REVIEW ARTICLE

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The frontal assessment battery in clinical practice: a systematic review

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Background: The frontal assessment battery (FAB) is a brief tool designed to evaluate executive function. Some studies have particularly focused on assessing its applicability addressing two issues: first, on detecting the brain regions responsible for the FAB performance, and second, on determining its capability for differential diagnosis. Our aim was to summarize and analyze critically the studies that assessed the neuroanatomical correspondence and the differential diagnostic value of the FAB in several study populations suffering from different pathologies.

Methods: We completed a literature search in MEDLINE (via PubMed) database by using the term "frontal assessment battery" and the combination of this term with "applicability" or "use" or "usefulness". The search was limited to articles in English or Spanish languages, published between 1 September 2000 and 30 September 2016, human studies, and journal articles.

Results: A total of 32 studies met inclusion criteria. Seventeen studies were aimed at identifying the brain regions or the neural substrates involved in executive functions measured by the FAB and 15 studies at verifying that the FAB was an appropriate tool for the differential diagnosis in neurological diseases.

Conclusion: Our study showed that the FAB may be an adequate assessment tool for executive function and may provide useful information for differential diagnosis in several diseases. Given that the FAB takes short time and is easy to administer, its usage may be of great interest as part of a full neuropsychological assessment in clinical settings. Copyright © 2017 John Wiley & Sons, Ltd.

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Introduction

Executive function (EF), a concept introduced by the neuropsychologist Alexander Luria (1966), has been defined as "a set of cognitive skills that allow the anticipation and setting of goals, the design of plans and programs, the initiation of activities and mental operations, self-regulation and monitoring of tasks, the precise selection of behaviors and flexibility of conduct, as well as their organization over time and space" (Vera-Cuesta *et al.*, 2006). The decline of these functions has been associated with pathology in the frontal lobes, especially lesions that affect the prefrontal region, and its connections to the thalamus and basal ganglia (Dubois *et al.*, 2000; Appollonio *et al.*, 2005; Bausela, 2007; Kenangil *et al.*, 2010).

Clinical signs of dysfunction in the frontal lobes include the inability to establish abstract relationships among objects, poor insight, and judgment to handle new situations, reduced verbal fluency, alterations of skills related to organization of time, and maintenance and execution of successive actions. Behavior self-

regulation deficits can be observed when attempting to execute tasks where there is a conflict between verbal demands and sensory or environmental stimuli; thus, response patterns that should have been inhibited are activated (Christensen, 1978; Lhermitte, 1986; Lhermitte *et al.*, 1986; Royall *et al.*, 1992; Peña-Casanova, 2005).

There is a large number of tests that assess EF decline, including the Wisconsin Card Sorting Test (Heaton *et al.*, 1993), the Trail Making Test (Reitan, 1958), the Tower of Hanoi Test (Culbertson and Zillmer, 2001), the Stroop Test (Stroop, 1935), and the Executive Interview (Royall *et al.*, 1992), among others. Some of these are very extensive and require long administration times. As an alternative to these instruments, the frontal assessment battery (FAB) (Dubois *et al.*, 2000) is a brief and simple tool that can assess EF. This instrument requires about 10 min to administer all six items: (i) similarities (conceptualization) explore abstract reasoning by presenting pairs of objects from the same semantic category; (ii) lexical fluency (mental flexibility) assesses self-organization, strategy, and change, generating as many words as possible that start with a given letter; (iii) motor series explores motor programming and planning by carrying out Luria's series (fist-side palm) (Christensen, 1978); (iv) conflicting instructions explore sensitivity to interference, giving the opposite response to that of the examiner; (v) go/no-go assesses inhibitory control and impulsivity; and (vi) prehension behavior assesses the ability to spontaneously inhibit prehension. A maximum score of 18 is obtained by adding each of its six tests, which are scored between 0 and 3.

The FAB not only allows creating a profile for executive dysfunction but also explores related syndromes. Its six items assess different cognitive and behavioral domains involved in different neural networks. For example, conceptualization (item 1) seems to be associated with dorsolateral frontal areas, mental flexibility (item 2) to the prefrontal dorsolateral cortex and medial frontotemporal cortex, motor planning (item 3) with the right prefrontal dorsolateral cortex and basal ganglia, and inhibition and interference control (items 4, 5, and 6) with orbitomedial areas (Appollonio *et al.*, 2005; Climent-Martínez *et al.*, 2014).

In the original study about the FAB (Dubois *et al.*, 2000), a sample of 42 healthy participants and 121 patients with different types of frontal damage (Parkinson's disease, corticobasal degeneration, frontotemporal dementia, multiple system atrophy, and progressive supranuclear palsy) was used, with an average age of 58 for the healthy participants and 64 for the patients. The analysis of the FAB's psychometric properties has shown that it is able to discriminate between patients and healthy participants 89.1% of the time. The FAB also correlates highly with other tests, such as the Mattis Dementia Rating Scale, and with two items from the Wisconsin Card Sorting Test (number of categories completed and perseverative errors).

The sensitivity of the FAB to frontal lobe dysfunction and its easy administration have made it popular in research and clinical settings. As a result of a rapidly growing literature on the FAB, some studies are aimed to evaluate its clinical usefulness focusing particularly on two issues: first, on detecting the brain regions responsible for the FAB performance in different neurological diseases, and second, on determining its ability to support the differential diagnosis in several pathological conditions. To the best of our knowledge, there are no systematic reviews on the evidence about the clinical usefulness of the FAB, which may potentially contribute to a solid development of the medical and therapeutic practice. Therefore, we aimed to summarize and analyze critically the studies that assessed the neuroanatomical correspondence and the differential diagnostic value of the FAB in several neurological pathologies. We also intend for this article to serve as a reference for further research in this area.

Methods

Literature search and selection of the studies

The literature search was conducted with the term "frontal assessment battery" and with the combination of this term with "applicability" or "use" or "usefulness" by using the electronic MEDLINE (via PubMed) database. Articles were included if they met the following criteria: (i) studies addressing the brain regions or neuroanatomical correlates of EF measured by the FAB and (ii) studies assessing the practical utility of the FAB for differential diagnosis in various neurological pathologies. Original articles whose aims did not encompass the evaluation of the clinical usefulness of the FAB, review articles, and studies that focused only on the process of adaptation or validation of the FAB were excluded.

After applying the search limits (i.e., English or Spanish language, articles published between 1 September 2000 and 30 September 2016, human studies, and journal article), a total of 422 articles remained. To ensure the accuracy of the search,

two researchers (MHP and DVG) independently examined all titles and abstracts to exclude the studies that did not fit search criteria. If necessary, a complete reading of the article was taken, leaving a final sample of 32 publications (see Figure 1). Data extraction from the selected studies was also independently conducted by both two researchers (MHP and DVG) who met weekly for the agreement of the outcomes. In case of major disagreement, all the members of the research team took part in the discussion.

Results

In general, the selected 32 studies are focused on testing the diagnostic congruence of the clinical and neuroanatomical aspects of the FAB, of which 17 studies were aimed at identifying the brain regions or the neural substrates involved in EFs measured by the FAB (Matsui *et al.*, 2006; Guedj *et al.*, 2008; Yoshida *et al.*, 2009; Gordon *et al.*, 2010; Kume *et al.*, 2011; Nagata *et al.*, 2011; Oshima *et al.*, 2012; Chapados and Petrides, 2013; Frota *et al.*, 2013; Kopp *et al.*, 2013; Le Pira *et al.*, 2014; Nakamura-Palacios *et al.*, 2014; Brugger *et al.*, 2015; Lee *et al.*, 2015; Pellechia *et al.*, 2015; Piatella *et al.*, 2015; Khoo *et al.*, 2016), and 15 studies at verifying that the FAB was an appropiate tool for the differential diagnosis in neurological diseases (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005; Paviour *et al.*, 2005; Castiglioni *et al.*, 2006; Oguro *et al.*, 2006; Fukui *et al.*, 2009; Mendez *et al.*, 2009; Woodward *et al.*, 2010; Yamao *et al.*, 2011; Boban *et al.*, 2012; Biundo *et al.*, 2013; Kawai *et al.*, 2013; Krudop *et al.*, 2015; Sitek *et al.*, 2015; Stamelou *et al.*, 2015).

Brain regions or neural substrates related to the FAB performance

Table 1 displays the main characteristics and results from the neuroimaging studies. Because executive dysfunction is a common symptom of neurodegenerative diseases, the majority of the studies have mainly focused on exploring how to correlate FAB scores with brain areas or with specific neural patterns in these pathologies. Specifically, four studies have addressed neurological disorders characterized by problems with movement (i.e., ataxias) such as Parkinson's disease (PD) and progressive supranuclear palsy (PSP) (Matsui *et al.*, 2006; Brugger *et al.*, 2015; Pellechia *et al.*, 2015; Piatella *et al.*, 2015), and seven studies have evaluated neurological disorders distinguished, to a large extent,

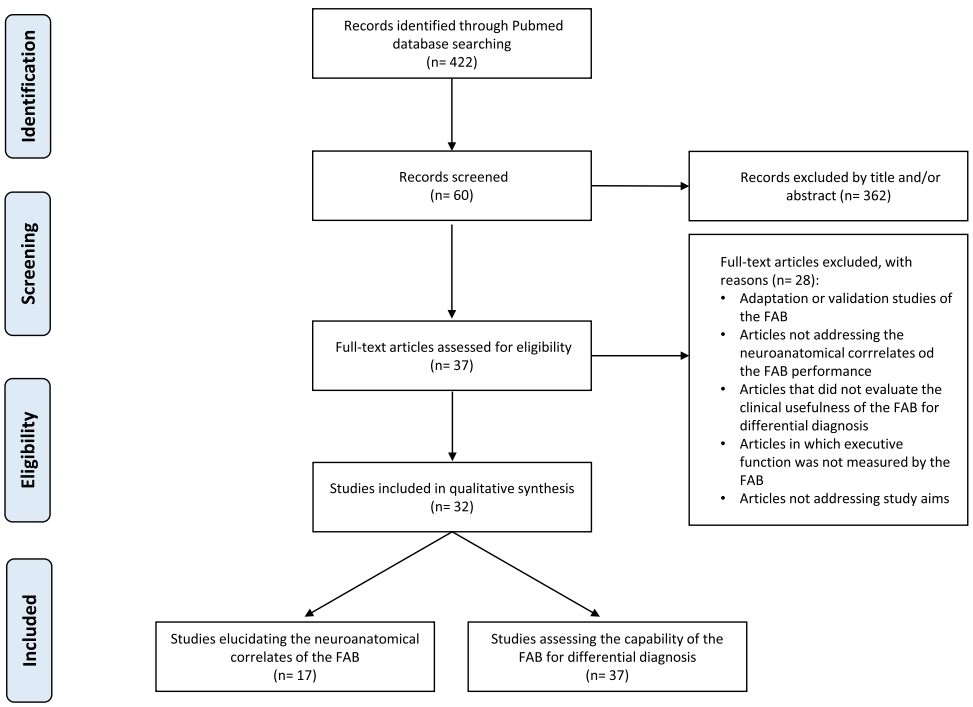

Figure 1 Flow chart of the literature search. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Studies on the relationship between the FAB performance and brain regions

	Study characteristics			
Author	Sample	Pathology	Brain regions	Main results
Matsui *et al.*, 2006	High-FAB group (n = 21, ≥12); low-FAB group (n = 9, ≤11)	PD	Parietal and temporal areas	Left inferior parietal lobule and left supramarginal gyrus perfusion of the low-FAB group decreased significantly compared with those of the high-FAB group. Correlation between the FAB score and the perfusion rate (r = 0.563, p = 0.0009).
Guedj *et al.*, 2008	47 patients	fv-FTD	Medial and dorsolateral frontal cortex	The total FAB score was correlated with bilateral perfusion in the dorsolateral prefrontal cortex (BA9 and BA10), medial premotor cortex (BA8), and anterior cingulate cortex (BA32) independently of age, gender, and MMSE (p-voxel < 0.005 and p-cluster = 0.005; r = 0.47; p = 0.0008). No correlations were found with other cortical and subcortical regions.
Yoshida *et al.*, 2009	117 participants (AD = 51, FTD = 14, VAD = 13, DLB = 7, psychiatric disease = 7, MCI = 11; controls = 14)	AD, FTD, VAD, DLB, psychiatric disease, and MCI	Callosomarginal and precentral segments	FAB had a moderately positive correlation with left callosomarginal (r = 0.425) and precentral (r = 0.468) rCBF. When controlling for the effect of MME scores, FAB had a significantly positive correlation with bilateral callosomarginal, bilateral precentral, left central, bilateral callosum, bilateral lentiform, and left thalamus rCBF. The multiple regression analysis showed that left precentral rCBF was the predictor of FAB score (β = 0.468, $p < 0.01$).
Gordon *et al.*, 2010	56 participants (FTLD = 32, bvFTD = 11, SemD = 10, PNFA = 10, controls = 24)	FTLD, bvFTD, SemD, and PNFA	Whole brain volume and ventricular regions (lateral ventricles and temporal horn of the lateral ventricles, excluding the third and fourth ventricles)	Decline in FAB scores at 1-year-follow-up was associated with increased whole brain atrophy rates (0.3%, p 0.005) and ventricular volume (0.6 mL, p 0.02) for FTLD cohort as a whole. The estimates were higher in SemD patients, although statistical significance was not reached.
Kume *et al.*, 2011	High-FAB group (n = 20, ≥13); low-FAB group (n = 18, ≤12)	A-MCI	Parietotemporal lobe, posterior cingulate, and frontal lobe	The high-FAB and low-FAB groups showed significant differences in z-scores. Regions with decreased rCBF included the left middle frontal (2.41) and inferior frontal gyri (2.17) and right medial frontal gyrus (2.24) in the low-FAB group, while regions with decreased rCBF included the right post-central gyrus (2.54), precuneus (2.21), and parahippocampal gyrus (2.35) in the high-FAB group.
Nagata *et al.*, 2011	107 patients (mild atrophy = 21, moderate atrophy = 46, severe atrophy = 40)	AD	Atrophy in total brain including the hippocampus	Only the go/no-go score of FAB was significantly lower for increasing atrophy severity ($p < 0.05$). Hippocampal atrophy significantly influenced the go/no-go score independently of interactions from whether the diagnosis was early AD or A-MCI ($p < 0.05$).
Oshima *et al.*, 2012	High-FAB group (n = 24, ≥12); low-FAB group (n = 24, ≤10)	AD	Left middle frontal gyrus and right superior frontal gyrus extending	AD patients with low-FAB scores showed significant hypoperfusion in the left middle frontal gyrus and right

(*Continues*)

Table 1. (Continued)

Author	Study characteristics			
	Sample	Pathology	Brain regions	Main results
			to left superior frontal gyrus	superior frontal gyrus compared with patients with high-FAB scores.
Frota *et al.*, 2013	40 participants (patients = 20, controls = 20)	WD	Hyperintense signal, hypointense signal, and global brain atrophy	FAB showed significantly worse scores (mean = 12.95, SD = 2.856, $p < 0.0001$) than controls. A significant correlation emerged between global cognitive impairment (all the altered tests) and MRI scale ($r = 0.535$), being higher for high-intensity signal plus atrophy ($r = 0.718$).
Chapados and Petrides, 2013	115 participants (F = 25, LF = 14, RF = 10, T = 1, LT = 12, RT = 8, controls = 25)	Frontal lesions	Left frontal excisions that involved extensively the dorsal part of the medial frontal lobe above the anterior cingulate gyrus	A poor performance on the FAB cannot be attributed to lesions restricted to the frontal cortex except for performance on the verbal fluency (mental flexibility) subtest, which is impaired by left frontal lesions. In this study, the FAB cannot be considered a sensitive test of frontal cortical dysfunction.
Kopp *et al.*, 2013	28 participants	Stroke	Right prefrontal cortex, lateral prefrontal cortical and subcortical brain areas	FAB performance can be considered as valid assessments of right hemispheric lateral frontal lobe dysfunction, specifically of focal lesions near the anterior insula, in the middle frontal gyrus and in the inferior frontal gyrus.
Le Pira *et al.*, 2014	44 patients (MA = 12; MO = 32)	Migraine	White matter lesions	MA group had significantly lower FAB performances (14.3, SD = 2.1); p 0.001) than MO group (16.0, SD = 1.3) or controls (16.7, SD = 0.5), although no differences in FAB scores were shown when distinguishing between migraineurs with or without white matter lesions (15.7, SD = 1.3 and 15.4, SD = 2.1, respectively). Therefore, executive dysfunction could be explained by other different pathogenetic mechanisms.
Nakamura-Palacios *et al.*, 2014	60 patients	Alcohol dependence	Left rostral middle frontal cortex and left cerebellar cortex	Gray matter volumes of a specific region from prefontal cortex, the rostral middle frontal gyrus, and of the cerebellar cortex, especially from the left hemisphere, were associated with the frontal executive function measured by the FAB in alcoholic subjects.
Pellechia *et al*., 2015	34 participants (MCI group = 15, non-MCI = 19)	PD	V3″ values calculated for the averaged striatum (mSPECT) and more affected and less affected caudate and putamen	MCI patients had worse FAB performances (12.8, SD (2.8); $p = 0.019$) than non-MCI. Reduced V3″ values in the more caudate (($r = 0.639$, $p = 0.019$) and less affected putamen ($r = 0.733$, $p = 0.004$) were significantly related with reduced performance in frontal assessment battery. Thus, the poor performance in executive functions of PD patients with MCI may be attributed to damage of striatal dopaminergic innervation.
Piatella *et al.*, 2015	19 patients and 12 healthy subjects	PSP	Subcortical volumes and functional connectivity	FC in the dMT FC map was significantly reduced in the left DLPF and supramarginal gyrus, as well as in the pregenual anterior cingulate cortex, bilaterally. Estimates of the dMT FC were directly correlated with FAB scores ($\beta = 42.16$, $p = 0.04$; $r = 0.26$), suggesting along with other results

(*Continues*)

Table 1. (Continued)

Author	Study characteristics			
	Sample	Pathology	Brain regions	Main results
				that decreased FC was associated with more severe manifestations of the disease.
Lee *et al.*, 2015	177 AD patients (less severe = 92, more severe = 85); 30 cognitively normal patients	AD	Dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex	In the less severe group, FAB performance was closely related to hypometabolism in the prefrontal regions. In the more severe group, FAB scores were significantly correlated to rCMglc in temporoparietal regions as well as frontal region. FAB performance reflects not only frontal lobe function but also functions of other cortical regions, which involves that FAB scores might be related to overall AD progression.
Brugger *et al.*, 2015	38 participants (FOG group = 18, non-FOG group = 20)	PD	Dorsolateral prefrontal cortex and parietal lobe areas	Gray matter values in the right DLPFC correlated with the FAB scores in all PD patients (one-sided; $r = -0.55$, $p < 0.001$) and the FOG-Q scores in PD patients with FOG (one-sided; $r = -0.52$, $p = 0.013$), but not in those without (one-sided; $r = 0.27$, $p = 0.117$). This study shows that executive dysfunction and FOG share the same patterns of neurological atrophy.
Khoo *et al.*, 2016	16 patients and 15 healthy controls	iNPH	Precuneus	A reduced DMN connectivity, localized between the posterior cingulate cortex/ precuneus and the rest of the DMN nodes, was observed in patients compared with healthy controls. DMN connectivity was significantly correlated with FAB score ($r = -0.919$).

Abbreviations: PD, Parkinson's disease; FTD, frontotemporal dementia; fv-FTD, Frontal variant of FTD; AD, Alzheimer's disease; VAD, vascular dementia; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; FTLD, frontotemporal lobar degeneration, rCBF, regional cerebral blood flow; bvFTD, behavioral variant frontotemporal dementia; SemD, semantic dementia; PNFA, progressive nonfluent aphasia; A-MCI, amnesic mild cognitive impairment; WD, Wilson's disease; F. frontal; LF, left frontal; RF, right frontal; BF, bilateral frontal; T, temporal; LT, left temporal, RT, right temporal; MRI, magnetic resonance imaging; LF, left frontal; RF, right frontal; LT, left temporal; RT, right temporal; MA, migraine with aura; MO, without aura; PSP, progressive supranuclear palsy; FC, functional connectivity; dMT, dorsal midbrain tegmentum; DLPF, left dorsolateral prefrontal cortex; rCMglc, regional cerebral glucose metabolism; FOG, freezing of gait; DLPFC, dorsolateral prefrontal cortex; iNPH, Idiopathic normal pressure hydrocephalus; DMN, default mode network.

by problems with cognitive functioning, commonly called dementias, such as Alzheimer's disease (AD) (Yoshida *et al.*, 2009; Nagata *et al.*, 2011; Oshima *et al.*, 2012; Lee *et al.*, 2015), several types of frontotemporal dementia (FTD) (Guedj *et al.*, 2008; Yoshida *et al.*, 2009; Gordon *et al.*, 2010), or certain condictions such as mild cognitive impairment (MCI) (Yoshida *et al.*, 2009; Kume *et al.*, 2011). The remaining studies include participants affected by frontal lesions (Chapados and Petrides, 2013), stroke (Kopp *et al.*, 2013), migraine (Le Pira *et al.*, 2014), alcohol dependence (Nakamura-Palacios *et al.*, 2014), and idiopathic normal pressure hydrocephalus (Khoo *et al.*, 2016).

Regarding brain regions in AD, a poorer FAB performance in early stages or in a lesser clinical severe progress of the disease was associated with frontal regions (Oshima *et al.*, 2012; Lee *et al.*, 2015), although FAB scores in a higher severe progress of AD were more related to functions of other cortical regions (Lee *et al.*, 2015). However, in patients with early AD or amnesic MCI (A-MCI), low-FAB scores were associated with hippocampal atrophy (Nagata *et al.*, 2011). In PD patients, low-FAB scores were correlated with parietal and temporal areas compared with PD patients with high-FAB score (Matsui *et al.*, 2006). When differentiating between PD patients with MCI and with non-MCI, low-FAB performance in

MCI subjects was related to damage of striatal dopaminergic innervation (Pellechia *et al.*, 2015). In PD patients with freezing of gait, FAB scores correlated with frontal lobe, although freezing of gait was more likely attributed to atrophic changes in the parietal lobe areas (Brugger *et al.*, 2015). In patients suffering from several types of FTD, total FAB scores were correlated to medial and dorsolateral frontal cortex in those with frontal variant of FTD (Guedj *et al.*, 2008), while increased whole brain atrophy and ventricular volume at 1-year follow-up were associated with lower FAB scores in a cohort with frontotemporal lobar degeneration (FTLD) patients (Gordon *et al.*, 2010). Moreover, another study including patients with various dementias (Yoshida *et al.*, 2009) indicated that FAB revealed the functions of the callosomarginal and precentral segments. In patients affected by A-MCI, Kume *et al.* found that FAB scores were linked to decreased regional cerebral blood flow in the parietotemporal lobe, posterior cingulate, and frontal regions. Frontal dysfunction measured by the FAB test in diverse pathologies such as stroke (Kopp *et al.*, 2013), alcohol dependence (Nakamura-Palacios *et al.*, 2014), and PSP (Piatella *et al.*, 2015) was largely localized in frontal regions, although a decline in FAB scores cannot be imputed to specific lesions in frontal cortex except for the performance of the verbal fluency subtest (Chapados and Petrides, 2013). More recently, FAB scores were also correlated with a reduced connectivity in the precuneus in subjects affected by idiopathic normal pressure hydrocephalus (Khoo *et al.*, 2016).

Use of the FAB for differential diagnosis

Table 2 shows the main features of the studies evaluating the clinical usefulness of the FAB for differential diagnosis. This specific application of the FAB has been mainly used for the distinction of AD and other types of dementia (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005; Castiglioni *et al.*, 2006; Oguro *et al.*, 2006; Fukui *et al.*, 2009; Mendez *et al.*, 2009; Woodward *et al.*, 2010; Yamao *et al.*, 2011; Boban *et al.*, 2012; Kawai *et al.*, 2013), although it has been also applied to differentiate the behavioral variant of FTD (bvFTD) from other neurological and psychiatric diseases (Krudop *et al.*, 2015) or PSP from FTDs (Stamelou *et al.*, 2015). In the remaining studies, the FAB has been used to distinguish pathologies particularly related to movement problems (Paviour *et al.*, 2005; Biundo *et al.*, 2013; Sitek *et al.*, 2015).

Among the studies that used the FAB for the differential diagnosis of AD and FTD, two of three studies have considered that this test may provide a helpful assessment for the clinical practice (Slachevsky *et al.*, 2004; Mendez *et al.*, 2009). However, the capability of the FAB for the distinction between FTLD and AD reflected several points of disagreement among the studies. Lipton *et al.* showed that the FAB had a poor predictive value in discriminating between both pathologies, although some FAB subtests (i.e., mental flexibility, motor programming, and environmental autonomy) might be useful in differential diagnosis. Similarly, when comparing AD, frontal variant of AD, and FTLD patients, the FAB could not give a clear differentiation among diseases (Woodward *et al.*, 2010), although it could among AD, subcortical vascular cognitive impairment, and FTLD patients (Boban *et al.*, 2012). Lower scores in the verbal fluency FAB subtest assessing mental flexibility also supported the differential diagnosis of AD and vascular dementia (Oguro *et al.*, 2006), while poorer performances in the conflicting instructions (i.e., sensitivity to interference) and go/no-go (i.e., inhibitory control) FAB subtests were useful to distinguish early AD (eAD) from A-MCI (Yamao *et al.*, 2011). In contrast, the FAB showed a limited capability to differentiate accurately AD subjects from patients with subcortical cognitive impairment (subCI) or vascular CI (VCI) (Fukui *et al.*, 2009) and from those with dementia with Lewy bodies (Kawai *et al.*, 2013). In parallel, recent studies have also shown that the FAB is not a useful tool to distinguish successfully between bvFTD and non-bvFTD (Krudop *et al.*, 2015). Regarding motor problems, the FAB could provide a differential diagnosis for PSP, multiple system atrophy (MSA) and PD patients (Paviour *et al.*, 2005), for PD with MCI (PD-MCI), PD without cognitive impairment and PD with dementia patients, and for frontal symptons in PSP (Sitek *et al.*, 2015). More specifically, the verbal fluency and motor series FAB subtests could differentiate between PSP from PD and MSA with predominant parkinsonism (MSA-P) (Stamelou *et al.*, 2015).

Discusion

In this systematic review, we found that executive dysfunction measured by the FAB correlates, to a great extent, with frontal brain regions in different neurological pathologies, which qualifies the FAB as

Table 2 Studies evaluating the clinical usefulness of the FAB for differential diagnosis

	Study characteristics			
Author	Sample	Pathologies	Main outcome measures	Main results
Slachevsky *et al.*, 2004	FTD = 26, AD = 64	FTD and AD	Comparison with MMSE	The FAB scores significantly differed between patients with FTD (mean = 7.6, SD = 4.2) and those with AD (mean = 12.6, SD = 3.7), but not MMSE scores. The FAB correctly identified 78.9% of the patients. In a subgroup of mildly demented patients, a cutoff score of 12 on the FAB was optimal to differentiate both disorders (sensitivity, 77%; specificity, 87%). The FAB provides an objective measure to distinguish FTD from AD in mildly demented patients.
Paviour *et al.*, 2005	PSP = 17, MSA = 11, PD = 12	PSP, MSA, and PD	Comparison with MMSE, NART, WAIS-R, Mattis Dementia Rating Scale-2, RAVLT, RMF, TMT, Beck, WCST, verbal fluency test, PASAT, and APATHY scale	FAB scores differed significantly among the three groups, of which PSP patients showed the lowest scores (mean = 11.7, $p < 0.001$). In this group, 82% of the patients had FAB scores of <15, unlike the lower proportions of the MSA (36%) and PD (8%) groups. The lexical fluency and motor series subscores of the FAB discriminated 70% of the PSP, MSA, and PD patients. The FAB scores correlated with tests of executive function, as well as with scores on the Mattis Dementia Rating Scale, the MMSE, and other tests of general cognitive function. Regression analyses showed that alternating semantic fluency accounted for 80% of FAB variance. The FAB is a valid and easily applicable bedside test to discriminate executive dysfunction in these three frequently confused bradykinetic rigid syndromes.
Lipton *et al.*, 2005	FTLD = 23, AD = 31	FTLD and AD	Comparison with MMSE, the Mattis Dementia Rating Scale, and WCST	The FAB did not have positive predictive value for FTLD. Total FAB scores did not differ between the FTLD and AD groups. However, three subtests of the FAB (mental flexibility, motor programming, and environmental autonomy) showed significant differences between the two groups, of which FTLD had the lower scores. Total FAB scores correlated with scores on the MMSE for AD ($r = 0.64$) and FTLD ($r = 0.52$). The FAB had poor predictive value in discriminating between subjects with FTLD from those with AD, and no clear cutoff score with acceptable sensitivity and specificity could be identified. The frontal assessment battery did not discriminate subjects with frontotemporal lobar degeneration from those with Alzheimer disease, although certain FAB subtests may be helpful in differential diagnosis.
Castiglioni *et al.*, 2006	FTD = 33, AD = 85	FTD and AD	Comparison with MMSE, story recall, Rey's complex figure, Corsi Span, digit span forward, Trail Making, RCPM, phonemic fluency, semantic fluency, token test,	FAB global scores in the two groups were very similar, even when considering only mildly demented subgroups (20 FTD and 38 AD patients). Considering FAB subscores, only the "go/no-go" subtest showed a significant difference, reflecting

(*Continues*)

Table 2. (Continued)

Author	Study characteristics			
	Sample	Pathologies	Main outcome measures	Main results
			constructional apraxia, and scrawl discrimination	a poorer inhibitory motor control in AD patients (mean = 1.0, SD = 1.0 vs. mean = 1.5, SD = 1.0). FAB scores in the two groups of patients correlated with MMSE and with executive and visuospatial test scores, showing good concurrent validity. The FAB does not differentiate patients with AD from those with FTD, like all other executive tests. However, it may be useful in the examination of executive function in AD, FTD, and several other pathological conditions.
Oguro *et al.*, 2006	AD = 25, VD = 27, normal controls = 80	AD and VD	Comparison of the total FAB and the FAB subtests among the three groups	The FAB scores were significantly decreased in both the AD (mean = 13.2, SD = 1.9) and VD (mean = 10.7, SD = 2.7) groups compared with the control (mean = 15.1, SD = 1.7) group, and the reduction was greater in the VD group. Among the FAB subtests, mental flexibility (phonological verbal fluency) was the only subtest that significantly discriminated VD (0.5) from the other two groups (NC = 1.9; AD = 1.7). The FAB test can provide useful information for differentiating AD and VD at the bedside, although it should be noted that some overlap of the FAB scores may occur.
Mendez *et al.*, 2009	89 patients (eAD = 23, SIVD = 23, FTD = 23), and 20 normal controls	eAD, SIVD, and FTD	Comparison with PAB with the ratio scores between the FAB and PAB	Compared with controls, SIVD and FTD groups were impaired on the FAB, whereas eAD and SIVD groups were impaired on the PAB. The FAB/PAB ratio further differentiated significantly the groups, except eAD versus SIV. For sensitivities and specificities of 93%, a cutoff score of 1.25 on the FAB/PAB distinguished eAD and a cutoff of 0.83 distinguishing FTD from other dementias and normal controls. This study indicates that the FAB, PAB, and its ratio may be helpful for clinicians to diagnose early onset dementias and dementias in general.
Fukui *et al.*, 2009	132 outpatients (60 = AD, VCI = 17, extrapyradimal diseases = 55)	AD and subCI	Comparison with several cognitive tests among different groups of diseases according to severity of global cognitive impairment (mild vs. moderate–severe stages)	In the mild stage, no differences in cognitive tests were shown between AD and subCI. In the moderate–severe stage, scores of CDT, CRT, CMT, FIG, and FAB were significantly lower in subCI. Given that global cognition is controlled for, visuoperception, visuoconstruction, and semantic-numerical analyses of visual information may be more impaired in subCI than AD. The FAB did not differentiate mild subCI from mild AD, although the FAB score was significantly lower in subCI than in AD in the moderate–severe stage. The FAB has limitations in differentiating between AD and subCI in the early

(*Continues*)

Table 2. (Continued)

Author	Study characteristics			
	Sample	Pathologies	Main outcome measures	Main results
				stages and between AD and VCI, even in the advanced stages.
Woodward *et al.*, 2010	523 patients (FTLD = 32, FvAD = 114, AD = 408)	FTLD, FvAD, and AD	Comparison of the changes from baseline for these three groups at 6 and 12 months. Controlling for dementia severity by matching AD and FTLD cases on a functional scale, the SMAF, and repeated the same comparisons with these severity-matched groups	Subjects matched at baseline for functional impairment, the FvAD, and FTLD groups were not significantly different on most assessment scales, although on the FAB, clock-drawing, and MMSE, the FvAD subjects were still significantly more impaired. The severity-matched FvAD group was significantly different from the AD group in almost all assessment scales. All three unmatched and matched groups declined similarly over 12 months. When severity was not considered, the FAB was more useful as a marker of dementia severity than as a scale to detect a frontal variant of AD or to distinguish AD from FTLD. When controlling for severity, the FAB could distinguish a subgroup of AD subjects that more closely resembled FTLD subjects than the remainder of the AD subjects. Subjects with dementia with greater executive impairment but without prominent behavioral symptoms are likely to have AD rather than FTLD, especially if they are quite functionally impaired. The progression of the disease increases executive dysfunction in FTLD subjects who resemble the more severely affected AD subjects.
Yamao *et al.*, 2011	48 patients (A-MCI = 26, eAD = 22)	AD	Comparison with MMSE between the two groups and exploring the interactions with MMSE subtests or the diagnosis (A-MCI or eAD)	Significant differences in the FAB total and subtest scores (conflicting instructions and go/no-go) were found between the groups. In the linear model analysis, only two FAB subtest scores (conflicting instructions and go/no-go) were significantly influenced by the diagnosis (A-MCI or eAD) independently of the interaction with the orientation or memory delayed recall. The FAB total score and subtest scores reflecting interference performances (conflicting instructions and go/no-go) significantly declined in patients with eAD, independent of the disorientation and memory disorder. Such characteristics of neuropsychological screening test scores may be useful to clinicians for differentiating eAD and A-MCI at bedside.
Boban *et al.*, 2012	AD = 37, scVCI = 31, FTLD = 13, cognitively healthy individuals = 29	AD, scVCI, and FTLD	Comparison of the FAB in among the three groups of patients	No statistically significant differences in the total FAB scores were found among the groups of patients with dementia. When comparing subtest scores, patients with FTLD had significantly lower scores on the lexical fluency subtest compared with the patients with AD ($p < 0$ .001) or scVCI ($p < 0.001$); scVCI patients had significantly lower scores on the motor series subtest compared with patients

(*Continues*)

Table 2. (Continued)

Author	Study characteristics			
	Sample	Pathologies	Main outcome measures	Main results
				with FTLD (p = 0.02) and AD (p = 0.035), as well as on conflicting instructions subtest compared with patients with AD (p = 0.033). The FAB test might be of help in distinguishing patients with executive dysfunction from normal patients. Some FAB subtests might enhance diagnostic accuracy taking into account clinical history and other tests of executive function.
Biundo *et al.*, 2013	104 patients (PD-CNT = 55, PD-MCI = 34, PDD = 15)	PD	ROC comparison with TMT, ROCF copy, RVLT, DS backward, letter fluency, category fluency, and MMSE	Only the TMT, ROCF copy, FAB, digit span backward, and RVLT immediate recall reached significant screening and diagnostic validity in predicting PD-MCI (AUC 0.705–0.795) with cutoff scores within normal range for normative data. Some specific neuropsychological tests covering verbal memory impairment, attention/set-shifting, and visual–spatial deficits are the best predictors of MCI in PD if valid cutoff scores are used. This may help cognitive preclinical diagnosis, ameliorate therapy selection, and be used to establish the rate of cognitive decline in prospective PD studies.
Kawai *et al.*, 2013	AD = 402, DLB = 38	AD and DLB	Comparison among MMSE, ADAS-Jcog, FAB, RCPM, digit span, and logical memory of the WMS-R	On the FAB total score, the DLB patients performed significantly worse than the AD patients. The phonemic fluency item in the FAB was more impaired in the DLB patients, but the corrected p-values did not reach significance. The AD–DLB discriminant index, consisting of backward digit span, RCPM set B, and logical memory 1 and 2, is useful to differentiate between AD and DLB.
Sitek *et al.*, 2015	PSP = 20 (probable = 12, possible = 8)	PSP-RS	Comparison of FAB results in a PSP-RS group on the level of each item in the context of neuropsychological assessment addressing language, working memory, and executive function	Sixteen PSP-RS patients scored below 15 on FAB. Among four patients having scored above cutoff (12 points) on FAB, two demonstrated both executive and language deficits, while the other two presented with only selective executive deficits on comprehensive neuropsychological evaluation. FAB is a useful screening measure in PSP, but it may not detect subtle executive deficits. Moreover, language performance seems to contribute significantly to FAB scores. FAB is a practical measure of frontal symptoms in the differential diagnosis of PSP. However, its score is related to language function, and it should not be regarded as a screening executive test. Patients with high-FAB scores should undergo full neuropsychological assessment with comprehensive testing of executive functions, as FAB is not sensitive to mild and isolated executive deficits.
Krudop *et al.*, 2015	137 patients (bvFTD = 55,	bvFTD	Comparison and ROC comparison among the	MMSE and FAB scores were not associated with a particular diagnosis.

(*Continues*)

Table 2. (Continued)

Author	Study characteristics			
	Sample	Pathologies	Main outcome measures	Main results
	psychiatry = 51, neurology = 31)		MMSE, FAB, FBI, and the diagnostic group (bvFTD/ non-bvFTD)	A score above 12 on the positive FBI subscale or a score above 5 on the SRI were indicative of a bvFTD diagnosis. The commonly used MMSE and the FAB could not successfully distinguish between bvFTD and non-bvFTD, but this could be achieved with the more specific FBI and SRI.
Stamelou *et al.*, 2015	210 patients (PSP = 70, bvFTD = 84, SD = 10, PNFA = 9, PD = 26, MSA-*p* = 11)	PSP, bvFTD, SD, PNFA, PD, and MSA-P	ROC comparison of the FAB among all the groups of patients	The FAB was clinically useful to differentiate PSP from PD and MSA-P (AUC = 0.927). In fact, the sum of two FAB subscores together (verbal fluency and Luria motor series) was also good at differentiating PSP from PD and MSA-P (AUC = 0.957). The FAB may not be a useful tool to differentiate PSP from FTDs. Information contained in the sum of only two FAB subscores was useful to differentiate PSP from PD and MSA-P. This should be taken into consideration in both clinical practice and the planning of clinical trials.

Abbreviations: AD, Alzheimer's disease; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; PD, Parkinson's disease; MMSE, Mini Mental State Examination; WCST, Wisconsin Card Sorting Test; RCPM; Raven's Colored Progressive Matrices; VD, vascular dementia; eAD, early-onset Alzheimer's disease; SIVD, subcortical ischemic vascular disease; VCI, vascular cognitive impairment; subCI, subcortical cognitive impairment; CDT/CRT/CMT, clock drawing/reading/matching tests; FIG, figure copying; FvAD, frontal variant of AD; FTLD, Frontotemporal lobar degeneration; A-MCI, amnesic mild cognitive impairment; scVCI, subcortical VCI; PD-CNT, PD without cognitive impairment; PDd, PD with Dementia; MCI, mild cognitive impairment; TMT, Trail Making Test; ROCF, Rey-Osterrieth Complex Figure Test; RVLT, Rey verbal learning test; DS, digit span; DLB, dementia with Lewy bodies; ADAS-Jcog, AD Assessment Scale-cognitive component-Japanese version; WMS-R, Wechsler Memory Scale-Revised; PSP-RS, Richardson's syndrome of PSP; bvFTD, behavioral variant of FTD; FBI, Frontal Behavioral Inventory; SD, semantic dementia; PNFA, progressive nonfluent aphasia; MSA-P, multiple system atrophy with predominant parkinsonism.

an adequate tool for identifying deficits in functions associated with the prefrontal cortex. Moreover, we also intended to assess the clinical utility of the FAB for differential diagnosis in one part of the selected articles included for this review. Although the FAB showed some limitations to differentiate AD subjets from other clinical populations, there is some evidence that suggests that several FAB subtests may have a good predictive value to distinguish AD from frontotemporal disorders. In patients affected by movement problems, verbal and motor series subscores from FAB could detect different bradykinetic rigid syndromes (i.e., PD, PSP, MSA, or MSA-P), several conditions in PD patients (i.e., PD-MCI and PD with dementia), and frontal symptons in PSP subjects. To the best of our knowledge, this is the first attempt to compile and compare studies from different clinical populations, in which the FAB performance was correlated with neuroanatomical aspects or used as a marker for differential diagnosis, to evaluate the clinical capability of the FAB.

Neuroimaging techniques have become powerful tools for comprehensing the neural structure and function underliying cognitive processes. In this regard, studies on EF using neuroimaging techniques have proliferated over recent years emerging as a productive area of investigation (Nowrangi *et al.*, 2014). Thus, in order to verify the accuracy and validity of neuropsychological tests assessing EF, these imaging methods have also become indispensable complements. Because the FAB is a relatively brief and easy cognitive test, in contrast to other EF screening tests that are difficult to apply and require long time, the interest in its usage has gained

importance in the last decade due to its potential practicality in the busy clinic setting (Chong *et al.*, 2010). As a result, there is currently a considerable amount of studies aiming to elucidate the functional neuroanatomical correlates the FAB.

Our main findings verified that executive dysfunction measured by the FAB performance was mostly localized in frontal areas of brain, although low-FAB scores were also associated with other brain areas or neural substrates, or, when a global approach was taken, with the whole brain atrophy, which may arise as a consequence of the progression of the disease in AD (Lee *et al.*, 2015) and dementia (Gordon *et al.*, 2010) patients, or as a general marker of the illness involving executive dysfunction in Wilson's disease (Frota *et al.*, 2013), PD-MCI (Pellechia *et al.*, 2015), PSP (Piatella *et al.*, 2015), and idiopathic normal pressure hydrocephalus (Khoo *et al.*, 2016). Interestingly, lower scores of the go/no-go and verbal fluency FAB subtests were associated with hippocampal atrophy (Nagata *et al.*, 2011) in eAD and with left frontal lessions (Chapados and Petrides, 2013), respectively, suggesting that core symptoms of these respective diseases such as problems in inhibition control and in mental flexibility may be revealed by certain items of the FAB. Obviously, neuroimaging studies are reinforcing the clinical usefulness of the FAB as a valuable screening tool, although more studies are still required. As displayed in this review, FAB performance has been identified in a wide range of neurological diseases, especially in neurodegenerative disorders. However, there is an important lack of information on the changes of EF that commonly occurs through the progress of these diseases, which is clinically considered of particular relevance due to their connection with functional decline and disability. Consequently, performing neuroimaging studies of the FAB performance on the basis of a longitudinal approach might provide a better understanding of the neurobiological correlates of variations in EF, which would significantly contribute to improve diagnostic criteria, treatment, and therapeutic interventions.

In terms of clinical practice, an early diagnosis and differential diagnosis constitute crucial elements to determine appropriate treatments and therapies. Although structural and functional brain imaging techniques can provide helpful and accurate information for these purposes, the use of screening tests may also represent noteworthy diagnostic tools for clinicians at beside. Particularly, one of the main issues of the rapidly growing literature on the FAB is focused on evaluating the capability of this instrument for differential diagnosis. Our findings showed that the FAB may have a good capability to discriminate several condictions in different clinical populations, although the evidence is still incipient. Nevertheless, it should be noted that, when the global FAB score could not make a successful distinction between the diseases, specific FAB subtests were the major determinants of the diagnosis in some cases. Specifically, the verbal fluency and motor series FAB subtests were the more sensitive items to discriminate between frontal disorders (i.e., FTDL and FTD) and AD (Lipton *et al.*, 2005; Castiglioni *et al.*, 2006) and between PSP and PD and MSA-P (Stamelou *et al.*, 2015). Although the FAB did not successfully discriminate PSP from FTDs (Stamelou *et al.*, 2015), the scores of similarities and go/no-go subtests were significantly worse in bvFTD compared with PSP, and the scores of total FAB, motor series, conflicting instructions, go/no-go subtests, and the sum of verbal fluency and motor series subtests were significantly higher in semantic dementia than in PSP, which should be considered in the examination of these patients. A likely explanation for the discrepancy with other studies also evaluating frontal disorders (Woodward *et al.*, 2010; Krudop *et al.*, 2015) may be the lack of a detailed assessment of the patients using the six FAB tasks because the breadth of functions mediated by the frontal lobes may be overlapped and could obscure specific executive performances as measured by the FAB subtests, which suggests a similar interpretation for the poor sensitivity in differentiating AD from subCI or VCI (Fukui *et al.*, 2009). In this sense, the FAB subscores may offer helpful information to enhance the diagnostic accuracy, which could be also of considerable importance in advanced stages in which the progression of disease intensifies executive dysfunction and the total FAB performance may function as a marker of disease severity rather than a screening test (Woodward *et al.*, 2010).

The role of certain study conditions such as the different groups of patients for comparison, the methodological approach, or the low number of patients recruited with a particular disease among other factors may partly explain the dissimilarity of the FAB performance between the studies, particularly with respect to studies addressing the same diseases. Thus, despite the differences observed in the results, the FAB total score or subscores were significantly lower in patients with FTDs in most studies addressing the differential diagnosis for AD (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005; Mendez *et al.*, 2009; Boban *et al.*, 2012), providing, to great extent, consistency

to the executive dysfunction measured by the FAB. Moreover, the similar results obtained from two studies (Paviour *et al.*, 2005; Stamelou *et al.*, 2015) may also suggest some evidence that the FAB is a valid instrument to differentiate bradykinetic rigid syndromes such as PSP, PD, and MSA. However, the capability of the FAB to distinguish AD from vascular dementia (Oguro *et al.*, 2006) or scVCI (Boban *et al.*, 2012), AD in moderate–severe stage from subCI (Fukui *et al.*, 2009), eAD from A-MCI (Yamao *et al.*, 2011), and PD from MCI in PD (Biundo *et al.*, 2013) is very limited, although the results supported that the FAB may provide a noted differentiation among these disorders. Nevertheless, it is important to notice that the studies evaluating the differential diagnosis of the FAB are still scarce, and the results should be interpreted with caution.

The present review has several limitations. First, the FAB was significantly related, to a large extent, to several brain regions, although we did not perform a meta-analysis to measure the global association. However, the different types of estimates calculated along with the difficulty in grouping several kinds of pathologies do not allow us to combine the results. Moreover, the possibility of limitations inherent in neuroimaging and neurocomputational methods cannot be discarded. Second, the studies included for differential diagnosis did not compare the same clinical populations, although AD and other types of dementia were the diseases mainly analyzed, and most of the remaining studies addressed neurological disorders related to movement problems. Third, this review is based on a literature search conducted in Medline database via Pubmed, although we previously used other databases obtaining similar results. Moreover, the search was limited to articles published in English or Spanish. Finally, some unpublished articles could not have been identified through our search strategy, and publication bias could exist.

Conclusion

This review showed that the FAB performance was correlated with some brain regions and neural substrates in different clinical populations, which confirms its clinical validity as a screening instrument of executive dysfunction. Moreover, the FAB may be helpful for discriminating several neurodegenerative disorders commonly confused in diagnosis, although the available evidence is still scant. Our findings indicated that the FAB may be a useful evaluation tool of EFs in different clinical populations, and therefore, it should be also considered of great interest as part of a full neuropsychological assessment in order to make appropriate diagnosis and therapeutic interventions. We hope that this study will serve as a reference for further research in this area.

Conflict of interest

None declared.

Key points

- The frontal assessment battery (FAB) was developed to assess executive function easily and quickly at the bedside.
- Some functional neuroimaging studies have elucidated the neuroanatomical correlates of the FAB performance in different clinical populations.
- There is some evidence of the clinical value of the FAB for differential diagnosis in several neurological diseases.
- The clinical usefulness of the FAB is supported by the diagnostic congruence of clinical and neuroanatomical aspects.

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Author contributions

The study concept was formulated by MHP, MCTC, and EMNM. The design of the study was carried out by MHP, MCTC, EMNM, and DVG. The selection and analysis of the data were performed by MHP and DVG. The interpretation of data was conducted by MHP, MCTC, ASP, PPG, DVG, and EMNM. The drafting of the manuscript was carried out by MHP and DVG. All the authors made a critical revision of the manuscript for intellectual content. The study supervision was made by MCTC and EMNM.

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