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REVISION

Title:

Screening for cognitive and behavioural change in Amyotrophic Lateral Sclerosis/Motor Neuron Disease: A systematic review of validated screening methods.

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ABSTRACT

Objective: Cognitive and behavioural change in Amyotrophic Lateral Sclerosis (ALS) is well accepted. Several screening tools have been developed to detect such changes. Further guidance on their use may come from a consideration of the rigour with which they were validated. This systematic review set out to critically appraise and present published data pertaining to the validation of six screening tools used to diagnose cognitive and/or behavioural change in patients with ALS.

Methods: The screening tools considered in this search included: The Edinburgh Cognitive and Behavioural ALS Screen (ECAS), The ALS Cognitive Behavioural Screen (ALS-CBS), The Motor Neurone Disease Behavioural Scale (MiND-B), The Frontal Behavioural Inventory ALS Version, The ALS Frontotemporal Dementia Questionnaire (ALS-FTD-Q) and The Beaumont Behavioural Inventory (BBI). MEDLINE, EMBASE and PsycINFO were searched until 4th week of June 2017.

Results: Fourteen eligible studies were included in the review. Papers either reported data concerning convergent validity or clinical validity. Validation data concerning the ECAS showed this screening tool to have strong clinical validity, although further work needs to consider how its use will affect diagnosis rates according to current diagnostic guidelines. When screening for behavioural change only, more limited information is available; the BBI may offer greater potential than the ALS-FTD-Q for detecting mild impairment as it assesses a wider range of behavioural changes.

Conclusions: Scores of sensitivity, specificity, positive predictive values and negative predictive values should be given considerable importance when considering which screening tools to incorporate into current clinical practice.

Keywords:

Amyotrophic Lateral Sclerosis; Cognition; Behaviour; Screening tests; Validity.

INTRODUCTION

Aside from the clinical signs suggestive of motor deficit revealed on examination, over 50% of patients with Amyotrophic Lateral Sclerosis (ALS) present with cognitive difficulties indicative of frontotemporal dysfunction (1,2); of these between 8% and 14% may meet criteria for frontotemporal dementia (FTD) (1,2). Approximately 35% have a milder form of cognitive involvement, characterised by executive and/or language dysfunction and possible deficits in social cognition (3). In ALS patients with behavioural involvement, apathy is the most commonly found presentation (seen in up to 70 percent of patients (4)); severe apathy tends to lead to a poorer prognosis (4). ALS patients may also show signs of disinhibition, reduced empathy and increased egocentric behaviour, a change in dietary habits and more stereotyped behaviour (4).

Although it is optimal for patients with ALS to undergo detailed neuropsychological assessments to identify and characterise cognitive and behavioural changes, sufficient clinical resources are not always available (5). Further, it may be inappropriate to subject all patients to a full neuropsychological battery given that a large proportion of patients remain cognitively intact. As a result, several screening assessment tools have been developed for use in clinical (as well as research) settings. The aim of these screening tools is to detect cognitive and behavioural change in a briefer timescale. However, it is important to consider how well such measures have been validated and their likely clinical validity when diagnosing cognitive and behavioural impairment, especially according to the new Strong et al. (4) consensus criteria. The aim of this review was, therefore, to identify available ALS-specific screening tests for detecting cognitive and/or behavioural change and to assess their validity and diagnostic accuracy.

METHODOLOGY

This systematic review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (6). The main aim was to evaluate the validity of six ALS-specific screening tools referred to by Strong et al. (4). Box 1 describes the screening tools in terms of who usually completes them and what they measure.

Eligibility criteria

The inclusion criteria included any original (observational) studies assessing validity of the screening tools against standardised batteries of neuropsychological function, questionnaires, current diagnostic criteria or recommended cut-offs from previous literature. No restriction was placed on the participants' gender or age.

Studies were excluded if they were not published in English or if the sample size was <30.

Search strategy

Papers were searched for in the MEDLINE, EMBASE, and PsycINFO databases. The databases were searched from their start-date until 4th week of June 2017, using the search format in Box 2.

Study selection

The titles and abstracts of all records in English identified by electronic search were screened for relevance. Most had no relevance to the search terms (Box 2) and some were conference abstracts. One study was excluded due to a cohort size of <30, leaving 14 studies to be included in the qualitative synthesis. A hand search was undertaken by examining reference lists of included studies; however, no additional records were identified.

Risk of bias and methodology analysis

Risk of bias was evaluated on the basis of the following domains: patient selection and representativeness of the general ALS population, the blinding of the study (i.e. whether impairment on the cognitive or behavioural screening measure being validated was identified by the researchers independently of knowledge about impairment on other screening tools/diagnostic criteria against which it was being validated) and whether validation was undertaken against a gold standard neuropsychological battery, appropriate diagnostic criteria or an accepted standardised ALS-specific screening tool. Blinding is essential to minimise expectation bias and a high degree of representativeness is important for the clinical relevance of the study data. Representativeness was judged by examining the sample size of ALS participants, their mean age and the percentage of males and females in each study. The rationale of rating allocation is detailed in Table 2. A study was classified as having a low risk of bias if it achieved a cumulative score of 4 or more on the above domains. A moderate risk of bias was defined as a score of 3 or 2 and a high risk of bias was defined as a score of 1 or 0.

Data synthesis and extraction

After selection, papers were examined carefully to extract data pertinent to the validity of the tools. Where available, measures extracted included specificity, sensitivity, positive predictive values (PPV), negative predictive values (NPV) and correlations. Cohort demographics were also extracted. Meta-analyses were not conducted due to study heterogeneity.

RESULTS

The electronic search yielded 180 studies after restricting studies to those in English and removing duplicates. Figure 1 shows the flow-chart of the search strategy as described above. After screening, 14 eligible studies were included in a qualitative synthesis.

Included studies

Table 1 presents the characteristics of the study cohorts in the 14 validation studies. Cohort sizes and disease duration varied considerably depending on sub-cohorts but all studies included a greater proportion of males than females. There was relatively little variation in years of education across studies. Some studies presented convergent validity in the form of correlations between the screening tools being investigated and well-validated equivalents. Control groups were used in most studies to provide normative data for cut-off scores.

Methodology analysis and risk of bias

Table 2 presents the risk of bias in the included studies. Bias estimates occasionally varied within studies depending on the type of validity being evaluated

Validity data analysis

Clinical validity data (see Table 3)

Eight of the 10 studies assessing clinical validity had a low risk of bias (7–14) and two studies had a moderate risk of bias (15,16) (Table 2) for clinical validity data. Four studies (17–20) had both a moderate or low risk of bias (Table 2) as sensitivities/specificities were calculated for two different cohorts. Thus, no studies had a high risk of bias (Table 2), supporting their clinical validity.

Clinical validity data for the ECAS

Niven et al. (9) validated the ECAS at five different cut-offs for both the ECAS total score and the ALS-specific total score. Pinto-Grau et al. (7) proposed multiple cut-offs from normative data generating age-and education- adjusted norms. Both of these studies (7,9) reported moderate to high sensitivity and specificity values across multiple cut-off scores.

Lulé et al.(18) estimated sensitivity and specificity data for ECAS subdomains assessing memory, language, fluency and executive function in comparison to identical domains on the Consortium to Establish a Registry for Alzheimer's Disease plus (CERAD plus) (21). Sensitivity was in the medium range across all subdomains and specificity was much higher for the executive function subdomain.

In summary, ECAS sensitivity and specificity data presented here indicate high clinical validity. All studies (7,9,18) validated the ECAS against either a gold standard neuropsychological battery or the appropriate accepted diagnostic criteria. Further, all studies had an overall low risk of bias (Table 2) when assessing clinical validity; however, blinding was not reported in any of the studies and, therefore, this aspect of potential bias cannot be ruled out. The neuropsychological batteries used in two of these studies (7,9) assessed ALS-specific and ALS non-specific domains including fluency, language, memory, executive function and visuospatial function. However, Lulé et al. (18) validated the ECAS against the Alzheimer's disease-specific CERAD plus (21) on only four domains with the omission of visuospatial function..

Clinical validity data for the ALS-CBS

Turon-Sans et al. (12) validated the ALS-CBS cognitive and behavioural sections independently for diagnosis of behavioural or cognitive impairment and for FTD. Across all of these cut-offs, sensitivity, specificity and NPV values were high but PPV showed considerable variation. Similar results were observed earlier by Woolley et al. (11) who had validated the ALS-CBS at different cut-offs for cognitive and behavioural deficits and for FTD and by Branco et al. (10) who validated the ALS-CBS at a single cut-off to differentiate between ALS patients with and without executive impairment.

The above data suggests that the ALS-CBS has high clinical validity. All studies had a low risk of bias (Table 2) with two studies blinding researchers (11,12) thereby reducing expectation bias. Moreover, all studies (10–12) validated the cognitive section of the ALS-CBS against a gold-standard neuropsychological battery using the original Strong et al. consensus criteria (5) to diagnose

impairment. Interestingly, the neuropsychological battery used by Branco et al. (10) also included domains used in the ECAS that evaluate visuospatial functions. Further, two studies (11,12) also validated the behavioural section of the ALS-CBS against these diagnostic criteria (5). Woolley et al. (11) validated the ALS-CBS behavioural section against the Frontal Systems Behavior Scale (FrSBe) considering it to be the gold-standard; however, the FrSBe only assesses behaviour on the basis of three domains: apathy, disinhibition and executive dysfunction (22,23). Turon-Sans et al. (12) validated the behavioural section of the ALS-CBS against a wider range of tests assessing behavioural function, including the Frontal Behavioral Inventory (24), Neuropsychiatric Inventory (25) and Apathy Scale (26).

Clinical validity data for the MiND-B

Although the MiND-B has only been validated at two cut-off scores in two studies (13,14), calculated sensitivity and specificity values are high. Further, both of these studies (13,14) had a low risk of bias (Table 2) and validated the MiND-B against consensus criteria (5). Unfortunately, blinding was not reported. Mioshi et al. (14) validated two different cut-off scores (33 and 35) for the differentiation of ALS plus (cognitive or behavioural impairment) from ALS pure (only motor symptoms). A cut-off score of 35 was shown to have a higher sensitivity but lower specificity for detection of ALS plus in comparison to a cut-off score of 33, indicating that a cut-off of 35 increases the proportion of false positives (14). Patient cohorts in both studies (13,14) were subject to limited cognitive and behavioural assessment to aid diagnosis through the consensus criteria (5). As assessment was limited, patients may have been underdiagnosed prior to validation of the MiND-B, leading to a higher proportion of false positives (i.e. a lower specificity).

Clinical validity data for the BBI

Two studies validated the BBI at cut-off scores indicating mild behavioural change (>7) and at cut-off scores indicating severe behavioural change (>23). Both validation studies (8,17) present high sensitivity and specificity values at cut-off scores for both mild behavioural impairment and ALS-

FTD. Pinto-Grau et al.'s (8) validation study had an overall low risk of bias (Table 2) and Elamin et al.'s original study (17) had an overall moderate/low risk of bias (Table 2). Like many of the validation studies evaluated here, blinding was not reported. In Elamin et al.'s (17) study, validation was carried out against the FrSBe (22). Additionally, a small cohort in this paper (17) were diagnosed with ALS-FTD using revised criteria (27). However, the study (17) itself highlighted a limitation in using the FrSBe (22) to validate the BBI; the FrSBe (22) does not consider the impact of motor impairment on behaviour (17). Therefore, Pinto-Grau et al. (8) cross-validated the BBI against the ALS-FTD-Q (20), both being ALS-specific measures that control for motor impairment, leading to validation data (8) that are more clinically applicable. Nonetheless, the BBI assesses a wider range of behavioural functions than the ALS-FTD-Q (20).

Convergent validity

Eleven studies presented correlation data as measures of convergent validity, correlating screening tools with other previously-validated screening tools assessing the same cognitive or behavioural function. The choice of measures against which to correlate the screening tools may be important in determining convergent validity; for example, the choice of a less ALS-specific measure incorporating fewer ALS-specific cognitive changes, such as the Mini Mental State Examination (MMSE), may have led to fewer high correlations being achieved.

Pinto-Grau et al. (7) and Branco et al. (10) correlated the ECAS and the ALS-CBS respectively against subcomponents of a full neuropsychological battery. Pinto-Grau et al. (7) reported a correlation of 0.791 between the ECAS total score and all domains on the full battery. Branco et al. (10) reported correlation data that was statistically significant in six domains. Woolley et al. (11) also provided statistically significant correlation data concerning the behavioural aspect of the ALS-CBS. Three other studies correlated aspects of the ECAS score against other non-ALS-specific cognitive screening tests. Poletti et al. (16) reported the correlation between ECAS total score and the Montreal Cognitive Assessment (MoCA) (28) and the Frontal Assessment Battery (FAB) (29) scores to be 0.700 and 0.680 respectively. Ye et al. (15) found the ECAS total score to correlate with the MMSE

(30) (0.480) and FAB (29) (0.520). Finally, Lulé et al. (18) assessed concurrent validity between the ECAS total score and scores on the MoCA (28) and FAB (29). The correlation between MoCA (28) score and ECAS total score was 0.580 and between FAB (29) score and ECAS total score it was 0.460. It is not surprising that data presented in two of these studies (15,18) show the ECAS to have modest correlation with non-ALS-specific measures.

Two studies (19,20) presented negative correlation coefficient scores between the ALS-FTD-Q and the FAB score (lower scores on the FAB are indicative of worse performance) and positive correlations between the ALS-FTD-Q and the Frontal Behavioral Inventory (FBI) (31) and Hospital Anxiety and Depression Scale (32) scores. Raaphorst et al. (20) reported the ALS-FTD-Q to have a lower correlation with the FAB (29) than with the FBI (24); the FBI (24) had a correlation of 0.79 with the ALS-FTD-Q, suggesting high convergent validity (20). Watanabe et al. (19) presented data concerning discriminant validity. Here, the ALS-FTD-Q-J discriminated between ALS and ALS-bvFTD patients, ALS and bvFTD patients and between ALS patients and controls. Raaphorst et al. (20) also demonstrated that the ALS-FTD-Q discriminated between ALS, ALS-bvFTD and controls. For both of these studies (19,20), discriminant validity was calculated against diagnoses made using either the Neary criteria (33) or the Rascovsky criteria (34), or both.

Hsieh et al. (13) reported a significant correlation (0.540) between MiND-B and the Mini-Addenbrooke's Cognitive Examination (M-ACE) (35) in an ALS-FTD cohort, showing behavioural impairment to correlate with cognitive impairment in ALS-FTD patients (13).

Finally, two studies (8,17) correlated the BBI with other measures of behavioural change in ALS. Pinto-Grau et al. (8) reported a high correlation of 0.807 between the BBI total score and the ALS-FTD-Q total score. This was expected as both screening tools are ALS-specific and cross-validation of the BBI against the ALS-FTD-Q revealed the BBI to have high clinical validity (Table 3) (8). In addition, Elamin et al. (17) showed the BBI to have moderate to high correlations with the domains of

apathy (0.727), disinhibition (0.638) and executive dysfunction (0.687) on the FrSBe (22). The same paper reported a medium size negative correlation of 0.442 between the BBI and the FAB (29).

DISCUSSION

This systematic review evaluated 14 papers. The majority of these papers presented validation data on the ALS-CBS and the ECAS, with some of the validation studies occurring as part of their translation into languages other than their original English (10,12,15,16,18,19) or as part of the development of more detailed norms (7)). The MiND-B, BBI and ALS-FTD-Q were validated in the remaining studies; this search detected no papers assessing the validity of the FBI-ALS.

The papers detected by the search were of variable quality although, using our criteria, none were at risk of a high degree of bias. Generally, though, classification of impairment on the basis of the screening tool did not appear to have been undertaken blind to classification on the basis of the "gold standard" measure being used, although most studies did not report on this and, therefore, for the majority of studies (7–10,13–20) it was not possible to rule out the possibility of expectation bias. It is important to highlight, however, that in some studies (8,13,14,17,19,20) proxy responders may have been blind to diagnosis of behavioural change/ALS-FTD, even if researchers' status was not reported by the study.

While the samples were generally of a reasonable size and representative gender split, most studies did not justify their sample sizes, and these varied considerably. In some studies (10,11,13,14) the participants' demographics were only provided for study subcohorts. Furthermore, data concerning years of education were not provided consistently. In one study assessing concurrent validity (18) of the ECAS total score by comparing it with the FAB and MoCA tests, 9.3% of patients were unable to complete the MoCA and 5.1% were unable to complete the FAB due to physical impairment. This exclusion of a notable proportion of the cohort could be of further relevance when assessing study methodology.

Ten studies assessed clinical validity (7–14,17,18). For the ECAS, a screening tool that includes items measuring language and social cognition deficits, the reported sensitivity and specificity is high across all studies (7,9,18). The ECAS has also been shown to have high convergent validity (7,15,16,18). Moreover, the ECAS accommodates for motor and speech dysfunction by incorporating the verbal fluency index and offering completion in either a written or spoken format (4). Taking into consideration the new revised consensus criteria and the data presented in this systematic review, ECAS offers an attractive option for clinicians in need of a rapid, easy to administer screening tool.

With regards to the ALS-CBS, clinical validity data is also promising, with high reported sensitivities and specificities (10–12). The ALS-CBS also accounts for motor dysfunction by allowing patients to answer questions using different means and is quicker to administer than the ECAS. However, the cognitive subscale of the ALS-CBS, which focuses on executive dysfunction, is somewhat limited in that it fails to assess domains of language and social cognition, now included aspects of cognitive impairment in the current consensus diagnostic criteria, and it is not yet known to what extent it may, therefore, underdiagnose cognitive impairment.

The MiND-B displayed high clinical validity at two defined cut-offs (13,14). However, better clinical validity is likely to be achieved (13) when it is used concurrently with the Mini-ACE (35), a non-ALS specific screening test for cognitive change. Whilst validity data analysed here are promising (13,14), caution should be taken as the MiND-B assesses a limited set of behavioural functions and may miss manifestations of behavioural impairment mentioned in the Rascovsky criteria (34), used in the new consensus criteria (4) to guide the diagnosis of ALS with behavioural impairment and ALS-FTD. The ALS-FTD-Q has no studies assessing its clinical validity but two studies presented data concerning convergent validity (19,20). These studies display strong correlations between the ALS-FTD-Q and other measurement tools of behavioural change.

The BBI screens for behavioural change in ALS by assessing a large range of domains assessing frontal behaviours as described in the Neary criteria (33). The BBI assesses a wider spectrum of behavioural involvement in ALS than the ALS-FTD-Q and, therefore, may detect mild behavioural change in a more representative way (8). Further, the BBI takes into consideration the effects that motor dysfunction may have on behaviour. Validity data is scarce (8,17), however, and the field would benefit from more studies assessing its validity in a larger population and at multiple age adjusted cut-offs.

Motor impairment affecting speech or writing is often unaccounted for during routine neuropsychological testing and proves to be a confounding factor limiting patient performance. Where the screening tools were validated against a gold standard neuropsychological battery (7,9–12,18), there remains some potential error in validation due to the gold standard neuropsychological measures not controlling adequately for motor slowing or speech impairment. Whilst it is likely that more recent validations (e.g. for the ECAS (9)) will have included such adjustments in their background neuropsychological assessments, this is not clear for all validation studies reported. It will be essential for future validation studies to take these potential limitations into account. The difficulty in choosing an inappropriate validation measure has been recognised in the use of the FrSBe when validating the behavioural subscale of the ALS-CBS (11) and the BBI (17) and it is important that cognitive and behavioural screening tool validations are undertaken against measures that do not unduly penalize patients' performance due to motor and speech limitations.

Taking into consideration the revised Strong et al. (4) consensus criteria and validation studies appraised here, the ECAS and ALS-CBS appear to offer clinical utility. It may be important to consider that the ECAS assesses a range of ALS-specific and non-specific cognitive functions while the ALS-CBS focuses more specifically on executive dysfunction. In particular, the ECAS allows for some detailed assessment of impairments in language and social cognition, two domains added to the most recent version of the consensus criteria. In terms of measuring behavioural change, the MiND-B and BBI have preliminary evidence of high clinical validity although the MiND-B has been used to

detect ALS-motor vs ALS-plus patients, with the latter classification incorporating patients with cognitive and/or behavioural changes; therefore, further work is needed to validate this measure in terms of its sensitivity and specificity with respect to behavioural change alone.

ETHICAL APPROVAL: This article does not contain any studies with human participants performed by either of the authors.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

Box 1 Description of screening tools

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (36)

The ECAS is an assessment tool that can be administered by healthcare professionals other than neuropsychologists who have undergone appropriate training and completed by the patient at home visits or in the clinic environment. The ECAS can be answered by patients in a written manner or verbally, accounting for the presence of motor dysfunction. Questions assessing cognitive impairment and behavioural impairment are included in the screen. ALS-specific cognitive impairment is evaluated through the assessment of executive functions, social cognition, fluency and language. In addition, the ECAS assesses cognitive changes seen in non-ALS disorders, in the ALS non-specific section of the screening tool. The domains included here include memory and visuospatial function. Completion time is described to be in the order of 20 minutes. The ECAS requires the healthcare professional to assess behavioural change in the patient by interviewing a relative/carer. This supplementary assessment is based on the Rascovsky criteria (34) for diagnosis of behavioural-variant FTD. The cut-off score for the ECAS-Total Score is 105/136 and the cut-off score for the ALS-Specific Score is 77/100.

The ALS Cognitive Behavioural Screen (ALS-CBS) (11)
This screen is divided into a cognitive and behavioural section. The cognitive section is completed by the patient and there is a separate questionnaire to be completed by a healthcare professional or carer. The cognitive section, described as taking about 5 minutes to complete, assesses the domains of attention, concentration, mental tracking and monitoring and word initiation and retrieval (i.e., verbal fluency). The domains assessed in the behavioural section assessing alteration in behaviour over time include apathy, inhibition, emotional control, empathy, frustration tolerance, cognitive flexibility, insight, judgement, food preferences, language and decision-making. The language domain primarily highlights the presence of aphasia in the formation of neologisms or instances where the patient says the wrong word more often than usual. Answers can be gathered through the use of speech output devices, verbally or in writing. The ALS-CBS is scored out of 20; a score of ≤10 is indicative of probable FTD. A score of ≤16 suggests cognitive impairment (ALSci). The behavioural component of the ALS-CBS contains 15 items; the behavioural component is scored from 0-45; with a score of ≤32 accurately classifying ALS patients with FTD and a score ≤36 detecting more general behaviour impairment (ALSbi or ALS-FTD).

The Motor Neurone Disease Behavioural Scale (MiND-B) (14)
The MiND-B questionnaire quantifies behavioural changes in the person with ALS over the previous month in the following domains: disinhibition, apathy and stereotypical behaviour. It comprises nine items and is completed by one of the patient's contacts. The cut-off scores for differentiating ALS from ALSci/ALSbi or FTD are 35/36 and 33/36 respectively. These cut offs have varying reported sensitivities and specificities.

The Frontal Behavioural Inventory - ALS (31)
The Frontal Behavioural Inventory (FBI) is a 24- question survey completed by the caregiver that quantifies behavioural change in terms of apathy, indifference, disorganisation, inattention, personal neglect, aspontaneity, inflexibility, concreteness, loss of insight, logopenia, verbal apraxia and alien hand (24) Responses are scaled numerically: 0 (none/never), 1 (mild/occasional), 2 (moderate/often) and 3 (severe/most of the time). The newer ALS version of the FBI has extra questions that help clarify the behavioural symptoms specific to an FTD clinical picture (37).

The ALS Frontotemporal Dementia Questionnaire (ALS-FTD-Q) (20)
The ALS-FTD-Q is a 25-item questionnaire completed by the healthcare professional or caregiver and assesses behaviour change either over three years or describes behaviour in the previous month. These items include irritability, disinhibition, emotional lability, altered food preference, egocentricity, delusions (paranoia) and apathy; three items assessing memory, concentration and orientation in time are also included. The ALS-FTD-Q identifies patients with the behavioural variant of FTD (ALS-bvFTD). A score ≥22 was set as indicative of mild disturbances, and scores ≥29 were indicative of severe disturbances.

The Beaumont Behavioural Inventory (BBI) (17)
The BBI is a new screening tool for behavioural change in ALS, over two timeframes, i.e. "in the last 10 years" and "since the onset of MND". It consists of 41 items and is a proxy-report behavioural assessment that takes around 5 to 10 minutes to complete. It builds on other behavioural questionnaires by taking into consideration effects that motor dysfunction may have on behaviour. The BBI has items that assess a larger range of frontal behaviours described in the Neary criteria (33) and the revised bvFTD criteria (34). The range of frontal behaviours assessed includes aspects of apathy, behavioural disinhibition, social cognition deficits, perseverative, behavioural stereotypes or obsessive-compulsive behaviours, dietary changes, utilisation behaviour, echolalia and altered response to sensory stimuli. The scale also includes 6 items examining cognitive changes representing frontotemporal change. A total BBI score ≥7 was indicative of behavioural abnormality; a score of 22.5 was held to indicate severe behavioural abnormality consistent with ALS-FTD.

Box 2 Search strategy used for searching MEDLINE, EMBASE and PsycINFO

(((Edinburgh Cognitive and Behavioural ALS Screen) or (Edinburgh Cognitive and Behavioral ALS Screen) or (Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen) or (Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen) or Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen or Amyotrophic Lateral Sclerosis Cognitive Behavioral Screen or ALS Cognitive Behavioural Screen or ALS Cognitive Behavioral Screen or ALS-CBS or Amyotrophic Lateral Sclerosis Frontotemporal Dementia Questionnaire or Amyotrophic Lateral Sclerosis Fronto-temporal Questionnaire or ALS-FTD-Q or Amyotrophic Lateral Sclerosis Fronto Temporal Dementia Questionnaire or Frontal Behavioural Inventory ALS Version or Frontal Behavioral Inventory ALS Version or Frontal Behavioural Inventory Amyotrophic Lateral Sclerosis Version or Frontal Behavioral Inventory Amyotrophic Lateral Sclerosis Version or The Motor Neurone Disease Behaviour Scale or The Motor Neuron Disease Behaviour Scale or The Motor Neurone Disease Behavior Scale or The Motor Neuron Disease Behavior Scale or MiND-B or BBI or Beaumont Behavioural Inventory or Beaumont Behavioral Inventory) and (valid* or specificit* or sensitivit* or accurac*))

Table 1: Characteristics of the study cohorts in the validation studies

Study	Screening test	Cohort size [subcohorts]	Age (mean) [subcohorts]	Male sex (%) [subcohorts]	Disease duration (months) [subcohorts]	Years of education (mean) [subcohorts]
	ECAS					
Pinto-Grau et al., 2017 (7)	ECAS	30	59.83	63	n.r	n.r
Poletti et al., 2016 (16)	ECAS	107	62.98	65	21.07	10.81
Lulé et al., 2015 (18)	ECAS	136	60	66.9	39	13.7
Niven et al., 2015 (9)	ECAS	40	64.45	65	n.r	11.15
Ye et al., 2016 (15)	ECAS	84	55.07	69	15.81	11.45
	ALS-CBS					
Branco et al., 2017 (10)	ALS-CBS	49 [ALSci (10) ALSni (39)]	ALSci (55.10) ALSni (56.50)	ALSci (60) ALSni (59)	ALSci (25.80)ALSni (39.80)	
Woolley et al., 2010 (11)	ALS-CBS	136 [ALS Cohort (105) ALS Validation (31)]	ALS Cohort (58.6) ALS Validation (58.03)	ALS Cohort (61) ALS Validation (55)	ALS Cohort (34) ALS Validation (22)	ALS Cohort (15.2) ALS Validation (14.5)
Turon-Sans et al., 2016 (12)	ALS-CBS	50	62.3	64	17.96	n.r
	ALS-FTD-Q					
Watanabe et al., 2016 (19)	ALS-FTD-Q-J	98	67.7	59.2	21	n.r
Raaphorst et al., 2012 (20)	ALS-FTD-Q	113	61.3	70.8	34	n.r
	MiND-B					
Mioshi et al., 2014 (14)	MiND-B	79 [Limb onset (55) Bulbar onset (24)]	Limb onset (60.4) Bulbar onset (58.7)	Limb onset (60) Bulbar onset (46)	Limb onset (27.6) Bulbar onset (15.2)	Limb onset (13.7) Bulbar onset (14.1)
Hsieh et al., 2016 (13)	MiND-B	70 [ALS-pure (27) ALS-plus (19) ALSFTD (24)]	ALS-pure (56.3) ALS-plus (57.6) ALSFTD (63.1)	ALS-pure (59.3) ALS-plus (63.2) ALSFTD (66.7)	ALS-pure (18) ALS-plus (28.9) ALSFTD (40.1)	ALS-pure (13.5) ALS-plus (12.5) ALSFTD (12.3)
	BBI					
Elamin et al., 2017 (17)	BBI	85	63.05	67.1	n.r	13.32
Pinto-Grau et al., 2017 (8)	BBI	60 [ALS (55) ALS-FTD (5)]	65.42 [ALS (65.18) ALS-FTD (68.00)	70 [ALS (69) ALS-FTD (80)]	n.r	13.3 [ALS (13.29) ALS-FTD (12.20)]

ECAS The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen; **ALS-CBS** Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen; **ALS-FTD-Q** Amyotrophic Lateral Sclerosis Frontotemporal Dementia Questionnaire; **ALS-FTD-Q-J** Amyotrophic Lateral Sclerosis Frontotemporal Dementia Questionnaire Japanese version; **MiND-B** The Motor Neuron Disease Behavioural Screen; **BBI**

Beaumont Behavioural Inventory; **ALSci** Amyotrophic Lateral Sclerosis with cognitive impairment; **ALSni** Amyotrophic Lateral Sclerosis without executive impairment; **ALS Cohort** Amyotrophic Lateral Sclerosis patient cohort, **ALS Validation** Amyotrophic Lateral Sclerosis patient cohort used in validation section of study; **Limb onset** Disease onset with clinical limb signs; **Bulbar onset** Disease onset with clinical bulbar signs; **ALS-pure** Amyotrophic Lateral Sclerosis with motor clinical features only;
ALS-plus Amyotrophic Lateral Sclerosis with non-motor clinical features; **ALSFTD** Amyotrophic Lateral Sclerosis Frontotemporal Dementia; **n.r** Not recorded.

Table 2: Methodology Analysis

Study	Patient representativeness (0-2)	Blinding (0-1)	Validated against a gold standard neuropsychological battery/ diagnostic criteria (0-2)	Risk of bias total score	Risk of bias category
ECAS					
Pinto-Grau et al., 2017 (7)	2	0 n.r	2	4	Low
Poletti et al., 2016 (16)	2	0 n.r	1	3	Moderate
Niven et al., 2015 (9)	2	0 n.r	2	4	Low
Lulé et al., 2015 (18)	2	0 n.r	1 (Concurrent validity) 2 (Clinical validity)	3/4	Moderate/Low
Ye et al., 2016 (15)	2	0 n.r	1	3	Moderate
ALS-CBS					
Branco et al., 2017 (10)	2	0 n.r	2	4	Low
Woolley et al., 2010 (11)	2	1	2	5	Low
Turon-Sans et al., 2016 (12)	2	1	2	5	Low
MiND-B					
Hsieh et al., 2016 (13)	2	0 n.r	2	4	Low
Mioshi et al., 2014 (14)	2	0 n.r	2	4	Low
ALS-FTD-Q					
Watanabe et al., 2016 (19)	2	0 n.r	1 (2 for discriminant validity)	3/4	Moderate/Low
Raaphorst et al., 2012 (20)	2	0 n.r	1 (2 for discriminant validity)	3/4	Moderate/Low
BBI					
Elamin et al., 2017 (17)	2	0 n.r	1 (2 for ALS-FTD patients)	3/4	Moderate/Low
Pinto-Grau et al., 2017 (8)	2	0 n.r	2	4	Low

Patient representativeness (0-2) 2 = highly representative cohort; 1= less representative cohort; 0 = unrepresentative cohort
Blinding 1= blinded; 0= not blinded/blinding not reported **n.r** =not reported
Validation against a gold standard neuropsychological battery (or diagnostic criteria for behavioural screens) 2= validation was against a gold standard neuropsychological battery (or diagnostic criteria for behavioural screens) or an accepted ALS-specific standardised measure; 1= validation against an accepted non-ALS-specific standardised measure; 0=validation was not against a gold standard neuropsychological battery (or diagnostic criteria for behavioural screens) or other accepted ALS-specific or non-ALS-specific standardised measures.
Two studies (13,14) were assigned a score of 2 in this category as they were validated against the 2009 Strong et al criteria; however, a limited number of tests were used to identify ALSci and it is not clear that measures were controlled for motor speed.

Table 3: Validation data: sensitivity, specificity, PPV, NPV and LR+

Study and reference groups used	Screening test	Sensitivity	Specificity	PPV	NPV	LR+
Pinto-Grau et al., 2017 (7)	**ECAS**					
Controls were used to create age and education adjusted cut-off scores. Validation data was calculated at cut-off scores for the diagnosis of cognitive impairment in an ALS cohort.	Cutoff varies					
	ECAS Total	1.000	0.800	0.375	1.000	n.r
	ECAS Specific	1.000	0.850	0.430	1.000	n.r
	ECAS Non-Specific	1.000	0.790	0.440	1.000	n.r
Niven et al., 2015 (9)	**ECAS**					
Controls were used to create population abnormality cut-off scores. Validation data was calculated at cut-off scores for the diagnosis of cognitive impairment in an ALS cohort.	ALS-Specific Score cut-off					
	≤ 77	0.770	0.890	0.770	0.890	n.r
	≤ 78	0.850	0.810	0.690	0.920	n.r
	≤ 80	0.920	0.810	0.710	0.920	n.r
	< 82	0.920	0.740	0.630	0.950	n.r
	≤ 83	1.000	0.740	0.650	1.000	n.r
	ECAS Total Score cut-off					
	≤ 105	0.690	0.890	0.750	0.860	n.r
	≤ 107	0.770	0.810	0.670	0.880	n.r
	≤ 108	0.850	0.810	0.690	0.920	n.r
	≤ 110	0.920	0.810	0.710	0.960	n.r
	≤ 115	1.000	0.520	0.500	1.000	n.r
Lulé et al., 2015 (18)	**ECAS**					
Controls were used to generate cut-off scores. Validation data was calculated at cut-off scores for the diagnosis of cognitive impairment in an ALS cohort.	ECAS Memory	0.330	0.920	n.r	n.r	n.r
	ECAS Language	0.330	0.750	n.r	n.r	n.r
	ECAS Fluency	0.500	0.910	n.r	n.r	n.r
	ECAS Executive Function	0.430	1.000	n.r	n.r	n.r
Turon-Sans et al., 2016 (12)	**ALS-CBS**					
Validation was completed at optimal cut-off scores (for both the cognitive and behaviour sections) differentiating between ALS with no impairment and ALS with cognitive/behavioural impairment and between ALS with FTD and ALS without FTD.	ALS-CBScog, cut-off: 8 No FTD vs. FTD	0.833	0.750	0.313	0.971	n.r
	ALS-CBScog, cut-off: 15 Normal vs. CI	0.862	0.620	0.758	0.765	n.r
	ALS-CBSbv, cut-off: 35 No FTD vs. FTD	0.833	0.690	0.250	0.967	n.r
	ALS-CBSbv, cut-off: 36 Normal vs. CI	0.933	0.743	0.610	0.963	n.r
Branco et al., 2017 (10)	**ALS-CBS**					

A pre-determined cut-off score of 10 to differentiate between ALS with and without executive impairment was set. The study included controls matched by age, gender and education.	Cutoff 10 ALS with executive impairment vs. ALS without executive impairment	0.900	0.872	n.r	n.r	n.r
Woolley et al., 2010 (11)	**ALS-CBS**					
Validation was completed at pre-determined cut-off scores considered optimal differentiating between ALS with cognitive impairment and ALS without cognitive impairment and between ALS with FTD and the remaining cohort (including ALS with no impairment, ALS with cognitive impairment, ALS with behavioural impairment, ALS with cognitive and behavioural impairment and healthy controls).	Cognitive section					
	Cut off 10 for FTD	1.000	1.000	1.000	1.000	n.r
	Cut off 17 for any cognitive deficit	0.850	0.860	0.690	0.710	n.r
	Behaviour section					
	Cut off 32 for FTD	0.880	0.800	0.940	0.670	n.r
	Cut off 36 for any behavioural deficit	0.900	0.860	0.820	0.920	n.r
Hsieh et al., 2016 (13)	**MiND-B**					
Pre-determined recommended cut-off scores were used. Validation was completed at the recommended cut-off score of 33 differentiating ALS pure (only motor symptoms) from ALS plus (cognitive and behavioural symptoms).	Cutoff 33	0.900	0.790	0.730	0.780	4.320
Mioshi et al., 2014 (14)	**MiND-B**					
Cut-off scores were determined by discriminant analysis. Validation was completed cut-off scores of 33 and 35 differentiating ALS pure (only motor symptoms) from ALS plus (cognitive and behavioural symptoms).	Cutoff 35	0.900	0.500	0.778	0.727	n.r
	Cutoff 33	0.810	0.750	n.r	n.r	n.r
Elamin et al., 2017 (17)	**BBI**					
Validity data was calculated relative to the FrSBe, considering it to be the gold-standard. Mild behavioural impairment cut-off scores	Cutoff 7	0.879	0.789	0.725	0.911	n.r
	Cutoff 22.5 (for ALS-FTD)	0.900	0.960	0.750	0.987	n.r

were determined using data from controls. The cut-off score of 7 identified mild behavioural change in an ALS cohort and the cut-off score of 22.5 identified ALS-FTD in an ALS cohort.						
Pinto-Grau et al., 2017 (8)	**BBI**					
Here, the BBI was cross-validated against the ALS-FTD-Q. The cut-off score of 7 identified mild behavioural change the cut-off score of 23 indicated severe behavioural change in an ALS cohort.	Cutoff 7	0.500	0.760	n.r	n.r	n.r
	Cutoff 23	1.000	0.920	n.r	n.r	n.r

ECAS The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen; **ALS-CBS** Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen; **ALS-FTD-Q** Amyotrophic Lateral Sclerosis Frontotemporal Dementia Questionnaire; **MiND-B** The Motor Neuron Disease Behavioural Screen; **BBI** Beaumont Behavioural Inventory; **FrSBe** Frontal Systems Behavior Scale; **PPV** Positive predictive value; **NPV** Negative predictive value; **LR+** Likelihood ratio (sensitivity/1-specificity); **ALS-CBScog** Cognitive section of ALS-CBS; **ALS-CBSbv** Behavioural section of ALS-CBS; **ALS-FTD** Amyotrophic Lateral Sclerosis Frontotemporal Dementia; **FTD** Frontotemporal dementia; **CI** Cognitive impairment; **n.r** Not recorded

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Figure 1. PRISMA Flow-Diagram for Search Strategy (http://www.prisma-statement.org/PRISMAStatement/Checklist.aspx)