Clinical signs in functional cognitive disorders: A systematic review and diagnostic meta-analysis

Journal of Psychosomatic Research 173 (2023) 111447

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Review article

Clinical signs in functional cognitive disorders: A systematic review and diagnostic meta-analysis

Verónica Cabreira [a,*], Lisbeth Frostholm [b], Laura McWhirter [a], Jon Stone [a], Alan Carson [a]

[a] Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom
[b] Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Keywords:
Cognition
Dementia
Diagnosis
Functional cognitive disorder
meta-analysis
Systematic review

ABSTRACT

Objective: Functional cognitive disorder (FCD) accounts for around a third of patients attending specialized memory clinics. It is also overrepresented in patients with other functional and somatic diagnoses. So far, no long-term diagnostic validity studies were conducted, and a positive diagnostic profile is yet to be identified. We aimed to review the literature on diagnostic signs and symptoms that allow for a discrimination between FCD and neurodegeneration.

Methods: Systematic review of Ovid-Medline®, Embase and PsycINFO databases. Relevant clinical features were extracted including demographics, symptom history, comorbidities, language and interaction profiles and cognitive assessments. Studies with quantifiable diagnostic accuracy data were included in a diagnostic meta-analysis.

Results: Thirty studies ($N = 8602$) were included. FCD patients were younger, more educated, and more likely to have a family history of older onset dementia, abrupt symptom onset, and higher rates of anxiety, depression and sleep disturbance. Promising language profiles include longer duration of spoken answer, elaborated examples of memory failures, ability to answer compound and personal questions, and demonstration of working memory during interaction. The pooled analysis of clinical accuracy of different signs revealed that attending alone and bringing a handwritten list of problems particularly increase the odds of a FCD diagnosis. Current evidence from neuropsychometric studies in FCD is scarce.

Conclusions: Our systematic review reinforces that positive signs contribute for an early differentiation between FCD and neurodegeneration in patients presenting with memory complaints. It is the first to attain quantitative value to clinical observations. These results will inform future diagnostic decision tools and intervention testing.

1. Introduction

The last decade witnessed a global increase in the number of referrals to specialist memory services. Many of the patients attending have a functional cognitive disorder (FCD)(12–56% of the new referrals) [1–7]. A recent audit in England showed that 47% of the patients under 65 years-old attending memory clinics did not have a dementia [7]. FCD is also overrepresented in patients with other functional and somatic diagnoses, including chronic fatigue syndrome, fibromyalgia, and post-traumatic brain injury [6,8,9]. It may present with multiple severities and possibilities of progression [3], but the initial clinical presentation often overlaps with dementia, posing a diagnostic challenge for clinicians [10].

In light of the current proposed definition, internal inconsistency (or subjective cognitive symptoms that are disproportional to the observed level of cognitive functioning) is the core diagnostic feature [1,3]. The new criteria arise from a need to positively identify FCD, instead of basing the diagnosis on exclusionary features. Typical clinical presentations include memory lapses, word finding difficulties and amnestic blocks, reflecting attentional dysregulation [6,11] and an inability to voluntarily assess certain cognitive functions, even though the automatic functions in the same cognitive domains appear preserved [1,2].

A previous narrative review including sixteen studies up to 2017 focused exclusively on features of communication and interaction of both neurodegenerative disorders and functional memory disorders [12]. A second study published in 2019 was a comprehensive review of the literature regarding FCD and its precedent terminologies [3]. Yet, so

* Corresponding author at: Centre for Clinical Brain Sciences, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, United Kingdom.
E-mail address: veronica.cabreira@ed.ac.uk (V. Cabreira).

https://doi.org/10.1016/j.jpsychores.2023.111447
Received 17 May 2023; Received in revised form 31 July 2023; Accepted 3 August 2023
Available online 5 August 2023

far, no long-term validity studies were conducted to evaluate the diagnostic features that distinguish the FCD population from others attending the memory clinic, and a clearcut positive diagnostic profile is yet to be identified. We aim to conduct an updated review of the patient characteristics, symptoms and bedside clinical signs that allow for a distinction between FCD and neurodegenerative conditions (mild cognitive impairment (MCI) and/or dementia) in patients presenting with cognitive complaints. Moreover, our review summarizes the diagnostic accuracy of the different clinical signs.

2. Methods

The review protocol was registered in OSF (https://osf.io/fbdm2). We report the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The current study is part of the innovative training network ETUDE (Encompassing Training in fUnctional Disorders across Europe;https://etude-itn.eu/), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment and stigmatization of Functional Disorders [14].

2.1. Search strategy

An initial exploratory search in Medline was undertaken to capture the target keywords, MeSH terms and free vocabulary. These were reviewed by VC and AC and adapted to each database. The final search strategy was performed in Ovid-Medline®, Embase and PsycINFO databases on 1 February 2022 (Table 1). We deduplicated studies using Covidence reference manager.

2.2. Eligibility criteria

All observational cross-sectional studies comparing diagnoses of FCD or equivalent with neurodegenerative disorders, including at least ten adults (>18 years) with cognitive symptoms; and quantitative or qualitative data regarding patient characteristics and bedside signs and testing were included. Studies with quantitative data were used for a diagnostic accuracy meta-analysis. Studies describing existing checklists, scoring aids or predictive models to discriminate between FCD and neurodegeneration were also included. We excluded treatment or prevalence studies, those describing automated methods or computerized analysis of speech or interactions with interpreters (comparison with manual methods without introducing new data for analysis), non-English studies, and those describing detailed psychometric cognitive testing that is not part of the initial memory clinic assessment (other than brief screening tests).

Table 1
Queries used for searching Ovid MEDLINE, Embase and PsycINFO databases.

#	Searches
1	((functional or dissociative or psychogenic or hysterical or conversion or medically unexplained or subjective) adj1 (memory or cognit* or forgetf*) adj1 (impairment or disorder or decline or worsening or complain* or symptom* or loss or disturbance or condition)).mp
2	(pseudodementia or "worried well" or "age-related forgetfulness" or "Benign senescent forgetfulness" or "nondemented" or "subjective forgetfulness" or "fear of dementia" or "cogniform disorder").mp
3	(((diagnostic* or screening) adj2 (tool or aid or score or index or criteria or method*)) or checklist or "decision aid" or "diagnostic adj2 model" or stratif* or assess* or diagnos* or interact* or communicat* or dialog or conversation).mp
4	((((memory or cognit* or neurology or dementia) adj1 (clinic or outpatient or service)) or (primary or secondary or tertiary)) adj1 care).mp
5	1 or 2
6	3 and 4 and 5

2.3. Data collection and synthesis

The search, screening, and data extraction were conducted by VC. If it was unclear whether a study met inclusion criteria it was discussed with a second reviewer (AC), who also reviewed the full text of included studies before extraction. Forward and back citation searching of included articles was performed to search for additional studies.

Data extraction included the following variables: study design, sample size, patient groups, mean age of participants, percent female, prevalence of FCD, study location and setting, terminology, diagnostic criteria applied to classify patients as FCD, investigations and significant findings. Clinical variables extracted included demographic characteristics, symptom history, non-cognitive concomitant symptoms, interaction and language, bedside cognitive testing, and metacognition measures. Diagnostic risk model studies were analyzed separately.

2.4. Quality appraisal

The quality of the included studies was assessed using the Quality Assessment with Diverse Studies (QuADS) tool [15], which was developed for use in reviews including multi-method or mixed-methods studies. It contains 13 criteria scored on a scale from 0 to 3 (Not at all/Very slightly/Moderately/Complete) whose sum provides an overall score which is expressed as a percentage of the maximum possible score.

2.5. Statistical analysis

In those studies that allowed for a diagnostic accuracy analysis, sensitivity, specificity, negative and positive predictive values of individual sign or patient characteristic were calculated. A summary statistic was calculated using a bivariate random effects meta-analysis using RevMan [16]. Hierarchical summary receiver operating characteristic models were used to plot the respective summary receiver operating characteristic (SROC) curves using MetaDTA [17].

3. Results

3.1. Characteristics of included studies

We found 30 studies describing data on 8602 patients, published between 1981 and 2021. Six studies [18–23] included diagnostic tools or risk models(Fig. 1). The median number of patients included in the studies was 169 (25–2000). All studies compared FCD patients to patients with neurodegenerative disease (MCI and/or dementia). Two studies included healthy control populations [24,25]. The median age of the participants was 66 years-old and 60% were female. The prevalence of FCD was 44% (10–76%). Sixteen studies were conducted in the UK (53%), seven in other European countries (23%), and seven outside Europe (23%). All studies were conducted in memory clinics, except one early study which included inpatient admissions for suspected dementia [26], and one which recruited volunteers attending community centers [27]. None of the included studies were set in primary care.

FCD was generally poorly defined with heterogeneous terminologies and diagnostic criteria. Internal inconsistency was only mentioned in four studies [21,24,28,29]. Six studies [20,23,25,30–32] adopted the Schmidtke criteria [33], and used the term 'functional memory disorder' to distinguish a group of patients with an acquired 'non-organic condition' characterized by significant deficits of memory and concentration, without objective evidence of cognitive impairment, and attributed to psychosocial burden and distress. 'Worried well' was used by one study [34] to refer to patients without a neurological diagnosis, and unremarkable neuro-imaging and cognitive performance on neuropsychometric testing. In four studies [35–39], 'non-organic' disorder was used interchangeably with 'non-demented' to distinguish an heterogeneous group of patients without evidence of cognitive dysfunction, a known diagnosis of a psychiatric disorder, 'benign senescent

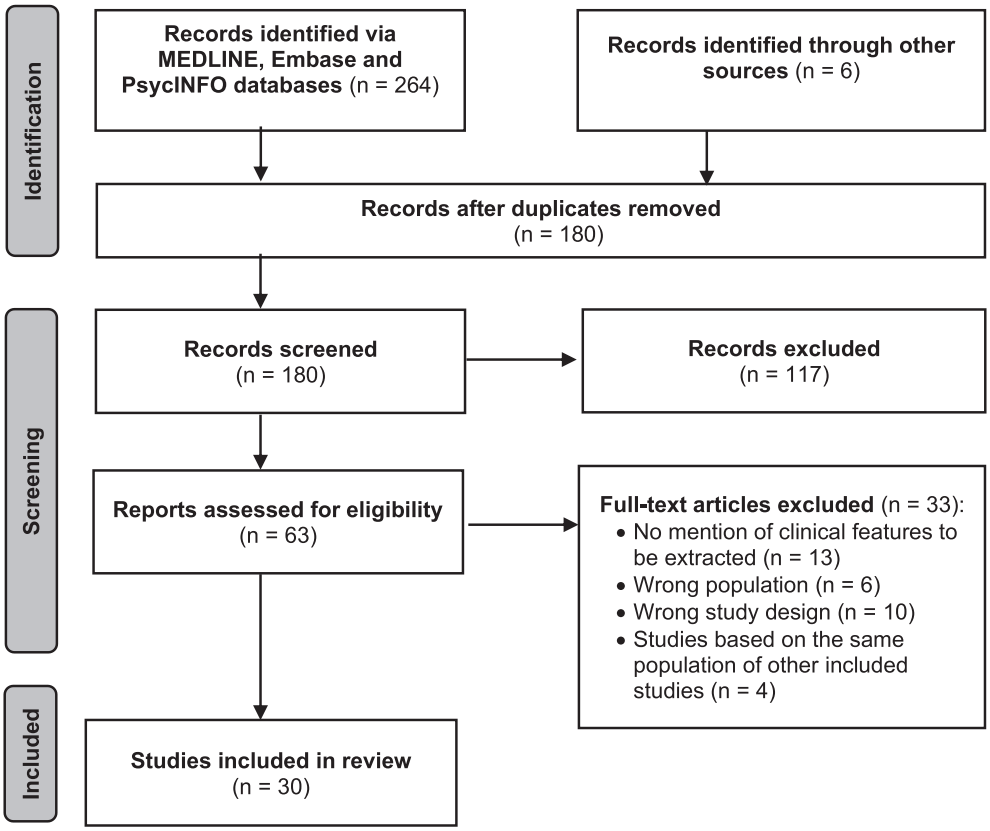

Fig. 1. PRISMA flowchart for study selection.

forgetfulness' or absence of decline at follow-up [35–39]. Three studies [18,19,26] used 'pseudodementia' as a synonym for a reversible cause either attributed to a depressive disorder or a systemic illness [18,19,26]. Four studies [27,40–42] used 'subjective cognitive impairment' to refer to patients with subjective complaints but normal cognitive performance and absence of functional decline or a psychiatric diagnosis. The remaining studies [22,43–48] included patients based on a normal cognitive performance either explicitly or inferred by the methodology used (namely the use of cognitive testing to stratify the patients). Terminologies used by individual studies were kept during the analysis.

Various investigations were used to evaluate the patients ranging from clinical assessment, questionnaires, cognitive testing, interviews, and conversational analysis (supplementary table 1).

3.2. Quality assessment

Four(13%) studies had a QuADS above 75% [21,23,24,35], thirteen (43%) between 50 and 75% [18,20,22,27,29–31,34,38,40,41,43,47], ten(33%) between 25 and 50% [19,25,26,28,36,37,42,44,48,49] and three(7%) below 25% [32,39](Fig. 2).

3.3. Demographic characteristics

Patients with FCD (and equivalent terminologies) were younger in comparison to patients with neurodegeneration (mean age (±SD) 61.3 (8.2) versus 70.7(6.1)). Three studies [40,41,44] reported a higher educational level in FCD, in comparison to MCI or dementia. Almeida et al. [37] found that among 418 patients attending a memory clinic, memory complainers (those with a normal cognitive performance or symptoms attributed to a mood disturbance) were more likely to have a family history of dementia. They were less likely to be married, more likely to live independently, and were predominantly female [37]. A positive family history of dementia was mentioned by three other studies [21,29,39], typically involving only isolated individuals, presenting later in life (>65 years). FCD patients were also less likely to have vascular risk factors [24].

3.4. Symptom history

We assessed whether the number and symptom description helped differentiate between FCD and neurodegeneration. FCD patients reported a higher number of memory complaints [21,40]. Regarding the way memory failure is recalled, an abrupt symptom onset, a short symptom duration and a rapid progression were encountered [26,37]. Yet, there were contradictory findings. Symptoms of longer duration, typically without progression were reported in two other studies [21,43]. Those with an abrupt symptom onset were usually able to date or specify their memory failures with precision [21]. Variability of symptoms on a day-to-day basis was also reported [29]. with the typical symptoms in FCD patients reflected attention deficits and word finding problems, in comparison to those with dementia, who were more likely to present with episodic memory impairment, orientation or visuospatial deficits [3,50,51].

3.5. Non-cognitive concomitant symptoms

We evaluated whether some of the non-cognitive symptoms (psychological and physical) were unique to the FCD group. Overall, a higher prevalence of primary psychiatric disorders (primarily anxiety and depressive disorders) was found in the FCD group (36–55% versus 11–24% in patients with dementia([18,19,21,26,34,37,40,44], especially in the 'pseudodementia' population [18,19,26], where psychiatric conditions were present in up to half of the patients. Mascherek et al. [40] found a positive correlation between a higher number of cognitive complaints and depression, despite severely depressed individuals

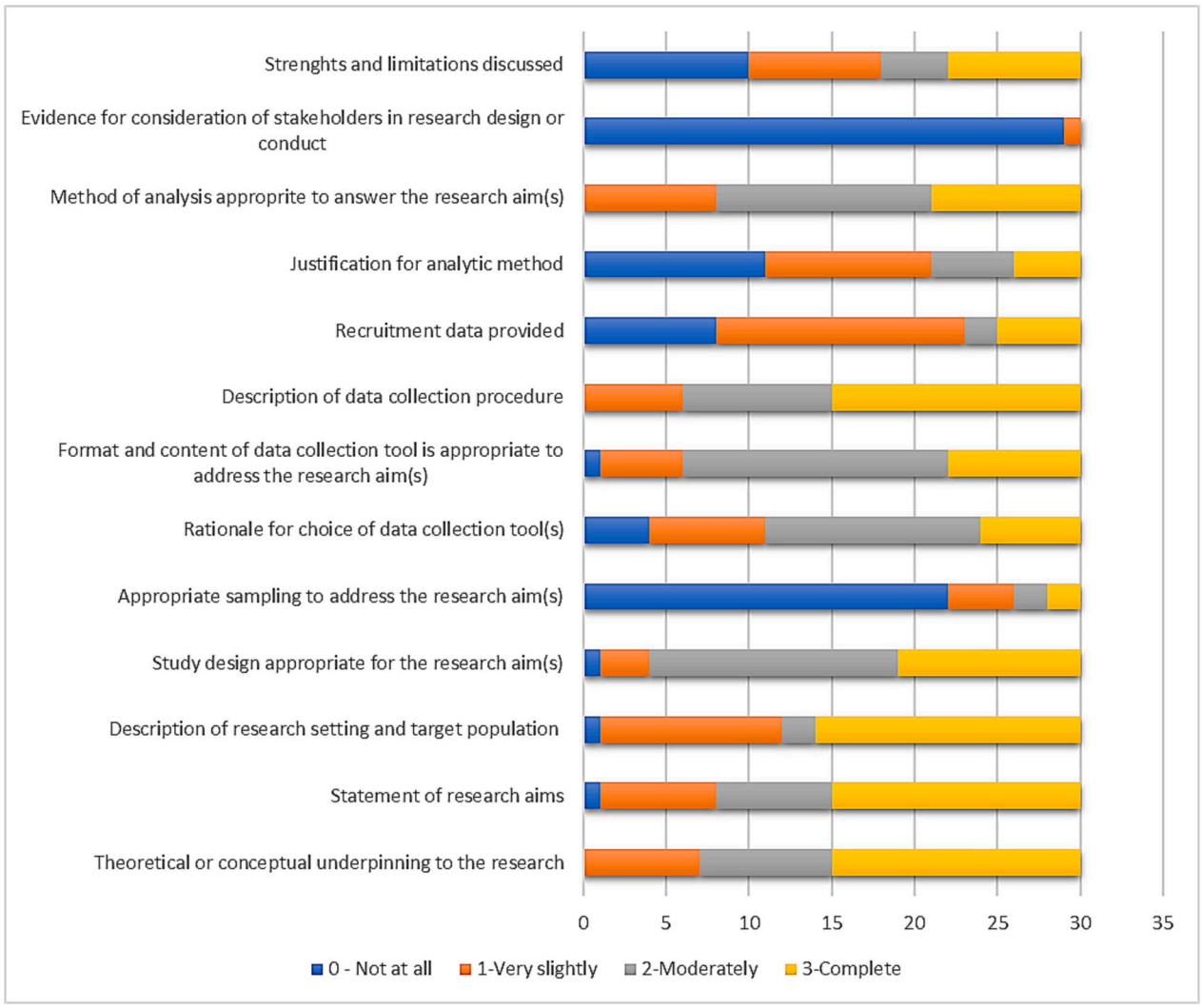

Fig. 2. Quality appraisal of included studies according to QuADS tool.

having been excluded from this study.

Among younger patients (under 60 years-old), the most frequent diagnoses were depression (14.6%) followed by personality disorder (4.5%), schizophrenia, anxiety disorder, post-traumatic stress disorder and persistent mood disorder [26]. Ball et al. [24] found that among 63 participants, 21 with FCD, 17 with neurodegenerative MCI, and 25 healthy controls, FCD patients had higher rates of depression or anxiety than healthy controls (20% versus 16%) and neurodegenerative MCI (no cases identified).

Similarly, a higher prevalence of other functional disorders (non-FCD) was found in FCD patients versus healthy controls (20% vs 16%) and neurodegenerative MCI (no cases identified), even if the difference was not statistically significant, as the study might have been underpowered to detect these differences. Only one study looked at physical somatic symptoms, using the Patient Health 15-Questionnaire, and higher scores were described for FCD (mean 5.2 versus 1.9 for the non-FCD group) [21].

Four studies commented on sleep disturbance [19,28,29,34]. Using a dichotomized Jenkins Sleep Scale, sleep disturbance was elicited in 83% of FCD patients (versus 50% in the neurogenerative group) and had a sensitivity of 83% and a specificity of 50% to discriminate between the two populations [29]. The combination of sleep disturbance and mood disorders using the Mood 2 Question screener, further increased the diagnostic specificity to 69% [28]. Two other studies similarly found a higher prevalence of self-reported poor quality of sleep [34], including delayed insomnia and early-morning awaking [19], in the FCD group in comparison to those with dementia.

3.6. *Profile of communication (interaction and language)*

FCD patients were more likely to attend alone («attending-alone-sign»), even when previously asked to bring an informant [21,29,30], while the opposite «attending-with-sign» is typically observed in those with a dementia diagnosis [42,49]. The «head-turning-sign», the observation of patients turning towards their caregivers when confronted with a question with the aim of looking for a correct answer, was found to be a highly specific sign for neurodegeneration (reflecting patients struggle to answer a question and the need to defer the answer to others) [29,42,46,47]. FCD were positively identified in some studies by bringing a handwritten or typed organized symptom list [32,49]. However, in a cohort of 169 patients, 100 of which with FCD, defined as absence of cognitive impairment or an underlying cognitive disorder, this sign was only identified in 8(5%) patients (6 FCD/2 MCI) [32]. Lastly, although not being a clinical sign per se, three studies highlighted that FCD patients were more likely to seek medical assistance for their memory for their own initiative (self-referred), rather than due to issues raised by their relatives or doctors, reflecting a higher degree of concern on the patient's side [37,38,40].

Despite the relatively small sample size of studies specifically focusing on profiles of verbal and non-verbal communication (25–30

participants, 15–16 FCD patients), some features suggest that language profiles can be used to reliably and consistently differentiate neurodegenerative dementia from FCD [23,30,31]. The profiles of sequential and grammatical details of the talk produced by patients in response to doctors' questions were analyzed. Three studies mentioned that FCD patients were more likely to display confidence during the interaction with less hesitations and no difficulties sustaining the communication, while those with neurodegeneration had their ability to communicate impacted by their memory failure [18,21,30]. As a result, FCD patients were more able to provide extensive and detailed accounts of their memory difficulties (volunteering unsolicited information) [21,23,25,30,31], emphasizing the impact of the symptoms in their daily life [25], whereas patients with neurodegeneration struggled to respond, and provided vague or generic responses such as 'all the time', 'I can't remember' or 'I don't know' [30,31]. As so, the duration of their spoken answers was longer when compared with their dementia counterparts [21,30,31]. Conversely, an absence of response or a delay in responding was more often observed in dementia patients [31]. FCD patients retained the ability to respond accurately to questions about personal information like age, while the neurodegenerative ones struggled and often answered the year or date of birth instead [30,31]. Patients with FCD also displayed working memory during the interaction, by retaining ability to reply to questions requiring two separate answers [29–31], or in recalling information that they had previously mentioned (marking self-repetitions with 'like I said'/'as I say') [31]. This contrasted with patients with dementia who were often unable to retain information, and were less aware of self-repetitions ('second first-time tellings') [31]. In contrast, when answering multi-component compound questions, dementia patients tended to miss parts of the question and pursued clarification from the doctor [30,31]. FCD patients were more often concerned about memory problems than the accompanying person, and the contrary was true for dementia patients [29,30]. FCD patients usually only sought help from an accompanying person for confirmation, and little disagreements were found between the patients and informants, in contrast with the neurodegenerative cases where the accompanying person was generally involved throughout history-taking, often acting as spokesperson [30].

3.7. Bedside cognitive assessments

We explored whether there was a specific bedside cognitive profile that differentiated FCD from neurodegenerative causes of cognitive complaints. No specific cognitive profile was identified for FCD patients, with the exception of one study in which FCD patients struggled with immediate recall and recognition tasks, but FCD patients performed surprisingly well on delayed recall, while the MCI group demonstrated difficulties mainly with the second [24]. Wakefield et al. [25] applied an extensive neuropsychological testing to a group of 20 FCD patients (defined as memory symptoms without an organic neurodegenerative disease or a significant active psychiatric morbidity), 20 patients with MCI and 20 controls. FCD patients outscored the MCI patients on Mini Mental Status Examination (MMSE) score (29 vs 26 points respectively), memory and language tests (including semantic memory and category fluency tasks) [25]. The performance of FCD patients did not differ from healthy controls, except in tests of attention and executive function like the Stroop test and digit cancellation test, where the control group performed better than the FCD group [25], although the difference was non-significant, suggesting a subthreshold deficit that might only become apparent in real busier environments. Overall, FCD patients scored higher than the neurodegenerative groups on the MMSE [23,27,37,38,40,41], and similarly or only slightly worse than healthy controls. FCD patients performed in the normative range of neurodegenerative MCI in the MoCA test [21,24]. FCD patients obtained higher scores on the Addenbrooke's Cognitive Examination (ACE) than the neurodegeneration group (93 points versus 58 points) in one study [23], but the same was not replicated in a second study using the Mini-ACE [29]. These results need careful interpretation as by definition in many of these studies the FCD diagnoses (including pseudodementia and subjective cognitive impairment) had been included based on a normal cognitive performance. Lastly, 21 patients with FCD had exactly the same chances of failing performance validity tests ('effort-tests'), measures commonly employed to assess motivation during the cognitive assessment, as 17 patients with MCI [24].

3.8. Metacognition

Metacognition refers to an individual's evaluation of their own cognitive processes [52]. Local metacognition refers to the individual's estimate of their cognitive performance on a single point in time or task, while global metacognition is an overall long-run self-evaluation of one's performance and is understood to be the key driver of the internal inconsistency that characterizes FCD. In the studies included in this review, McWhirter et al. [21] examined global metacognition in individuals with FCD compared to those without FCD, using a clinician-administered performance scale to access metacognition - Multifactorial Memory Questionnaire (MMQ). The results consistently showed that FCD patients reported lower satisfaction with their memory and had a lower perception of their memory ability. Bharambe et al. [29] used a self-assessment measure of subjective memory complaints, a five-point Likert scale, which has also been used as a global measure of metacognitive performance. The authors found that FCD patients were more likely to have a negative perception of their own memory compared to individuals with dementia or MCI. However, this was not replicated by McWhirter et al. [21].

3.9. Diagnostic risk models

Yousef et al. [18] proposed a checklist to identify the 'pseudodementia syndrome' based on 44 (yes/no) questions extracted from a literature review. The filtered 18-question scale was tested in 128 patients (63 with 'pseudodementia') and evaluated the ability to provide an accurate history, brief cognitive assessment, insight and conviction of a cognitive problem, and performance on several tasks. It achieved a high sensitivity (98%) and specificity (95%) to differentiate between dementia and depressive pseudodementia, with good interrater reliability ($k = 0.89$).

Reynolds et al. [19] proposed a symptom checklist (anxiety, delayed insomnia and loss of libido) for bedside differentiation of cognitive impairment in depressed patients ($n = 14$) from dementia ($n = 28$). It correctly classified 90.5% of the patients.

Schmidtke et al. [20] proposed a 10-item questionnaire focusing on the evaluation of working memory and concentration (e.g. forgetting errands on the way to their execution or going blank during conversations), deficit of registration of new contents, word searching difficulties, variability, and difficulty retrieving well-known content (e.g. names, PIN codes) while typically recalling it later. It obtained a sensitivity of 96% and a specificity of 100% to identify FCD ($n = 45$) vs dementia ($n = 50$).

Okudur et al. [22] analyzed the combination of a triple clinical bedside observation («attending alone-sign», «head-turning-sign», and «applause-sign») plus a rapid cognitive screening test (ability to recall 5 words, clock drawing test, and story recall) to identify neurodegeneration in adults attending a geriatric outpatient clinic due to memory complaints. The patients were stratified in three groups (AD, MCI and 'cognitively robust') based on their cognitive performance. The model yielded a sensitivity of 73–87% to distinguish MCI or AD ($n = 357$) from those without cognitive impairment ($n = 237$).

McWhirter et al. [21] evaluated the diagnostic accuracy of different characteristics in patients with cognitive complaints excluding AD ($n = 49$, 31 with FCD). A model including optimum cut points for age (<74 years) and duration of spoken response (>67 s) obtained a sensitivity of 93%, a specificity of 78%, and an AUC of 0.91 for a diagnosis of FCD.

Reuber et al. [23] developed a quantitative diagnostic scoring aid using 14 discriminating interaction and language characteristics, which was validated retrospectively in 30 patients and prospectively in 10 patients. The tool achieved a sensitivity of 86.7%,a specificity of 100%, an AUC of 0.98, and a high interobserver agreement rate (k = 0.8).

3.10. Meta-analysis of diagnostic accuracy of selected clinical features

Thirteen studies [28–32,34,37,39,42,46–49] contributed with diagnostic accuracy data for six clinical features: «attending-alone-sign», «head-turning-sign», bringing an organized written list of symptoms, sleep disturbance, history of psychiatric disorders and higher education (≥high school) (summary estimates are shown in Table 2 and forest plots in Fig. 5). Higher education and sleep disturbance achieved moderate sensitivity (76% and 79% respectively), but relatively low specificity for a diagnosis of FCD (48% and 43% respectively). The history of a psychiatric disorder, the «attending-alone-sign» and bringing an organized written list of symptoms were very specific (specificity ranging between 86% and 98%) for FCD. Also, in patients attending the clinic alone and those bringing a written list of symptoms the odds of a FCD diagnosis increase by 8.7 (3.92–19.5) and 3.9 (0.88–17.23), respectively. On the other hand, the «head-turning-sign» makes it very unlikely for a diagnosis of FCD to be made (negative likelihood ratio < 0.1). SROC graphs are represented in Fig. 3.

A summary of these results including all the validated historical and clinical signs for FCD (evaluated against a neurodegeneration group in one or more studies) is presented in Table 3 and Fig. 4.

4. Discussion

This is the first review focusing on a direct comparison between FCD and neurodegenerative populations and attaining a discriminative power to clinical symptoms and signs that help differentiate between the two diagnoses. Our study confirms that clinical history and bedside diagnostic signs remain paramount when assessing patients with cognitive complaints who present to primary care, memory clinics and other medical and psychiatric services, despite advances in fluid biomarkers. In comparison with dementia patients, having a younger age, high educational level, symptoms with shorter duration and/or abrupt onset, and comorbidities such as psychiatric disorders or sleep disturbance all increase the pre-test probability of FCD. Interaction and language profiles show promise but require further validation with larger samples and diverse populations (Fig. 4).

Although FCD typically occurs in mid-life to early sixties [3], age alone is not a definitive diagnostic marker. First, early-onset neurodegeneration can present with striking mood symptoms resembling FCD, even in younger patients [3,11]. Second, FCD symptoms may represent a prodrome of neurodegeneration, and elderly populations require additional care and close follow-up to account for this possibility [4,53,54], similarly to what is observed in anxiety and mood disorders. So far, there is still uncertainty as to whether incipient dementia triggers FCD or if their co-occurrence is simply coincidental in advanced age. Our hypothesis is that only a minor proportion of FCD patients eventually develop dementia. This is supported by a prospective cohort study of 46 patients diagnosed with 'functional memory disorder', in which only one patient was diagnosed with dementia at 20 months follow-up [33]. Similarly, population-based analysis of MCI showed that 53% of individuals did not progress, and 35% reverted to normal cognition after 7 years [55]. While further research is needed on disease trajectory, this should not invalidate a diagnosis of FCD, for potential treatment and to facilitate more in-depth research in cognitive disorders.

We found that higher educational attainment increases the sensitivity of FCD diagnosis, but with limited isolated discriminative value. One possible explanation is a protective effect of education on cognitive decline, particularly in those with >10 years of education [56,57]. Additionally, job demands associated with having a higher education may contribute to increased concern about cognitive abilities, and the ability to provide extensive descriptions [58,59]. Having a close relative with dementia is reported to increase the likelihood of seeking memory clinic evaluation, even in those without a dementia [60]. So, a positive family history does not necessarily indicate a neurodegenerative disorder. Consideration of the inheritance pattern and age of onset in the relatives is important as FCD patients often report a family history in a single individual with a late symptom onset. Possible contributors are the background effects on illness perceptions driving increased concern over genetic causes of dementia [61–63]. The prevalence of certain personality traits, such as overachievement or perfectionism, known to reinforce memory-related worry, were surprisingly not explored in the

Table 2
Summary estimates of sensitivity and specificity for each diagnostic sign, using a bivariate random effects model.

Characteristic	Studies	No. of patients	Summary Sensitivity % (95% CI)	Summary Specificity % (95% CI)	Summary +LR (95% CI)	Summary -LR (95% CI)
Higher education (≥high school)	Almeida [37] Verity [34]	375	76 (66–84)	48 (38–58)	1.47 (1.27–1.70)	0.49 (0.37–0.66)
History of a psychiatric disorder	Almeida [37] Elberling [39] Verity [34] Bharambe [29]	1740	30 (20–42)	86 (77–92)	2.20 (1–62-2.98)	0.81 (0.74–0.89)
Sleep disturbance[a]	Elhadd [28] Verity [34] Bharambe [29] Elsey [30]	405	79 (71–85)	45 (38–52)	1.43 (1.22–1.66)	0.47 (0.33–0.68)
Attending alone sign	Jones [31] Larner [48] Larner [49] Soysal [47] Bharambe [29]	1558	46 (38–54)	95 (87–98)	8.73 (3.92–19.5)	0.57 (0.51–0.63)
Absence of head-turning sign[b]	Ghadiri-Sani [46] Larner [45] Soysal [47]	958	97 (80–100)	61 (34–83)	2.52 (1.33–4.75)	0.05 (0.01–0.25)
Bringing a written list of symptoms	Bharambe [29] Randall [32]	258	7 (4–13)	98 (93–100)	3.90 (0.88–17.23)	0.95 (0.90–1.00)

+LR = positive likelihood ratio; −LR = negative likelihood ratio

[a] One study assessed sleep disturbance by quantifying its presence and intensity; two studies used the Jenkins sleep scale (JSS).

[b] The discriminative value of head-turning sign was explored as an exclusionary feature, given its specificity for neurodegeneration. If present, it practically excludes a diagnosis of FCD (very low negative likelihood ratio).

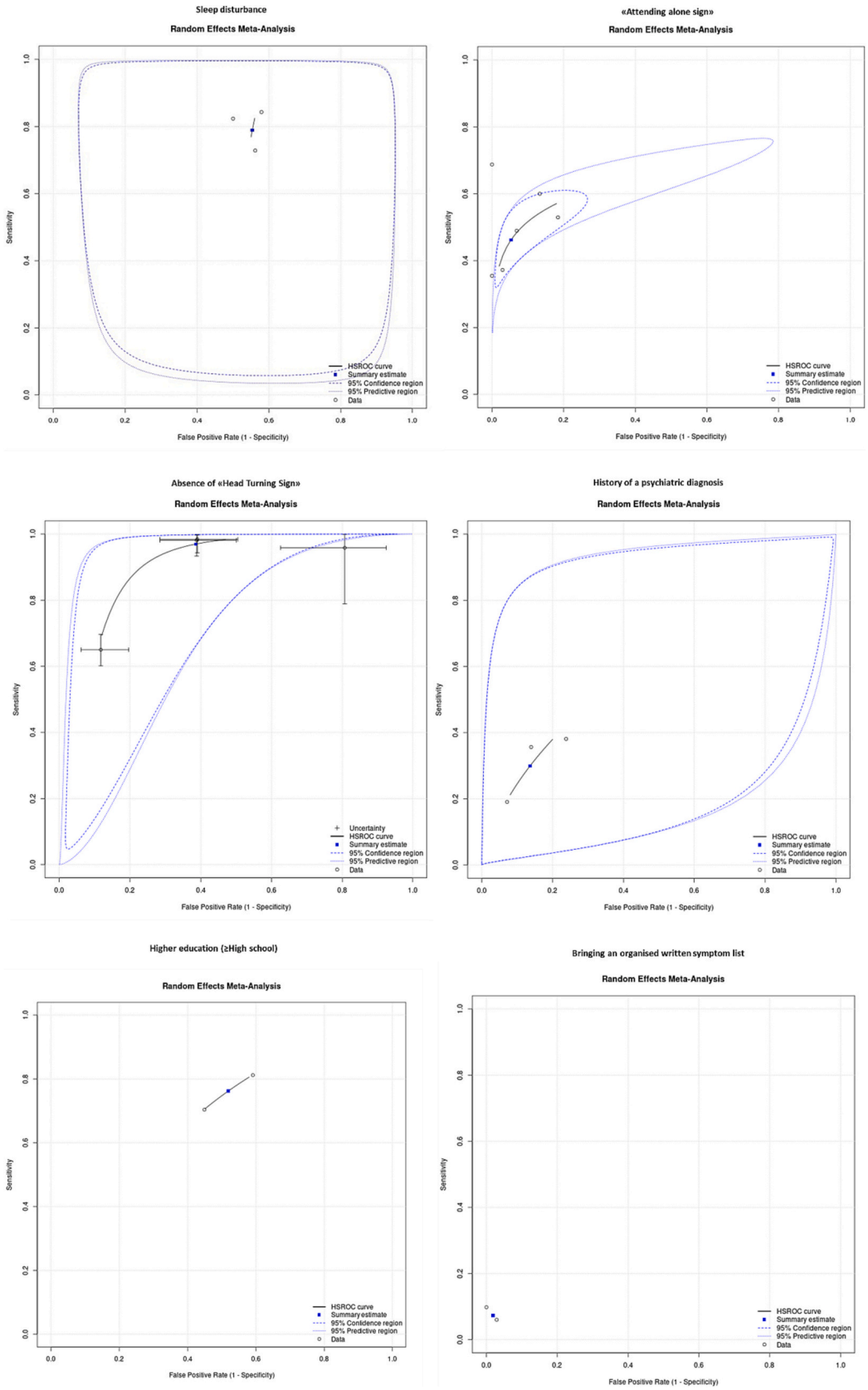

Fig. 3. Receiver operation characteristic graphs with 95%-confidence region and 95%-prediction region for two patient characteristics and two clinical signs.

Table 3
Validated historical and clinical signs for Functional cognitive disorders (evaluated against a control group of MCI and/or dementia).

Observations	Findings favoring a functional cognitive disorder (FCD) diagnosis	No. of studies (no. of patients)	Interpretation and limitations
Clinical Characteristics			
Age [18,21,23,24,26,29,34–37,39,41,43,44]	Patients with a FCD present at a younger age relatively to patients with a neurodegenerative disorder.	14 (n = 5154)	Age is an helpful discriminative variable if integrated with other positive features. A model including longer duration of spoken response (>67 s) and age (<74 years-old) achieved a sensitivity of 93%, a specificity of 78%, and area under the curve of 0.91 for a diagnosis of FCD [21].
Higher educational level [34,37,40,41,44]	In comparison with patients with dementia, FCD patients tend to study more years and more commonly hold a degree level.	5 (n = 3037)	Having a higher education is a protective dementia factor and a more suggestive feature of FCD. This characteristic achieved a pooled sensitivity of 76.2% and a specificity of 48.1%.
Vascular risk factors [24]	A lower prevalence of vascular risk factors was ascertained to FCD patients.	1 (n = 63)	Data derived from a single study recruiting patients with well-defined FCD, based on internal inconsistency features. In isolation, this sign needs to be interpreted with caution, especially in older populations.
Family history of dementia [29,37,39]	A higher proportion of FCD patients have at least one relative with dementia, generally at an older age, influencing patient's own illness perception.	3 (n = 1507)	Although relevant, this is arguably a rare finding, probably more specific than sensitive. Having a relative with dementia increases the chances of attending a memory clinic without dementia. A fourth study reported the same finding, although the results were not statistically significant [21].
Symptom history			
Symptom duration [21,26,35,37,43]	An abrupt onset of symptoms has been reported in some series, especially after significany life events, for whom a shorter time until patients seek medical attention is found. Two studies otherwise reported a longer duration of symptoms without progression as discriminative.	5 (n = 1071)	Both extremes of symptom duration might suggest FCD.
Symptom onset [21,26]	FCD patients relate the start of cognitive symptoms to a specific event, injury, or illness in time. As so, for these, symptoms commonly have an abrupt onset.	2 (n = 249)	An abrupt onset after a specific event is a highly recognized feature of FCD and points against a neurodegenerative condition. Longitudinal studies are needed to clarify symptom onset, trajectory of symptoms, predisposing conditions and whether there are any specific events posing a higher risk of FCD.
Number of cognitive complaints [21,40]	FCD patients report a higher number of cognitive complaints in comparison to patients with neurodegeneration, which is associated with giving specific examples and detailed answers when asked about their memory failures.	2 (n = 218)	FCD patients are more likely to report a higher number of cognitive symptoms, which they describe in detail. This finding is integrated with other interactional and language profiles.
Other concomitant symptoms			
Psychiatric comorbidities [18,19,21,26,28,29,34,37,38,40,44]	Higher rates of anxiety and depression are reported for patients with FCD (present or previous history of at least one psychiatric diagnosis).	11 (n = 2040)	Psychiatric comorbidities are more often present in FCD, both in populations selected based on cognitive internal inconsistency, and in older cohorts, such as 'pseudodementia'. As this information is extracted from cross-sectional studies, they may represent both risk factors or comorbidities, including overlapping negative thoughts and lower global metacognition. Depression or a mood disturbance can be prodromal symptoms of early neurodegeneration, so clinicians need to exclude this. Further studies are needed to explore presentations of FCD both in patients with and without psychiatric comorbidities. In our meta-analysis, a history of a psychiatric disorder achieved a specificity of 86.4% and a sensitivity of 29.9% for FCD.
Physical symptoms [21]	FCD patients report more physical symptoms in comparison to non-FCD populations.	1 (n = 49)	Only one of our included studies assessed physical symptoms. So far, the value of this as a discriminant feature is limited, but potentially relevant in a subset of FCD populations, including those with comorbid pain, chronic fatigue or other functional disorders.
Sleep disturbance [19,28,29,34]	FCD patients more often report sleep disturbance, with great impact in their daily life.	4 (n = 595)	Sleep disturbance and its characterization were promising positive features in our meta-analysis, with a sensitivity of 78.9% and a specificity of 44.7%.
Bedside cognitive testing			
Immediate and late recall [24]	Patients with FCD struggle with immediate recall and recognition tasks but not with delayed recall.	1 (n = 63)	Only a single small study reported this finding, but this was conducted in a well-defined FCD population recognized by the presence of several inconsistency features. Future studies are needed to validate this finding and explore further neuropsychometric distinctive profiles of FCD.

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Table 3 (*continued*)

Observations	Findings favoring a functional cognitive disorder (FCD) diagnosis	No. of studies (no. of patients)	Interpretation and limitations
MMSE score [23,25,27,37,38,40,41]	FCD patients tend to demonstrate higher MMSE scores on cognitive examination in comparison to MCI, dementia or other cognitive disorders.	7 (n = 3189)	It remains unknown whether FCD populations with poor cognitive performance are missed or misdiagnosed, since five of these studies recruited patients to the FCD group, based on normal cognitive performance. Plus, MMSE might not be the most sensitive cognitive test to assess attention and executive functions, the two most affected in FCD patients, especially if patients are depressed. Currently, the evidence does not support an extrapolation of the MMSE from a screening instrument to a diagnostic tool. However, psychometric tests can help to provide a measure of cognitive ability at baseline, to guide future decisions, but they do not themselves should support the diagnosis in isolation.
ACE score [23]	Higher ACE score is reported for FCD patients.	30	Given the reduced sample size, the evidence supporting the use of ACE score is sparce. A second study included in this review did not find differences on the mini-ACE between dementia and FCD [29]. As above, psychometric tests can help to provide a measure of cognitive ability at baseline, to guide future decisions, but they do not themselves should support the diagnosis in isolation.
Metacognition			
Metacognition assessment [21,29]	FCD patients show both lower satisfaction with their memory and poorer perception of their own memory ability. They appreciate their own memory as "poor" or "fair" on subjective ratings of memory complaints.	2 (n = 138)	Metacognition is altered in people with FCD, being the key determinant of symptom expression. Despite some evidence to suggest that FCD patients tend to appraise their own memory as bad, the same was not replicated by the second study. Further studies are needed to collect more information regarding the diagnostic predictive value of the use of metacognition measures and Likert scales for subjective memory complaints.
Interactional and language profile			
Confidence demonstrated during interaction [18,21,30]	FCD patients interact more confidently with their doctor and complain of memory loss with vigor. Patients firmly believe on a cognitive problem and tend to underline the need for treatment.	3 (n = 207)	Noting the pattern of interaction between patients and their doctors is a useful and costless way of correctly assessing patients with memory complaints. Evaluating the worry and insight patients usually retain is a positive feature of FCD. Note that one of the studies recruited pseudodementia patients, and another attributed memory symptoms to psychological causes.
Duration of spoken response [21,23,31]	Patients with FCD tend to speak for longer time without interruption, especially when asked about their memory failures.	3 (n = 79)	Duration of spoken response represents an easy assessable sign which can be integrated into future diagnostic risk models. This sign is a direct reflection of other linguistic features demonstrated by these patients, like providing an extensive account of their memory failures, with examples, elaboration of responses and often with unsolicited details. A model integrating duration of spoken response (>67 s) and age (<74 years-old) achieved a sensitivity of 93%, a specificity of 78%, and area under the curve of 0.91 for a diagnosis of FCD [21].
Language content [18,21,23,25,30,31]	FCD patients provide extended and detailed accounts of their memory lapses. They retain the ability to handle and recall all parts of compound questions and personal questions. Repetitions (self or others') are less common in comparison to patients with neurodegenerative disorders, and when self-repetitions are present these are noticed and highlighted by the patients.	6 (n = 267)	These signs reflect intact episodic and working memory. Training in conversational analysis and time is needed to assess these futures. Intelligent virtual agents and automated methods for speech analysis are being explored, with higher accuracy, but these are not yet widely available and require prospective testing.
Comparison with a standard of normal [21]	FCD patients tend to talk about their memory in contrast with a standard of 'normal', reporting their previous memory as 'excellent'.	1 (n = 49)	Importantly, these were derived from many patients diagnosed based on the assumption that the symptoms are attributed to psychological features. Despite tested in only a few patients, this sign connects with the metacognition deficiency and negative thoughts about their own memory, figuring as a potentially clinically useful sign if detected during the clinical interview.
Attending the clinic alone and assistance from accompanying person [21,29–31,46–49]	Patients with FCD are more likely to attend the clinic alone, even if previously asked to bring someone along. When coming with a companion, they tend to seek less assistance than their neurodegenerative counterparts.	8 (n = 1278)	«Attending-alone-sign» demonstrated high specificity (94.7%) and intermediate sensitivity (46.2%) for a diagnosis of FCD. Given the high number of patients evaluated and the recognition of this as a common clinically observable sign, there is solid evidence to

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Table 3 (*continued*)

Observations	Findings favoring a functional cognitive disorder (FCD) diagnosis	No. of studies (no. of patients)	Interpretation and limitations
			support its use as a discriminative feature (positive LR of 8.7).
Bringing an organized written list of symptoms [29,32]	Some FCD patients bring a written or typed symptom list.	2 (n = 258)	It is a very specific but not a sensitive sign for a diagnosis of FCD and was only rarely demonstrated (<5% of the patients). The context of the patient is important. For instance, the level of detail/ organization/grammar and syntax of the list, and whether the severity of symptoms reported in the list is congruent with the level of functioning and insight of the patient. Moreover, certain personality traits, including high monitoring/obsessive, highly educated people, and early neurodegeneration can also display this sign.
Absence of «head-turning-sign» [29,45–47]	When patients turn their head to their companions when asked a question to look for an answer from them, that is nominated «head-turning sign». It suggests the presence of dementia, instead of FCD.	4 (n = 1016)	If the «head-turning sign» is present, it almost certainly excludes the diagnosis of FCD. It was validated in a high number of patients and is accepted as a specific sign for neurodegeneration. However, care should be taken as some FCD also turn their head to their companions, with the intent of looking for a confirmation instead of a correct answer.
Seeking medical assistance for their own initiative (self-referral) [37,38,40]	Patients with FCD were more likely to be the ones seeking medical assistance for their own initiative (self-referred), rather than by a relative or concerns raised by a doctor.	3 (n = 993)	Clinically, it correlates with the fact that these patients are frequently worried and aware of their memory failures, being often more worried than their companions. Careful interpretation is needed because the three studies included patients based on normal cognitive performance, and so capable of self-referral.

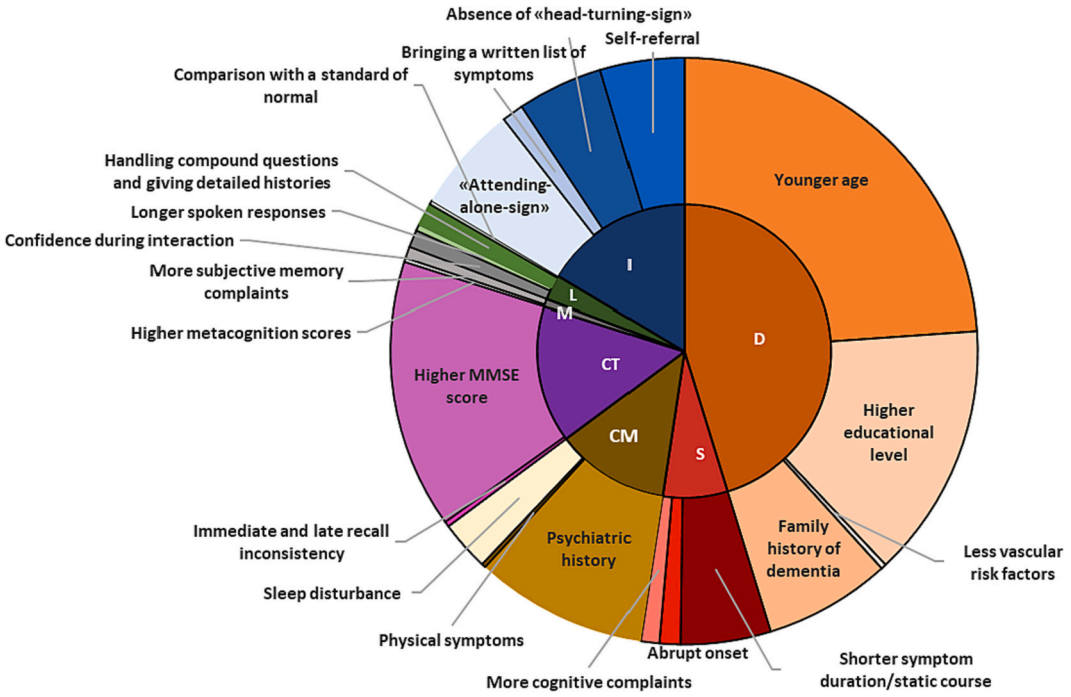

Fig. 4. Pie chart illustrating sample size of studies assessing each individual clinical feature.
Slice sizes are proportional to the number of patients studied. D - demographic characteristics; S - symptom description; CM – comorbidities; CT – cognitive testing; M – metacognition; L – language profile; I – interaction profile.

included studies [8,9].

As for comorbidities, psychiatric comorbidities increased the diagnostic specificity, while sleep disturbance is a sensitive supportive sign of FCD. Sleep is essential in memory consolidation and has a bidirectional association with memory, pain and fatigue. Whether this is a bystander in FCD, or a useful biomarker, remains to be explored both as pathophysiological mechanism and possible treatment targets [6]. In line with our results, in two studies in FCD patients, about half had features of depression, anxiety, obsessiveness, fatigue, pain, sleep disturbances and dissociation, which were in excess in comparison to healthy controls [64,65]. In this review, only two studies reported on the prevalence of other functional disorders in FCD patients [21,24]. This implies that a subset of patients will only present with cognitive complaints and primarily attend the memory clinic, while in other groups

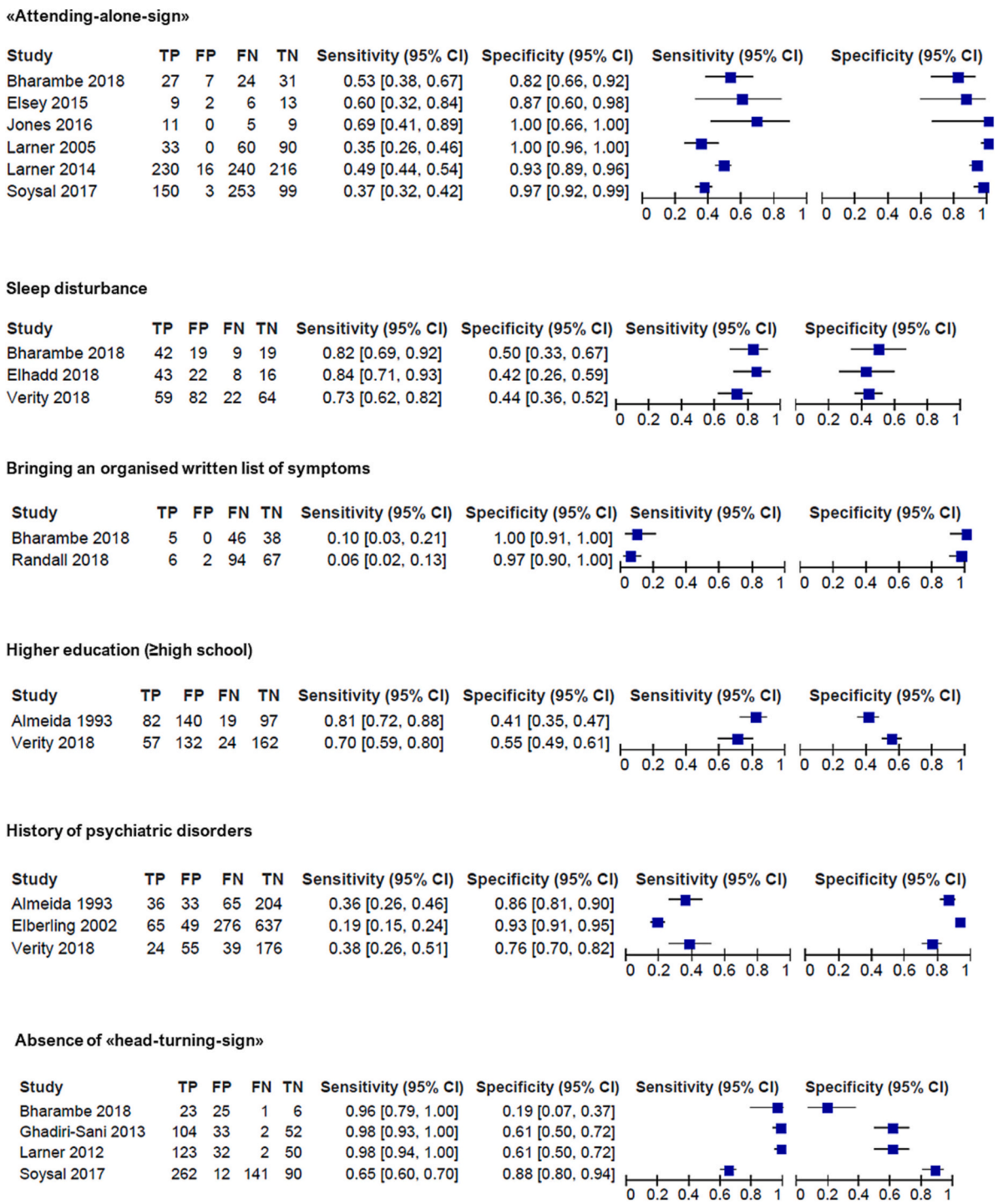

Fig. 5. Forest plots representing estimates for each individual characteristic or sign, using random effects model.

functional cognitive symptoms are part of a complex list of symptoms, and often will improve once the main symptoms are managed [6].

The studies included in this review corroborate that the use of measures of metacognition, particularly 'global' subscales, to diagnose FCD is limited and perhaps contradictory. While some evidence favors the use of 'local' measures of metacognitive sensitivity instead of the first, a recent study conducted in 19 FCD patients and 23 healthy controls reported that despite an accurate rating of point performance is observed in FCD patients, they still rated their overall memory as poor, suggesting a selective deficit in global metacognition [52,64]. A similar pattern was observed in patients with depression, justifying an overlapping trend between the two conditions to focus on negative aspects, overinterpretation of normal memory lapses as permanent cognitive impairment [8,10,40,52], and avoidance of cognitive tasks in an attempt to prevent symptoms ('cogniphobia') [65]. Evaluating low metacognition in patients with and without mood disorders can improve understanding and diagnosis [52,64].

Additionally, high memory-related anxiety, negative attitude, and high subjective norm (e.g. what society will think about memory failures/comparison with a standard of normal) are important correlates of perceived forgetfulness [66], and should be explored as potential targets for interventions [6,65].

We found that the level of detail provided, with specific examples and elaborative answers with unsolicited details is further discriminative of FCD [23]. An abrupt onset of memory symptoms following a significant event is suggestive of FCD, but both a short or prolonged static symptom history might support a diagnosis of FCD, sometimes with inconsistency or fluctuation over time. Inquiring about specific complaints, including examples of memory failures is exceptionally informative. The analysis of interaction and language profiles are some of the most promising diagnostic tools. Of the clinical signs, the «attending-alone-sign» presents the best balance between sensitivity and specificity, while «head-turning-sign» is highly specific for neurodegeneration [46], with the caveats discussed in Table 3. Differential conversational profiles emerged recently and can be used to timely differentiate between neurodegenerative disorders and FCD, facilitating a triage of these patients [23,30,31]. Following on these studies, the feasibility of using automatically detectable features to train machine learning models such as acoustic, lexical, semantic and visual information, has been tested. Similar approach was explored with intelligent virtual agents simulating doctors to uniformize interactions and facilitate automated speech recognition. Both approaches achieved an accuracy over 90% to correctly classify neurodegeneration versus FCD [67–70]. The main limitations of these methods are validation in a single center, dependance on trained conversation analysts, being time-consuming and costly, and overall still largely inaccessible. Exploration of language content in response to other questions could also be of interest, such as effect of 'thinking' on the symptoms, concerns about the future and having a dementia, and engagement in daily activities such as work, house chores or hobbies.

Traditionally, emphasis has been placed on psychometric testing, but in the data reviewed here, no psychometric profile was found to be specific to FCD patients apart from a better performance on delayed recall than immediate recall [24]. Based on older studies in which FCD was often diagnosed under the premise of a normal cognitive performance, FCD patients are reported to have a better performance on MMSE than MCI patients and only slightly worse than healthy controls [23,27,37,38,40,41]. Not enough data was found regarding MoCA or ACE, so we advise against extrapolations of screening cognitive instruments to diagnostic tools in FCD [18,71,72]. Yet, psychometric tests can provide baseline information of cognitive ability, useful for future decisions. Subthreshold deficits in attention tests may be found in FCD and need to be further explored [25]. Recently, slower reaction times were described for FCD patients versus healthy controls [64]. Detection of these subthreshold differences in FCD could be a potential avenue for future research, and whether these differences are supported by functional or anatomical correlates. Re-thinking qualitative (inconsistencies) rather than quantitative interpretations of cognitive tests are likely to be more discriminative [73]. Although routine assessments commonly include performance validity tests, care needs to be taken as the easier tasks evaluated by these tests often require other cognitive resources including attention. Single 'effort tests' do not discriminate well between MCI and neurodegeneration, as FCD patients do not consistently fall these tests [24], and failure rates up to 42% have been described for MCI patients [8,24,74].

This review has some limitations. The included studies vary in terminologies and diagnostic criteria, with some relying on normal cognitive performance or psychiatric comorbidities for the diagnosis, and others excluding patients with depression or anxiety. Sample sizes were relatively small for many of the signs identified in the studies. Signs like «attending-alone», «head-turning-sign», bringing a written list of symptoms, and language profiles, were only validated in single centers, raising the possibility of diagnostic suspicion bias, especially in a field where the diagnosis is usually established by group consensus (lack of 'gold-standard'). Due to the nature of these studies, the final diagnosis was established in a retrospective manner, and recall bias is a concern especially in participants with memory complaints. The lack of follow-up is also a limitation, as some patients with depression could have later developed dementia, although the current evidence does not support a higher risk in comparison to the general population. Lastly, data extraction and quality rating of individual studies were performed by only one researcher.

In conclusion, the findings of this study can contribute to a future development of enhanced diagnostic tools and predictive models, leading to better screening and early referral for treatment of patients with FCD. While many of the diagnostic signs identified in our review should not be considered in isolation, they increase the pretest probabilities and enhance our understanding of the various causes of cognitive impairment. It is important to note the lack of neuropsychometric studies in well-characterized FCD populations, indicating a research gap. Exploration of personality traits, contact with dementia patients, sleep disturbance, and engagement with daily activities holds promise for further investigation in this field.

Funding

VC has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 956673. This article reflects only the author's view, the Agency is not responsible for any use that may be made of the information it contains. L. McWhirter receives funding from the Scottish Government Chief Scientist Office. L. McWhirter provides independent medical testimony in court cases regarding patients with functional disorders, is secretary of the British Neuropsychiatry Association, and receives research funding from the Scottish Government Chief Scientist Office. JS reports personal fees from UptoDate, outside the submitted work, runs a self-help website for patients with functional neurological symptoms (www. neurosymptoms.org) which is free and has no advertising, provides independent medical testimony in personal injury and negligence cases regarding patients with functional disorders, and is secretary of the International Functional Neurological Disorder Society. He is a Chief Scientists Office NHS Research Scotland Career Researcher. AJC is a director of a limited personal services company that provides independent medical testimony in court cases on a range of neuropsychiatric topics on a 50% pursuer 50% defender basis, a paid associate editor of the Journal of Neurology Neurosurgery and Psychiatry, and unpaid president elect of the International Functional Neurological Disorder Society.

Declaration of Competing Interest

VC has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 956673. This article reflects only the author's view, the Agency is not responsible for any use that may be made of the information it contains. L. McWhirter receives funding from the Scottish Government Chief Scientist Office. L. McWhirter provides independent medical testimony in court cases regarding patients with functional disorders, is secretary of the British Neuropsychiatry Association, and receives research funding from the Scottish Government Chief Scientist Office. JS reports personal fees from UptoDate, outside the submitted work, runs a self-help website for patients with functional neurological symptoms (www. neurosymptoms.org) which is free and has no advertising, provides independent medical testimony in personal injury and negligence cases regarding patients with functional disorders, and is secretary of the International Functional Neurological Disorder Society. He is a Chief Scientists Office NHS Research Scotland Career Researcher. AJC is a director of a limited personal services company that provides independent medical testimony in court cases on a range of neuropsychiatric topics on a 50% pursuer 50% defender basis, a paid associate editor of the Journal of Neurology Neurosurgery and Psychiatry, and unpaid president elect of the International Functional Neurological Disorder Society.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2023.111447.

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