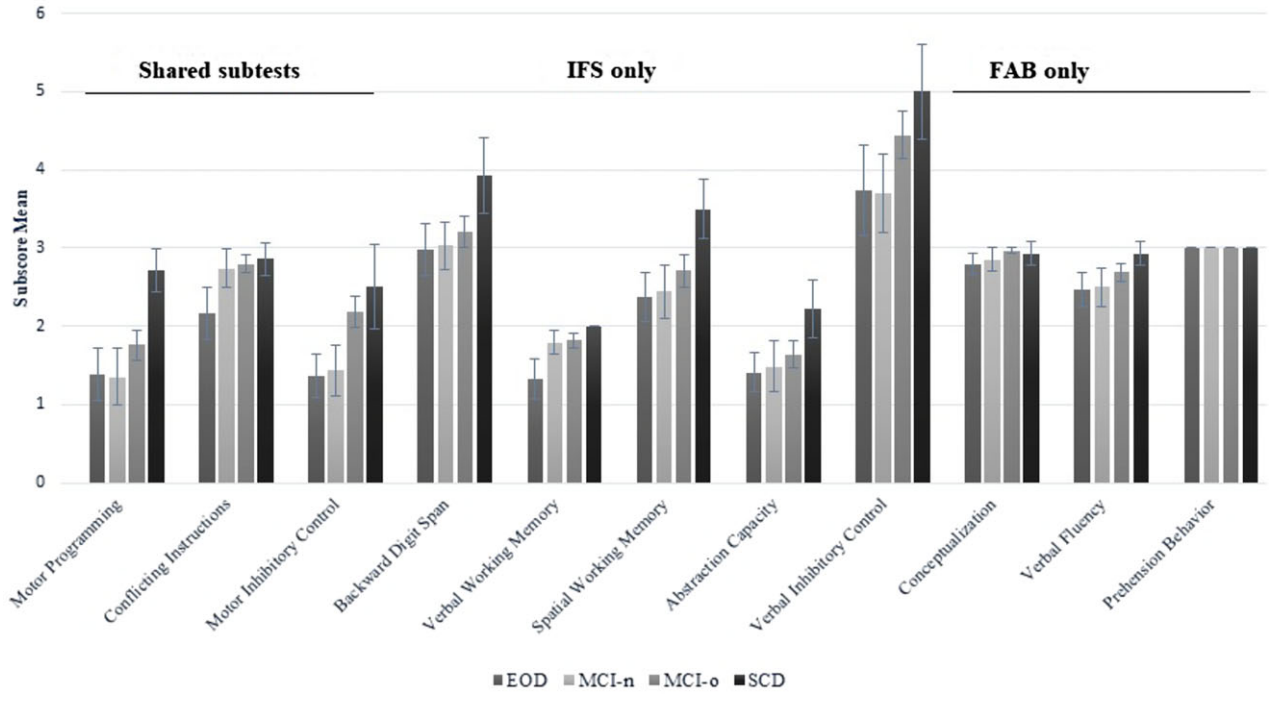

Figure 2. The INECO Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) subtests (mean scores with 95% confidence intervals) for early-onset dementia (EOD), mild cognitive impairment-neurological (MCI-n), Mild cognitive impairment-other (MCI-o), and subjective cognitive decline (SCD) patients.

https://doi.org/10.1017/S1355617723000619 Published online by Cambridge University Press

Table 4. Spearman correlation coefficients between the frontal assessment methods and clinical neuropsychological impairment levels

			Shared subtests			Only IFS					Only FAB		
	IFS	FAB	MP	CI	MIC	BDS	VWM	SWM	AC	VIC	C	PB	VF
Clinical assessment													
General impairment	**−.63**	**−.56**	−.38	−.31	**−.43**	**−.43**	−.39	**−.40**	−.35	−.27	−.18	–	**−.42**
Verbal memory	**−.42**	**−.43**	−.25	−.22	−.33	−.18	−.23	−.16	−.25	−.23	−.17	–	−.28
Visual memory	−.38	−.38	−.21	−.21	−.36	−.14	−.32	−.29	−.17	−.17	−.10	–	−.23
Working memory	**−.45**	−.35	−.24	−.30	−.20	**−.56**	−.21	−.34	−.23	−.11	−.14	–	−.27
Attention	−.30	−.24	−.16	−.14	−.22	−.25	−.16	−.18	−.05	−.15	−.00	–	−.14
Executive functions	**−.57**	**−.48**	−.37	−.35	−.32	−.32	−.34	−.36	−.32	−.34	−.14	–	−.32
Processing speed	**−.45**	**−.44**	−.34	−.16	−.35	−.31	−.35	−.20	−.25	−.15	−.10	–	−.34
Language skills	**−.52**	**−.47**	−.30	−.30	−.27	−.24	−.33	−.25	**−.54**	−.24	−.20	–	**−.52**
Visuospatial skills	**−.48**	−.34	−.25	−.21	−.26	−.35	−.26	**−.40**	−.33	−.23	−.14	–	−.21
Test Scores													
TMT-B (s)	**−.59**	**−.52**	−.37	−.31	−.39	−.36	−.34	**−.44**	−.35	−.21	−.21	–	−.32
Stroop (s)	−.38	−.35	−.30	−.15	−.26	−.34	−.27	−.23	−.34	−.03	−.14	–	−.30

Abbreviations: IFS = INECO Frontal Screening; FAB = Frontal Assessment Battery; MP = Motor Programming; CI = Conflicting Instructions; MIC = Motor Inhibitory Control; BDS = Backward Digit Span; VWM = Verbal Working Memory; SWM = Spatial Working Memory; AC = Abstraction Capacity; VIC = Verbal Inhibitory Control; C = Conceptualization; PB = Prehension Behavior; VF = Verbal Fluency.
Note. When $r \leq -0.15$, $p < .05$. When $r \leq -0.20$, $p < .01$. Correlations ≤ −0.40 are highlighted.

Table 5. The INECO Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) follow-up results

	Baseline[a]	6 months		12 months		Baseline vs. 6 months		Baseline vs. 12 months		6 months vs. 12 months	
	Mean (*SD*)	*n*	Mean (*SD*)	*n*	Mean (*SD*)	*p*-value	*r*	*p*-value	*r*	*p*-value	*r*
IFS results											
EOD	16.5 (5.3)	40	16.6 (5.3)	40	16.2 (4.7)	.989	−.00	.997	.00	.456	−.13
MCI-n	18.0 (3.3)	29	19.0 (3.7)	27	19.5 (3.7)	**.046**	.37	**.044**	.39	.287	.21
MCI-o	20.6 (4.0)	92	21.2 (3.8)	89	21.7 (3.7)	.056	.20	**.017**	.27	.152	.15
SCD	24.4 (2.0)	13	24.5 (2.0)	12	24.8 (2.8)	.636	.13	.237	.34	.443	.22
FAB results											
EOD	13.2 (2.5)	40	13.4 (2.6)	40	13.6 (2.7)	.438	.13	.438	.12	.771	−.05
MCI-n	13.9 (2.1)	29	14.6 (2.1)	27	14.4 (2.2)	**.041**	.38	.257	.22	.674	−.08
MCI-o	15.4 (2.2)	92	15.7 (2.0)	89	16.0 (2.0)	.259	.12	**.006**	.32	.170	.15
SCD	16.9 (1.2)	13	17.3 (0.9)	12	16.8 (1.3)	.190	.36	.803	−.07	.119	−.45

Abbreviations: EOD = Early-onset dementia; MCI-n = Mild cognitive impairment-neurological; MCI-o = Mild cognitive impairment-other; SCD = Subjective cognitive decline. Statistically significant ($p < .05$) *p*-values are highlighted.
[a]The calculated baseline mean and standard deviation (*SD*), including those who participated at 6 and 12-months follow-up.

Subtests included only in the FAB

In the subtests unique to the FAB, the only statistically significant group difference was found in the Conceptualization task, wherein the EOD group performed worse than the MCI-o group. All subjects scored a full 3 points in Prehension Behavior, reflecting a notable ceiling effect for this subtest.

Correlations between the IFS/FAB scores and neuropsychological measures

In the complete sample, there were several significant associations between the IFS and the FAB test scores and the clinical neuropsychological impairment levels (Table 4). In particular, the general cognitive impairment correlated strongly with the IFS ($r = -.63$) and moderately with the FAB ($r = -.56$). Moderate correlations were observed between the scores for the executive function impairment and frontal screening tests (for IFS, $r = -.57$; for FAB, $r = -.48$) and the TMT-B test (for IFS, $r = -.59$; for FAB, $r = -.52$). The correlations between the neuropsychological measures and the IFS total score and subtests were more often statistically significant and were also slightly stronger than those of the FAB total score and subtests. The correlations for the Prehension Behavior subtest could not be calculated due to the lack of variance in the results.

Results related to the longitudinal setting

The IFS and the FAB scores and the results of the statistical analyses at baseline, 6 months and 12 months are shown in Table 5 and Figure 3. The performance of the EOD group in the IFS test did not change from baseline to follow-up. When examining only those EOD patients diagnosed with AD, we found significantly ($p < .05$) lower scores at the latter measurement points than at baseline (mean scores for baseline: 18.2; 6 months: 17.3; 12 months: 16.9). The MCI-n group's scores increased in the follow-up: scores after 6 and 12 months were higher than at baseline ($p < .05$). The MCI-o group's IFS scores increased from baseline to 12 months ($p = .017$). No significant changes in the SCD test scores were observed. The FAB scores increased significantly ($p < .05$) for the MCI-n group from baseline to 6 months and for the MCI-o group from baseline to 12 months. No other statistically significant differences were observed. The AD group's FAB scores did not change during the follow-up.

Discrimination accuracy of the IFS and the FAB

The ability to distinguish EOD and MCI-n patients from MCI-o and SCD patients was studied (Figure 4). The IFS (AUC = .74) and the FAB (AUC = .75) showed moderate and similar ($p = .689$) accuracies in differentiating between EOD and MCI-n patients

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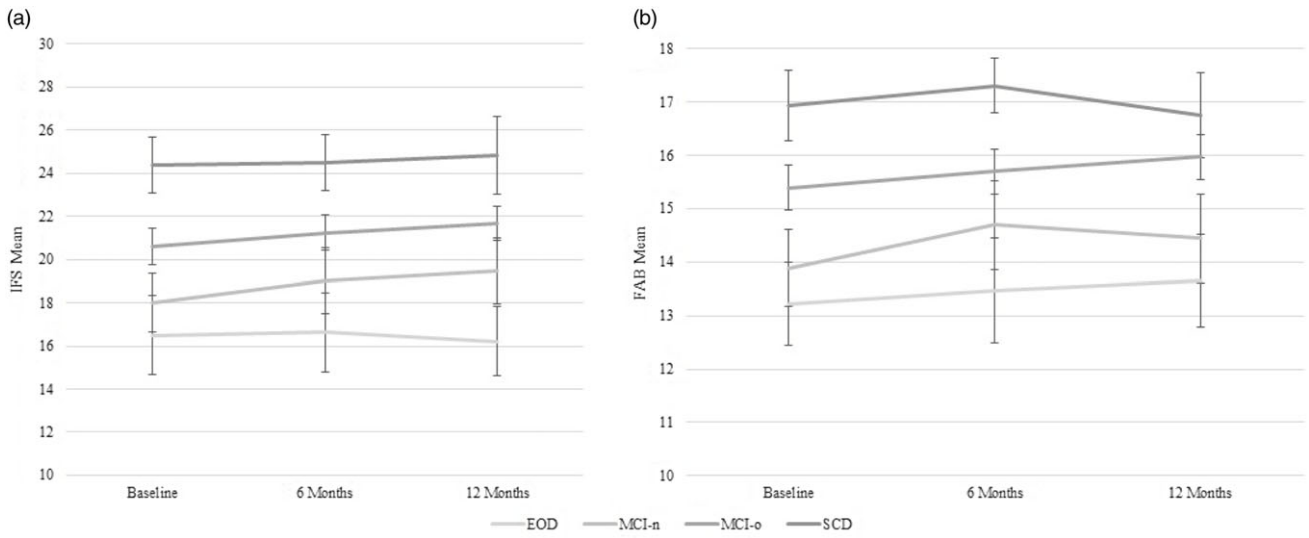

Figure 3. The mean scores and 95% confidence intervals at baseline, 6 months and 12 months for (a) the INECO Frontal Screening (IFS) and (b) the Frontal Assessment Battery (FAB). Abbreviations: EOD = Early-onset dementia; MCI-n = Mild cognitive impairment-neurological; MCI-o = Mild cognitive impairment-other; SCD = Subjective cognitive decline.

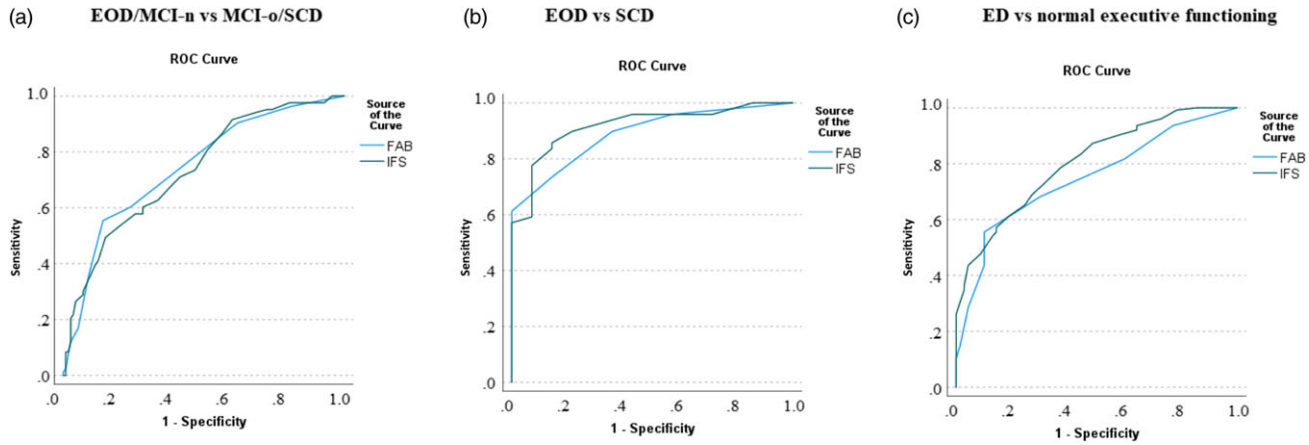

Figure 4. The INECO Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) receiver operating characteristic (ROC) curves in comparing (a) Early-onset dementia (EOD) and Mild cognitive impairment-neurological (MCI-n) vs Mild cognitive impairment-other (MCI-o) and Subjective cognitive decline (SCD), (b) Early-onset dementia (EOD) vs Subjective cognitive decline (SCD), and (c) executive dysfunction (ED) vs normal executive functioning.

from MCI-o and SCD patients. The optimal cutoff values for the group discriminations were defined by visually inspecting the ROC curves and selecting the highest combination of sensitivity and specificity when the sensitivity value exceeded 80%. For the IFS, a cutoff score of 22.5 produced a sensitivity and a specificity of 86.7% and 43.4%, respectively, whereas the corresponding values for a score of 23 were 91.6% and 39.8%. For the FAB, a cutoff score of 16 produced a sensitivity of 73.5% and a specificity of 59.5%, whereas the corresponding values for a cutoff score of 17 were 90.4% and 38.1%, respectively.

Furthermore, both tests showed similar ($p = .409$) abilities to differentiate EOD patients from the SCD group (IFS AUC = .92, FAB AUC = .89). With 22.5 points as a cutoff value for the IFS, the sensitivity was 83.7%, and the specificity was 85.7%. Considering the FAB, a cutoff value of 17 points produced a sensitivity of 89.8%; however, specificity was notably lower (64.3%).

In differentiating patients with ED from those who showed normal performance, the difference in discriminatory accuracy between the IFS and the FAB was statistically significant ($p = .036$, for IFS, AUC = .80 and for FAB, AUC = .75). With the same cutoff values (i.e. 22.5 and 17 points), the sensitivity and specificity of the IFS in detecting ED were 83.3% and 55.7%, respectively, whereas the corresponding values for the FAB were 81.7% and 40.0%.

Discussion

To our knowledge, this is the first study to evaluate the IFS and the FAB tests in assessing patients younger than 65 years in a memory clinic setting. The main finding reveals that both tests are applicable in detecting EOD patients from memory clinic patients who do not have neurological causes behind their cognitive problems. We also found that the IFS is more accurate than the FAB in differentiating individuals with ED from those with intact executive functioning. These findings have important clinical application potential because short and accurate cognitive tests targeted to capture ED are of great value for initial assessment in primary healthcare.

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The results of the current study are in line with previous reports on older patient cohorts reporting that the IFS and the FAB can effectively differentiate dementia (Custodio et al., 2016) and MCI patients (Fernández-Fleites et al., 2021) from healthy controls. The patient groups differed significantly in the total scores and in many individual subtests. In particular, the subtests included in both tests seem to tap into relevant aspects of ED in younger patients. In general, the EOD group scored lower than the other groups, whereas the SCD group tended to score the highest. Specifically, the Motor Programming subtest can differentiate SCD from other patient groups, while the Conflicting Instructions subtest can distinguish patients with EOD from other memory clinic patients.

In line with previous findings, there were more significant group differences in the subtests included only in the IFS than in the FAB (Gleichgerrcht et al., 2011). In the subtests unique to the FAB, only one significant group difference was observed. The Prehension Behavior subtest seemed unsuitable for assessing younger memory clinic patients with cognitive symptoms, as all participants performed without errors. Our result is consistent with earlier findings suggesting that this subtest has low sensitivity and that the clinical usefulness of the FAB might be better without this specific subtest (Ilardi et al., 2022). In fact, the scores of all of our patient groups on the FAB-only subtests were close to the maximum scores. Thus, these subtests may not be challenging enough for this patient population, or, alternatively, the scoring should be stricter. Furthermore, considering the stronger total score effect sizes, it may be more reasonable to use the total scores when making clinical evaluations of ED. As the IFS has a wider score range than the FAB, it may be less prone to the ceiling effect and more likely to capture differences in the mild impairment range.

To analyze concurrent validity, we examined the correlations between the IFS and the FAB performances and the patients' cognitive impairment levels. The strongest correlations were found between the IFS and the FAB total scores and the general cognitive impairment level. Such a result can be interpreted as an indicator of low specificity. Conversely, we argue that our patient cohort's characteristics (i.e. high prevalence of ED) and the operationalization of general cognitive impairment (i.e. based on thorough neuropsychological assessment instead of a narrow battery, such as MMSE) explain these results. Moreover, the correlation between the frontal screening tests' total scores and the impairment of language skills was moderate, reflecting that many tests of language processing require executive functions, and vice versa (O'Callaghan et al., 2013). A single neuropsychological test rarely succeeds in strictly assessing one domain of cognition, and a poor test result may be due to several reasons (Sitek et al., 2015). For example, difficulties in verbal fluency may be due to language processing, executive functions or processing speed deficits (Aita et al., 2019; Stolwyk et al., 2015; Whiteside et al., 2016). In our study, verbal fluency and similarity tests were used to assess language abilities. However, these can also be used to measure executive functions, and in fact, versions of them are included in the FAB. This likely explains the relatively high ($r = -.52$) correlation between the verbal fluency subtest and the language skills domain.

Some differences in the IFS and the FAB correlations with the neuropsychological variables were observed in favor of the IFS. For example, we found a moderate correlation between working memory impairment level and the IFS, whereas the correlation was weak between the FAB and working memory impairment. In accordance with a previous comparison study (Gleichgerrcht et al., 2011), the correlations were more often higher for the IFS than for the FAB. However, the differences are very small, so their clinical significance is likely to be minor.

Considering the assessment of symptom progression, Da Silva et al. (2021) found that the scores of both tests remained unchanged at 12-months follow-up for bvFTD and AD patients. Custodio et al. (2017) reported that the IFS scores of stroke patients with and without vascular cognitive impairment decreased at 12 months follow-up. In the present study, the IFS and the FAB scores of the EOD group were already abnormal at baseline, and against our hypothesis, no significant changes in follow-up were observed. When examining patients diagnosed with AD, the IFS scores decreased at follow-up. This may be due to AD patients typically having a greater impairment of memory functions than other patients with dementia, resulting in a lower practice effect in retesting. However, such an effect was not observed for the FAB scores of AD patients. The IFS and the FAB scores of the MCI-n group tended to increase at the follow-up, and the same effects were also observed in the MCI-o group, although only for the IFS. This indicates that MCI patients may have benefitted from retesting more than EOD patients.

Interestingly, no significant practice effect was observed in the SCD group, which may be due to a ceiling effect, i.e., high performance already at baseline (IFS = 24.7 and FAB = 16.9). Taken together, our results reveal that both tests should be used with caution as a follow-up measure in younger patients, at least when the test-retest interval is as short as 6 months. The results also suggest that the unchanged scores in relatively short-term retesting should not be considered as an exclusion criterion for EOD. In general, the assessment of ED in a longitudinal setting might be problematic because retesting might reduce the task's ability to capture the target executive process. This might be a general feature of executive tasks (Calamia et al., 2013; Lemay et al., 2004) rather than a specific weakness of the present methods.

Finally, we evaluated and compared the discriminatory accuracy of the IFS and the FAB in different settings. Given the importance of early diagnosis for patients and their caregivers, one of the main purposes of a screening test is to recognize potential dementia patients. Therefore, it was important to evaluate the tests' accuracy in distinguishing EOD and MCI-n patients from the MCI-o and SCD groups, and we found it to be moderate for both tests. With cutoff scores of 22.5 for the IFS (sensitivity = 0.87, specificity = 0.43) and 17 for the FAB (sensitivity = 0.90, specificity = 0.38), the tests had higher sensitivity but lower specificity. In the case of screening tests, the emphasis on sensitivity rather than specificity does not lead to wrong diagnosis, because the tests are used to assess the need for referral to a more detailed diagnostic evaluation. Furthermore, sensitivity would likely have been higher had we compared the patient groups to healthy controls instead of other memory clinic patients. Notably, the cutoff score of 17 is only one point lower than the maximum score of the FAB, indicating that the participants performed well on the test. Thus, in clinical practice, the discrimination power of the FAB might turn out to be weak. Moreover, when examining the ability to differentiate subjects with ED from those with intact executive functioning, the IFS proved to be superior to the FAB. This might be related to the fact that the former covers a wider range of executive functions and includes tests for verbal inhibitory control and working memory. These subtests have demonstrated high sensitivity in detecting subtle EDs also in a previous study (Gleichgerrcht et al., 2011).

One of the strengths of our study was the prospective study design and the nonselective nature of the study population, as all

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patients referred to the memory clinics were offered the opportunity to join the study, regardless of the diagnosis they received. By having no exclusion criteria other than age at symptom onset, we wanted to capture the whole spectrum of patients with unclear etiologies to cognitive symptoms. Furthermore, we used a comprehensive neuropsychological assessment in the study and measured the correlations between the screening tests and cognitive domains more extensively than most of the earlier studies (Gleichgerrcht et al., 2011; Ihnen et al., 2013; Kugo et al., 2007). The screening tests were completed at a later study visit, and the results were not given to the neurologist. Therefore, there was no risk that the screening test results would influence the neuropsychological assessment or the diagnosis. As the IFS and the FAB tests were conducted before the patients received a diagnosis, the results reflect the early phase of the evaluation process.

The major limitations of the study are its relatively small group sizes and the lack of a healthy population-level representative reference group. Instead, the SCD group served as a reference group, because it is clinically relevant to compare groups of patients referred for a memory clinic rather than to compare patients with healthy individuals. Due to the small group sizes, we were unable to analyze the dementia subgroups separately. However, the aim of the study was to compare the IFS and the FAB performances of cognitively symptomatic patients within the early-onset category and with different etiologies of cognitive impairment. Although our results do not tap into the exact differential diagnostics, we provide clinically relevant information for initial assessment purposes in differentiating patient groups and in identifying those who might need a referral towards a more thorough evaluation due to ED. Another weakness of the study is the lack of general screening tests. Having for example MoCA in the test battery would have enabled us to evaluate the possible additional benefits of the joint use of a specific ED assessment and global screening tools in assessing younger memory clinic patients. Finally, as all patients were native speakers of Finnish, the generalisability of the results to other groups remains to be addressed in future studies.

In conclusion, the IFS and the FAB seem to be useful in assessing younger memory clinic patients whose cognitive symptoms are due to different underlying causes. In line with previous reports on older or mixed patient cohorts, the IFS seems to have a slightly better ability to differentiate subjects with ED from those with intact executive functioning and to correlate with standard neuropsychological tests than the FAB. In the future, further research on the IFS and the FAB is needed in larger study samples and with separate disease groups and healthy controls in the study setting.

Acknowledgements. The authors have no conflicts of interest to report. The *Cognitive Impairment and Work Ability* study was funded by the Finnish Work Environment Fund (Grant Number: 180038). The first authors received personal research grants from the Finnish Brain Foundation sr (A-LH, VT) and the University of Oulu Scholarship Foundation (A-LH). This study was also supported by a grant from the Academy of Finland (Grant Number: 315460, AMR). No funding source had any role in the design, analysis or interpretation of the results in this study. We would like to thank Kia Gluschkoff for her support in the statistical analyses. We are also grateful to all the volunteer participants who made this study possible.

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https://doi.org/10.1017/S1355617723000619 Published online by Cambridge University Press