Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: Isabel K. Gosselt, Tanja C. W. Nijboer & Michael A. Van Es (2020) An overview of screening instruments for cognition and behavior in patients with ALS: selecting the appropriate tool for clinical practice, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 21:5-6, 324-336, DOI: 10.1080/21678421.2020.1732424

To link to this article: https://doi.org/10.1080/21678421.2020.1732424

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 21: 324–336

REVIEW ARTICLE

An overview of screening instruments for cognition and behavior in patients with ALS: selecting the appropriate tool for clinical practice

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Abstract

Objective: Patients with amyotrophic lateral sclerosis (ALS) not only show motor deficits, but may also have cognitive and/or behavioral impairments. Recognizing these impairments is crucial as they are associated with lower quality of life, shorter survival, and increased caregiver burden. Therefore, ALS-specific neuropsychological screening instruments have been developed that can account for motor and speech difficulties. This study provides an overview and comparison of these screeners. *Methods:* A systematic review was conducted using Medline and Embase. Articles describing cognitive/behavioral screening instruments assessed in ALS patients were included. Screening instruments were compared on multiple factors, such as domains, adaptability, required time, and validation. *Results:* We included 99 articles, reporting on nine cognitive screeners (i.e. ACE-R, ALS-BCA, ALS-CBS, ECAS, FAB, MMSE, MoCA, PSSFTS, and UCSF-SB), of which five ALS-specific. Furthermore, eight behavioral screeners (i.e. ALS-FTD-Q, AES, BBI, DAS, FBI, FrSBe, MiND-B, and NPI) were reported on, of which three ALS-specific. *Conclusion:* Considering the broad range of cognitive domains, adaptability, and satisfying validity, the ALS-CBS and ECAS appear to be the most suitable screeners to detect cognitive and behavioral changes in ALS. The BBI appears to be the best option to screen for behavioral changes in ALS, since all relevant domains are assessed, motor-related problems are considered, and has a satisfactory validity. The MiND-B and ALS-FTD-Q are promising as well. In general, all screening instruments would benefit from additional validation research to gain greater insights into test characteristics and to aid clinicians in selecting screening tools for use in clinical practice.

Keywords: *ALS, cognition, behavior, screening instruments*

Introduction

Up to 50% of patients with amyotrophic lateral sclerosis (ALS) not only have motor deficits, but also cognitive impairments, particularly in the frontotemporal domains (i.e. fluency, language, social cognition, and to a lesser extent executive functions and delayed verbal memory (1,2). Moreover, 10–15% of ALS patients have co-morbid frontotemporal dementia (FTD) (1,2). ALS and FTD are, therefore, currently seen as two extremes of one disease spectrum, based on clinical, pathological and genetic overlap (3).

Recognizing cognitive impairment in ALS is important as it is associated with diminished quality of life, certain genetic mutations (e.g. *C9orf72*, *TBK1*) and a shortened lifespan, as well as increased caregiver burden of and lower adherence to treatment recommendations (4–6). Additionally, the presence of cognitive impairment also needs to be taken into account in clinical care with respect to communication, interventions and the use of technological tools.

There is general consensus that an extensive neuropsychological battery is required to confirm

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Supplemental data for this article can be accessed here.

This article has been republished with minor changes. These changes do not impact the academic content of the article.

(Received 9 December 2019; revised 30 January 2020; accepted 10 February 2020)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2020.1732424

the presence of cognitive impairment, and in particular to assess which cognitive domains are affected. In clinical practice, however, it is not always feasible for all ALS patients to undergo such a broad assessment, because it is time-consuming, expensive, requires qualified personnel, and fatigues patients. Moreover, ALS patients may not be capable of completing a full neuropsychological battery due to motor and/or speech impairment. Therefore, several brief cognitive screeners have been developed, specifically designed for testing ALS patients. Cognitive screeners for ALS patients should (a) assess multiple cognitive domains, and most importantly cognitive domains which are often affected in ALS patients (i.e. executive function, social cognition, fluency, language, and (verbal) memory (1,7)); (b) take motor deficits into account (e.g. be adaptable for physical ability); and (c) be simple, validated, and time-efficient, to be easily incorporated for daily clinical use (1,2). Likewise, behavioral screeners should preferably have similar characteristics and include behavioral symptoms which are common in ALS-FTD patients (i.e. disinhibition, apathy/inertia, sympathy/empathy, perseverations/stereotyped/compulsive/ritualistic behavior, hyperorality/dietary changes (8)).

Recently, a systematic review on the validity of six different ALS-specific neuropsychological screeners was published (9). In this present review, we included all screeners frequently used in clinical care or scientific studies (regardless of whether they were designed specifically for use in ALS) and provided an overview/comparison of the practical aspects of these instruments; which screeners are most commonly used, which cognitive and behavioral domains are assessed, whether can they be adapted to physical disability, availability in multiple languages, availability of alternate versions for longitudinal use, time required to administer each test, etc. Hereby, we aim to support clinicians and researchers in selecting the most appropriate screening tools for use in daily practice.

Methods

Literature search

A literature search was conducted using Medline and Embase using the search format as represented in Figure 1.

The search was completed on the 28 February 2019 and was limited to peer reviewed articles written in English. Articles were screened for inclusion based on title and abstract at first. Conference proceedings were excluded. Relevant articles were read full-text and screened for inclusion criteria. Related citations and relevant references in articles and/or reviews were also considered for inclusion and used to check completeness of the search. Two individuals performed a systematic search of the literature and screened titles and abstracts for including full-text manuscripts. The first author performed a follow-up check, by removing duplicates, and checking the screened titles, abstracts and full-text manuscripts for inclusion. PRISMA guidelines were followed (10).

For articles to be included in this study, we required that (a) a cognitive/behavioral screening battery was assessed in ALS patients; (b) the diagnosis of ALS patients was made according to the (revised) El Escorial criteria (11) or AWAJI criteria (12); (c) participants were free from major comorbid medical, neurological of psychiatric history, except for ALS patients with pre-diagnosed dementia; and (d) mean test scores and standard deviations were reported. For non-ALS-specific cognitive/behavioral screening instruments to be included, these should be reported on in >1 article.

Overview and comparison screening instruments

An overview of the number of included studies dedicated to different screening instruments was given.

Information on each of the screening instruments was extracted from full-text of the included articles. The following characteristics were

('amyotrophic lateral sclerosis':ab,ti OR 'als':ab,ti OR 'sals':ab,ti OR 'fals':ab,ti OR 'als-ftd':ab,ti OR 'als-bv':ab,ti OR 'alsbi':ab,ti OR 'alsci':ab,ti OR 'charcot disease':ab,ti OR 'gehrig':ab,ti OR 'guam disease':ab,ti) AND ('neuropsychological':ab,ti OR 'neuropsychology':ab,ti OR 'screen':ab,ti OR 'screening':ab,ti OR 'screenings':ab,ti OR 'monitor':ab,ti OR 'monitors':ab,ti OR 'assessment':ab,ti OR 'als brief cognitive assessment':ab,ti OR 'als-bca':ab,ti OR 'als cognitive behaviour screen':ab,ti OR 'als-cbs':ab,ti OR ('edinburgh cognitive':ab,ti AND 'behavioural amyotrophic lateral sclerosis screen':ab,ti) OR 'ecas':ab,ti OR 'penn state screening':ab,ti OR 'pssfts':ab,ti OR 'ucsf screening battery':ab,ti) AND ('cognition':ab,ti OR 'cognitive':ab,ti OR 'mental':ab,ti OR 'dementia':ab,ti OR 'dementias':ab,ti OR 'frontotemporal':ab,ti OR 'frontal lobe':ab,ti OR 'temporal lobe':ab,ti OR 'ftd':ab,ti OR 'ftld':ab,ti OR 'behavior':ab,ti OR 'behavioral':ab,ti OR 'behaviors':ab,ti OR 'behaviour':ab,ti OR 'behavioural':ab,ti OR 'behaviours':ab,ti) NOT ('abstract':it OR 'letter':it OR 'congress':it) AND [1-1-1900]/sd NOT [28-2-2019]/sd AND [english]/lim AND ([embase]/lim OR [medline]/lim)

Figure 1. Search strategy used for searching Medline and Embase.

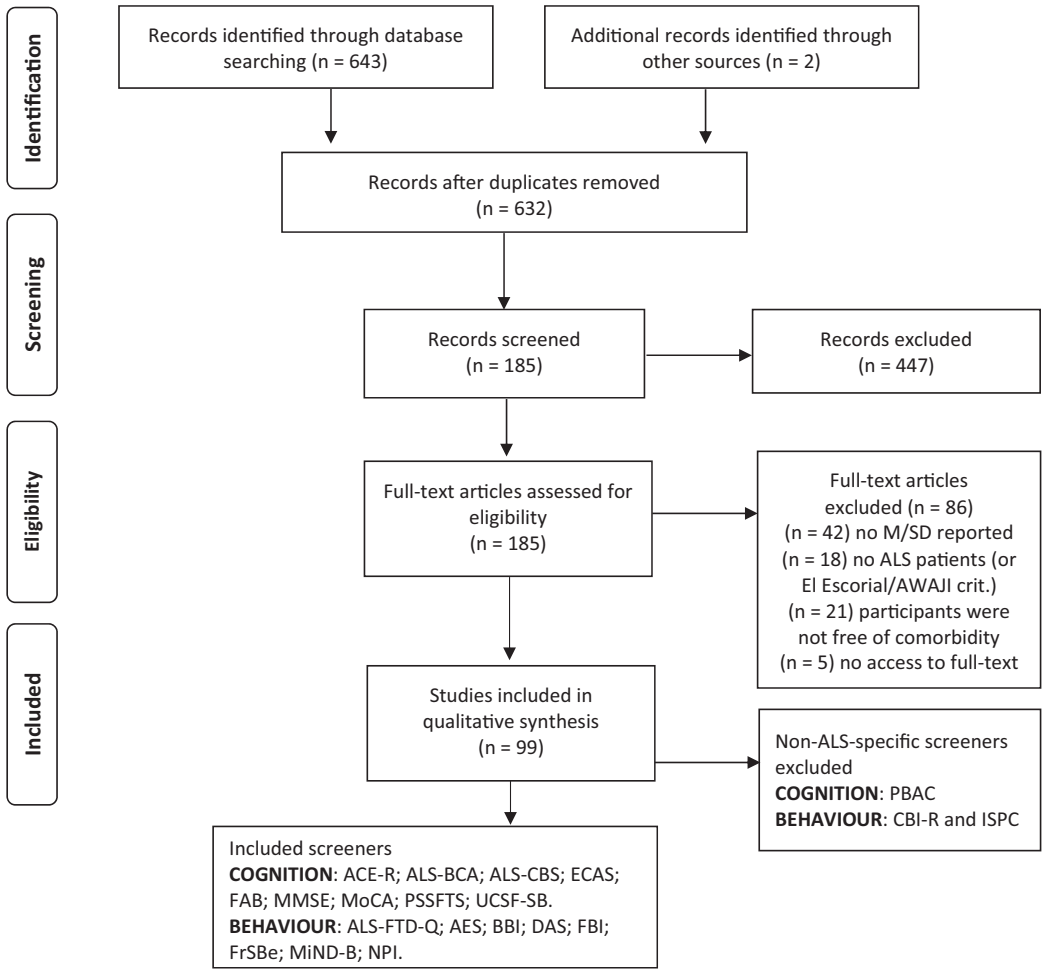

Figure 2. PRISMA flowchart of the literature search strategy.

reported for the cognitive screening instruments: (a) cognitive domains assessed (i.e. executive, attention, fluency, language, memory, social cognition and visuospatial), based on domains which are often affected in ALS patients (1,7); (b) adaptability for motor problems; (c) % participants who completed the screener; (d) administration time; (e) validation (i.e. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)); (f) % patients with cognitive deficits assessed with the concerning screening instrument; (g) available alternative versions, translations, and cutoff score; (h) corrected factors for cutoff score (e.g. age); and (i) references of articles on which the information was based. Regarding behavioral screening instruments, similar information was reported, but information on domains was adjusted to behavioral symptoms, and several factors were added: (a) reporter (i.e. close relative (proxy), self-report, or clinician); (b) number of items; (c) output scores (e.g. composite score); and (d) type of questions. The listed behavioral domains were based on Rascovsky's criteria for the behavioral variant of FTD (8).

The screening instruments were compared based on the following aspects: *domains*, *adaptability*, *required time*, and *validation*.

Results

Literature search

Our literature search identified 643 articles. After removal of duplicates ($n = 13$), 630 articles were screened based on title/abstract. Related citations and relevant references were considered for inclusion ($n = 2$). Remaining relevant articles were screened on full-text for inclusion ($n = 185$). In total, we included 99 articles (Figure 2) in our overview which included cognitive and behavioral screeners used in ALS patients. Several articles ($n = 5$) had to be excluded since no full-text was available, even after contacting the corresponding author(s).

Overview screening instruments

An overview of the number of included studies dedicated to different screening instruments is shown in Figure 3. See also Supplementary A for a detailed overview (13–60).

Overview cognitive screening instruments. Cognitive screening instruments that have been described in ALS patients are (a) the Addenbrooke's Cognitive Examination – revised (ACE-R (61)); (b) the ALS-Brief Cognitive Assessment (ALS-BCA (62)); (c) the ALS-

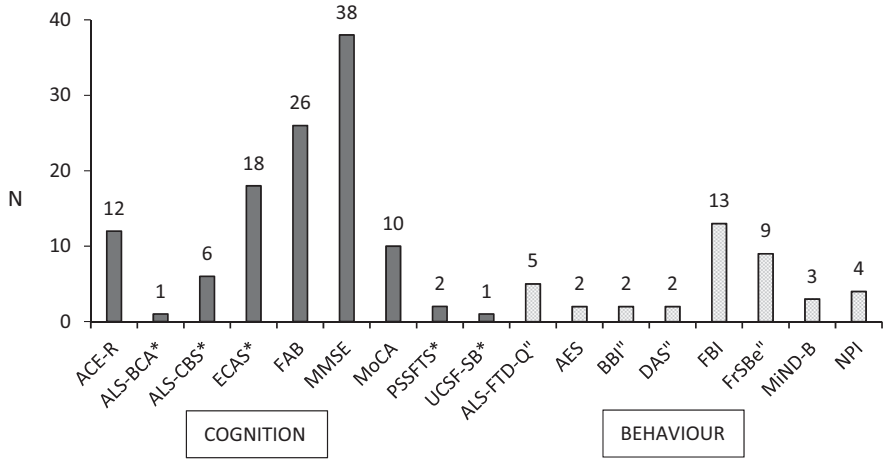

Figure 3. Included studies dedicated to the different screening instruments, split on cognition and behavior. Some of the cognitive screeners also included a behavioral domain (marked with *), and vice versa (marked with ").

Cognitive Behavioral Screen (ALS-CBS (63)); (d) the Edinburgh Cognitive and Behavioral ALS Screen (ECAS (64)); (e) the Frontal Assessment Battery (FAB (65)); (f) the Mini-Mental State Examination (MMSE (66)); (g) the Montreal Cognitive Assessment (MoCA (67)); (h) the Penn State Screening examination of Frontal and Temporal dysfunction Syndromes (PSSFTS (68)); and (i) the University of California San Francisco – Screening Battery (UCSF-SB (69)). An overview of their characteristics is shown in Table 1.

One non-ALS-specific cognitive screening instrument was used in only 1 study and therefore excluded for the overview: the Philadelphia Brief Assessment of the Cognition (PBAC (70)).

Comparison cognitive screening instruments. In general, executive functions, fluency, verbal memory, language, and social cognition are impaired in some, yet not all, ALS patients (1,7). Executive functions, fluency, and memory are screened for in all ALS-specific screening instruments (i.e. ALS-BCA, ALS-CBS, ECAS, PSSFTS, and UCSF-SB). Focusing on the ALS-specific screeners, language is only screened for in both the ECAS and PSSFTS and social cognition solely in the ECAS. Several cognitive screening instruments include the FBI, a behavioral screener, additionally (i.e. ALS-BCA, PSSFTS, and UCSF-SB). Whereas the ALS-CBS and ECAS include a separate behavioral subdomain (see Table 2 for the characteristics of these subdomains).

Regarding adaptability, the ALS-BCA, ALS-CBS, ECAS, PSSFTS, and UCSF-SB could easily be adapted in case of (severe) motor impairments and/or speaking disabilities. The utility of these screening instruments could be improved by relatively easy task modifications, such as answering by writing, typing, blinking, or eye movements (in case of dysarthria) and the use of oral and written verbal responses to compensate for writing or slow verbal responses. On the contrary, some specific tasks (e.g. copying, drawing, Trail Making Test and reading aloud) in the ACE-R, FAB, MMSE, and MoCA could not be adapted, making them less useful for ALS patients with more advanced disease.

Required administration time vary considerable among the cognitive screeners. Whereas the ALS-BCA, ALS-CBS, and FAB require only 5–10 min, a bit more time (10–15 min) is needed to administer the ACE-R, MMSE, and MoCA. The PSSFTS, UCSF-SB, and ECAS take the most time to administer (i.e. respectively 15–20 min, and 40 min, 15–45 minutes).

So far, only the ALS-BCA, ALS-CBS, ECAS, FAB, and MMSE have been validated as screening instruments specifically for ALS patients. Until now, superior validity was found for the FAB, although sensitivity and specificity of the other screening instruments were also moderate to high, except for the MMSE. However, a considerable percentage of ALS patients (up to 50%) are not capable of completing the FAB due to physical disability.

Overview behavioral screening instruments. Behavioral screening instruments that have been described in ALS patients are (a) the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q (71)); (b) the Apathy Evaluation Scale (AES (72)); (c) the Beaumont Behavioral Inventory (BBI (73)); (d) the Dimensional Apathy Scale (DAS (74)); (e) the Frontal Behavioral Inventory (FBI (75)); (f) the Frontal Systems Behavior scale (FrSBe (76)); (g) Motor Neuron Disease Behavior scale (MiND-B (77)); and (h) Neuropsychiatric Inventory (NPI (78)). An overview of their characteristics is shown in Table 2.

Two non-ALS-specific behavioral screening instruments were used in only one study and therefore excluded for the overview: the

Table 1. Characteristics of cognitive screening instruments used for ALS patients.

	ACE-R	ALS-BCA	ALS-CBS	ECAS	FAB	MMSE	MoCA	PSSFTS	UCSF-SB	BBI	DAS	FrSBe
Specific for	Dementia and MCI	ALS	ALS	ALS	Executive dysfunction	General cognition	Dementia and MCI	ALS(-FTD)	ALS	Executive /language subscale	Executive subscale	Executive subscale
Cognitive domains												
Executive	–	+	+	+	+	+	+	+	+[b]	+	+	+
Attention	+	–	+	–	–	+	+	+	+[b]	–	+	+
Fluency	+	+	+	+	+	–	+	+	+	–	–	–
Language	+	–	–	+	–	+	+	+	–	+	–	–
Memory	+	+[recall]	+[WM]	+	–	+[recall]	+[recall]	+	+[b]	–	–	+[WM]
Social cognition	–	–	–	+	–	–	–	–	–	+	–	–
Visuospatial	+	–	–	+	–	+	+	+	–	–	–	–
Behavioral domain	–	+[a]	+	+	–	–	–	+[a]	+[a]	+[Table 2]	+[Table 2]	+[Table 2]
Adaptability[c]	V/W +/–	Ty/W/V +	V/W/SD/E +	V/W/E +	V/W/H/F/T +/–	V/W –	V/W +/–	V/W/B/SD +	+	Table 2	Table 2	Table 2
Participants who completed screener	54–87%	–	–	100%	50-100%	91–100%	60-100%	–	–	Table 2	Table 2	Table 2
Administration time	±15 min	5-10 min	5-10 min	15-45 min	5-10 min	10-15min	10-15 min	15-20 min	40 min	Table 2	Table 2	Table 2
Validation												
Sensitivity	–	64%	85-90%	50-100%	89-100%	8-13%	–	–	–	Table 2	Table 2	Table 2
Specificity	–	–	62-87%	80-95%	59-100%	100%	–	–	–			
PPV	–	–	69-76%	38-73%	57-100%	100%	–	–	–			
NPV	–	–	77-86%	92-100%	89-100%	42-63%	–	–	–			
Patients with cognitive deficits	30–45%	53%	46–59%	18–37%	14–55%	0–15%	53%	1–56%	–	–	–	20–46%
Alternative versions	+ A,B,C	–	–	+ A,B,C	–	–	+ 1,2,3	–	–	Table 2	Table 2	Table 2
Available languages[d]	17	1	3	23	8	73	±100	1	1	Table 2	Table 2	Table 2
Available cutoff[e]	+	+	+	+	+	+	+	+[f]	+[g]	Table 2	+	Table 2
Cutoff corrected for	–	–	–	Age, education	Age, education	–	Education	–	–	Table 2	Table 2	Table 2
References	(94–96)	(62)	(63,82,97,98)	(64,85,88,99–106,120)	(73,88,90,95,105, 107–113)	(71,94,98,109,110, 112,114–117)	(105,111,117,118)	(68,119)	(69)	(73,125)	(81,121)	(71,73,122–124)

ACE-R: Addenbrooke's Cognitive Examination – revised; ALS-BCA: ALS-Brief Cognitive Assessment; ALS-CBS: ALS-Cognitive Behavioral Screen; ALS-FTD: amyotrophic lateral sclerosis-frontotemporal dementia; ECAS: Edinburgh Cognitive and Behavioral ALS Screen; FAB: Frontal Assessment Battery; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; NPV: Negative Predictive Value; PBA: pseudobulbar affect; PBAC: Philadelphia Brief Assessment of the Cognition; PPV: Positive Predictive Value; PSSFTS: Penn State Screening examination of Frontal and Temporal dysfunction Syndromes; UCSF-SB: UCSF screening battery; WM: working memory; –: not available/unknown; +: available.

[a]Behavioural domain is assessed with the use of the Frontal Behavioral Inventory (FBI).

[b]Cognitive domains are assessed with the use of the ALS-CBS.

[c](B) blinking (E) eye tracker (F/H/T) tapping with feet/hands or clicking with teeth (SD) speech devices (Ty) typing (V) verbal (W) written.

[d]See Appendix for a list of the available languages; not all languages were used before in ALS patients.

[e]Cutoff scores are often based on other patient groups than ALS.

[f]% within deficient range.

[g]Separately for each subtest.

Table 2. Characteristics of behavioral screening instruments used for ALS patients.

Specific for	ALS-FTD-Q ALS(-FTD)	AES Acquired brain injury	BBI ALS	DAS Neurodegenerative diseases[a]	FBI FTD	FrSBe Frontal behavior	MiND-B ALS	NPI Dementia	ALS-CBS Behavioral subscale	ECAS Behavior interview
Behavioral domain[b]										
Disinhibition	+	–	+	+	+	+	+	+	+	+
Apathy; inertia	+	+	+	+	+	+	+	+	+	+
Sympathy; empathy	+	–	+	+	–	+	–	–	+	+
Perseverations; stereotyped; compulsive/ ritualistic behavior	+	–	+	–	+	–	+	–	–	+
Hyperorality; dietary changes	+	–	+	–	+	–	–	+	+	+
Cognitive domain	+[c]	–	+	+	–	+	–	–	+Table 1	+Table 1
Considers motor-related problems	+	+/–[d]	+	+	–	–	+[e]	–	–	–
Reporter	Proxy	Self-report/ proxy/clinician	Proxy	Self-report/proxy	Proxy	Self-report/proxy	Proxy/clinician	Proxy	Proxy	Proxy
Number of items	25	18	41	24	24	46	9	12	15	10
Administration time	5–10 min	10–20 min	5–10 min	10–15 min	15–30 min	10 min	–	5 min	Table 1	25–50 min
Output scores	composite score	composite score	composite score	3 subscales[f]	2 subscales[g]	3 subscales[h]	3 subscales[i]	3 subscales[j]	composite score	composite score
Type questions	4-point rating scale	4-point rating scale	4-point rating scale	4-point rating scale	4-point rating scale	6-point rating scale	4-point rating scale	3/4-point rating scale	3-point rating scale	2-point rating scale
Validation										
Sensitivity	–[k]	–	50–100%	62%	–	–	81–90%	–	83–93%	–
Specificity	–	–	76–96%	82%	–	–	50–75%	–	69–86%	–
PPV	–	–	72.5%	58%	–	–	77.8%	–	25–94%	–
NPV	–	–	91.1%	85%	–	–	72.7%	–	67–97%	–
Patients with (mild) behavioral changes	18–32%	24%	14–47%	24–43%	33–46%	13–56%	39–75%	19–75%	9–34%	14–65%
Available languages[l]	9	10	1	4	5	14	1	75	Table 1	Table 1
Available cutoff[m]	+	+	+	+	+	+	+	–	+	–
References	(71,90,95,125)	(121)	(73,125)	(81,121)	(68,71,126)	(71,73,122–124)	(77,95)	(109,127,128)	(63,82,97, 98)	(64,85,88, 99–106,120)

AES: Apathy Evaluation Scale; ALS-FTD-Q: Amyotrophic Lateral sclerosis – Frontotemporal Dementia – Questionnaire; BBI: Beaumont Behavioral Inventory; DAS: Dimensional Apathy Scale; FBI: Frontal Behavioral Inventory; FrSBe: Frontal Systems Behavior scale; MiND-B: Motor Neuron Disease Behavior Scale; NPI: Neuropsychiatric Inventory; –: not available/unknown; +: available.

[a]With motor impairments

[b]Rascovsky criteria (8).

[c]3 items on memory, concentration, and orientation in time.

[d]Marin's definition of apathy was modified, adding: *"lack of motivation not attributable to diminished level of .., motor dysfunction; …"* (129).

[e]Instrument to detect non-motor symptoms in ALS.

[f]Executive, emotional, initiation.

[g]Negative and positive behavior.

[h]Apathy, disinhibition, executive dysfunction.

[i]Disinhibition, apathy, stereotypy.

[j]Number of symptoms, severity of symptoms, caregiver distress.

[k]Construct validity was assessed (71,90).

[l]See Appendix for a list of the available languages; not all languages were used before in patients with ALS.

[m]Cutoff scores are often based on different patient groups.

Cambridge Behavioral Inventory-Revised (CBI-R (79)) and the Iowa Scales of Personality Change (ISPC (80)).

Comparison behavioral screening instruments. In general, behavioral changes in ALS patients reported most frequently are apathy, disinhibition, loss of sympathy/egocentric behavior, perseverative and stereotyped behavior, and change in dietary habits (7,8). All of these domains are assessed with the ALS-FTD-Q, BBI and the ECAS. The other screening instruments assess a selection of the behavioral domains, whereas the AES only assess apathy.

Regarding adaptability, behavioral screeners developed for ALS specifically and motor problems-related neurodegenerative diseases (i.e. ALS-FTD-Q, BBI, DAS, and MiND-B) have been adapted to accommodate for physical disability. Behavioral screeners which do not consider motor problems (i.e. NPI, FrSBe, FBI) might overestimate behavioral changes.

Required administration time is only 5–10 min for the ALS-FTD-Q, BBI, FrSBe, and NPI. More time (10–20 min) is needed to complete the AES and the DAS. The FBI and ECAS require most administration time (i.e. respectively 15–30 min and 25–50 min).

Only the instruments BBI, DAS, MiND-B, and ALS-CBS were validated against other commonly known (sometimes non-ALS-specific) behavioral screeners (e.g. FrSBe, AES, and ALS-FTD-Q). These screening instruments show a moderate to high sensitivity and specificity. The BBI offers a cutoff score of 22.5, showing 90% sensitivity and 96% specificity for moderate changes (73). The optimal cutoff score for the DAS (26.5) showed a 62% sensitivity and 82% specificity (81). Two cutoff scores were identified for the MiND (35/36 or 33/36) showing 81–90% sensitivity and 50–75% specificity (77). For the ALS-CBS to differentiate between patients with and without dementia, the cutoff was set on 35, with a 83% sensitivity and 69% specificity (82).

Discussion

The current systematic review provides an overview of cognitive and behavioral screening instruments used in ALS patients, based on information gathered from 99 articles. We compared nine cognitive and eight behavioral screeners based on a number of factors: *domains*, *adaptability*, *required time*, and *validation*.

Since a broad variety of cognitive deficits and/or behavioral problems in ALS patients have been reported, a broad screening instrument, assessing multiple domains, seems to have advantages above a brief, but limited screening instrument. Two cognitive screening instruments assess a broad spectrum of cognitive domains (i.e. ECAS and PSSFTS). However, one should keep in mind though, that all the cognitive domains are generally built up from several different subdomains (e.g. executive functions encompass mental flexibility, planning, inhibition, etc.) which are not all assessed with any of the screening instruments. All ALS-specific screening instruments assess verbal fluency, and the ECAS and PSSFTS assess language as well. However, identifying language impairments (i.e. primary progressive aphasia; PPA (83)), and distinguishing between different variants of PPA (i.e. non-fluent/agrammatic, semantic, and logopenic) can be complex. Effects can be subtle and difficult to detect with clinical measures (7). Moreover, it can be challenging to distinguish language deficits from motor speech deficits in ALS patients and from ALS-FTD (showing similarities to non-fluent and semantic variants of PPA) (7). Therefore, a broad range of tasks are essential in assessing speech and language functions in PPA (83). In short, cognitive screening instruments may be too concise to detect language impairments. Regarding behavioral screening instruments, the ALS-FTD-Q, the BBI, and the subdomain of the ECAS assess all behavioral domains often affected in ALS patients (7,8). However, output scores per subdomain, unlike the ALS-FTD-Q, BBI and ECAS which give one composite score, can give insight into specifically affected behavioral changes, and might, therefore, be preferred.

Correcting for motor problems during an assessment in ALS patients is crucial in order to prevent an overestimation of cognitive deficits and/or behavioral problems. The degree of disability on bulbar, gross, and fine motor skills as well as respiratory function in ALS is most commonly assessed using a specific questionnaire, the ALS Functional Rating Scale – revised (ALSFRS-R (84)). Patients with lower scores on the ALSFRS-R (more disability) can more easily complete a cognitive screening battery when it is adaptable. All ALS-specific cognitive screeners are well-adaptable to motor problems, unlike the non-ALS-specific screeners. Furthermore, cognitive deficits and behavioral impairments are more frequent in ALS-patients who are in a more severe disease stage (85,86). According to King's stages (87), patients within the most severe disease stage (stage 4) experience respiratory or nutritional insufficiency requiring intervention. Ideally, the effects of these insufficiencies on cognitive performance and/or behavioral changes should be taken into account while screening in ALS patients. In particular, in patients with respiratory insufficient hypercapnia (stage 4), only a small group is free of cognitive and behavioral impairments (85). However, possible overestimation of the cognitive and behavioral

impairments between disease stages should be taken into account due to bulbar symptoms.

In clinical practice, a broad assessment is often not possible because of different reasons such as time, shortage of qualified personnel, and fatigue in patients. Time-efficiency is, therefore, an important factor for screening instruments. The variety in administration time across the different screening instruments should be considered in relation to the other factors in order to make an informed decision when choosing a suitable screening instrument.

Until now, only a selection of screening instruments was examined on validity. Ideally, a comprehensive study should be performed in which ALS patients undergo screening by a combination of different cognitive/behavioral instruments plus a formal extensive (neuro)psychological assessment. In this way, the instruments could be accurately compared in terms of validity and applicability. Regarding the cognitive screening instruments, the FAB, ALS-CBS, and ECAS show a promising validity (9). Furthermore, no practice effects of the ECAS were found for ALS patients after 6 months and up to 18 months (88). Practice effects are preferably examined in other screeners as well. Regarding behavioral screening instruments, only the BBI, DAS, MiND-B, and ALS-CBS have studies assessing their clinical validity, varying from moderate to high. For the ALS-FTD-Q, sensitivity and specificity have not reported to date, but studies have showed strong correlations with other validated instruments (9,71), indicating construct validity (89,90).

The percentage of patients found to have deficits, ranges widely between different screeners. This may due to the fact that there are differences in the number and in which cognitive domains are assessed as well as in test characteristics. Furthermore, we did not evaluate the potential differences between study populations (e.g. disease stage, genetics, and sample size), which may also influence the percentage of cases found to have impairments (85,86).

Conclusion

Overall, the cognitive screening instruments ALS-CBS, ECAS, and FAB show good clinical validity. However, considering the FAB cannot be adapted, and, therefore, not all patients are capable of completing the FAB due to physical disability (91–93), this is a serious disadvantage of this screener (2). Both the ECAS and ALS-CBS take motor problems into consideration, but the ALS-CBS requires shorter administration time (5–30 min less) than the ECAS. On the other hand, the ECAS assesses the domains language and social cognition, unlike the ALS-CBS, and might, therefore, be more suitable for this population. Furthermore, the ALS-CBS and ECAS screen for cognitive, as well as behavioral problems, which can be considered as a great advantage. On the other hand, using a separate behavioral screener additionally can possibly provide more detailed and/or reliable information. Regarding behavioral screening instruments, the BBI, MiND-B, and ALS-CBS show a satisfying clinical validity. Despite that the MiND-B only assesses a limited number of domains, it does offer the ability to screen for ALS-FTD specifically (77). However, caution should be taken as the MiND-B may miss specific behavioral impairments that are part of the Rascovsky criteria (9). In contrast, the ALS-FTD-Q, BBI and ALS-CBS assess a broad spectrum of behavioral changes, and might, therefore, be more suitable for screening for behavioral changes in ALS-(FTD) patients (9).

Moving forward, ALS-specific screening instruments can benefit from additional validation studies to improve reliability and therefore usability in clinical practice. Validation studies in different countries, providing cutoff scores for specific patient subgroups, age groups, and education levels are warranted. Additionally, the screening instruments should preferably be adaptable to different disease stages. Preferably, alternative versions should be available for longitudinal use and to prevent practice effects.

Acknowledgments

The authors thank Ineke den Braber and Carin Schröder for their work they put into a first draft of the literature search and overview of available cognitive screeners.

Declaration of interest

The authors report no conflict of interest.

Funding

M. A. v. E. received grants from the Netherlands Organization for Health Research and Development (Veni scheme), Joint Program Neurodegeneration (JPND), The Thierry Latran foundation, and the Netherlands ALS foundation (Stichting ALS Nederland). He received travel grants from Shire (formerly Baxalta) and has consulted for Biogen.

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References

1. Beeldman E, Raaphorst J, Twennaar MK, De Visser M, Schmand BA, De Haan RJ. The cognitive profile of ALS: a systematic review and meta-analysis update. J Neurol Neurosurg Psychiatry. 2016;87:611–9.
2. Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol. 2013;12:368–80.
3. Burrell JR, Halliday GM, Kril JJ, Ittner LM, Götz J, Kiernan MC, et al. The frontotemporal dementia-motor neuron disease continuum. Lancet 2016;388:919–31.
4. Byrne S, Elamin M, Bede P, Shatunov A, Walsh C, Corr B, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol. 2012;11:232–40.
5. Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology 2011;76:1263–9.
6. Khin Khin E, Minor D, Holloway A, Pelleg A. Decisional capacity in amyotrophic lateral sclerosis. J Am Acad Psychiatry Law. 2015;43:210–7.
7. Strong MJ, Abrahams S, Goldstein LH, Woolley SC, Mclaughlin P, Snowden J, et al. Amyotrophic lateral sclerosis – frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria. Amyotroph Lateral Scler Front Degener. 2017;18:153–74.
8. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–77.
9. Simon N, Goldstein LH. Screening for cognitive and behavioral change in amyotrophic lateral sclerosis/motor neuron disease: a systematic review of validated screening methods. Amyotroph Lateral Scler Front Degener. 2019; 20:1–11.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement (Reprinted from Annals of Internal Medicine). Ann Intern Med. 2009;151:264–70.
11. Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, et al.; for The WFN Research Group On ALS/MND. A revision of the El Escorial criteria – 2015. Amyotroph Lateral Scler Front Degener.2015;16:291–2.
12. Carvalho M. de, Dengler R, Eisen A, England JDD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008;119:497–503.
13. Staios M, Fisher F, Lindell AK, Ong B, Howe J, Reardon K. Exploring sarcasm detection in amyotrophic lateral sclerosis using ecologically valid measures. Front Hum Neurosci. 2013;7:178.
14. Branco LMT, de Rezende TJR, Roversi C de O, Zanao T, Casseb RF, de Campos BM, et al. Brain signature of mild stages of cognitive and behavioral impairment in amyotrophic lateral sclerosis. Psychiatry Res – Neuroimaging. 2018;272:58–64.
15. Keller J, Krimly A, Bauer L, Schulenburg S, Böhm S, Aho-özhan H, et al. A first approach to a neuropsychological screening tool using eye-tracking for bedside cognitive testing based on the Edinburgh Cognitive and Behavioural ALS Screen. Amyotroph Lateral Scler Front Degener. 2017;18:443–50.
16. Poletti B, Solca F, Carelli L, Madotto F, Faini A, Monti A, et al. The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS). Amyotroph Lateral Scler Frontotemporal Degener. 2016; 8421:489–98.
17. Irwin DJ, McMillan CT, Brettschneider J, Libon DJ, Powers J, Rascovsky K, et al. Cognitive decline and reduced survival in C9orf72 expansion frontotemporal degeneration and amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013;84:163–9.
18. Devenney EM, Landin-romero R, Irish M, Hornberger M, Mioshi E, Halliday GM, et al. The neural correlates and clinical characteristics of psychosis in the frontotemporal dementia continuum and the C9orf72 expansion. NeuroImage Clin. 2017;13:439–45.
19. Savage SA, Lillo P, Kumfor F, Kiernan MC, Hodges JR, Savage SA, et al. Emotion processing deficits distinguish pure amyotrophic lateral sclerosis from frontotemporal dementia. 2014;15:39–46.
20. Leslie FVC, Hsieh S, Caga J, Savage SA, Hornberger M, Kiernan MC, et al. Semantic deficits in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2015;16: 46–53.
21. De Silva D, Hsieh S, Caga J, Leslie FVC, Kiernan MC, Hodges JR, et al. Motor function and behaviour across the ALS-FTD spectrum. Acta Neurol Scand. 2016;133: 367–72.
22. Lillo P, Mioshi E, Burrell JR, Kiernan MC, Hodges JR, Hornberger M. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One. 2012;7:e43993.
23. Trojsi F, Santangelo G, Caiazzo G, Siciliano M, Ferrantino T, Piccirillo G, et al. Neuropsychological assessment in different King's clinical stages of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2016;8421:228–35.
24. Keller J, Böhm S, Aho-özhan HEA, Loose M, Gorges M, Kassubek J, et al. Functional reorganization during cognitive function tasks in patients with amyotrophic lateral sclerosis. Brain Imaging Behav. 2018;12:771–84.
25. Lulé D, Böhm S, Müller HP, Aho-Özhan H, Keller J, Gorges M, et al. Cognitive phenotypes of sequential staging in amyotrophic lateral sclerosis. Cortex. 2018; 101:163–71.
26. Iyer PM. Mismatch negativity as an indicator of cognitive sub-domain dysfunction in amyotrophic lateral sclerosis. Front Neurol. 2017;8:395.
27. Hübers A, Kassubek J, Georg G, Gorges M, Aho-Oezhan H, Keller J, et al. Pathological laughing and crying in amyotrophic lateral sclerosis is related to frontal cortex function. J Neurol. 2016;263:1788–95.
28. Nakamagoe K, Yamada S, Kawakami R, Miyake Z, Tozaka N, Okune S, et al. Vestibular dysfunction as cortical damage with amyotrophic lateral sclerosis. J Neurol Sci. 2019;397:4–8.
29. Sukockienė E, Allali G, Janssens J, Ferfoglia RI. Does executive functioning contribute to locomotion in amyotrophic lateral sclerosis patients? Amyotroph Lateral Scler Front Degener. 2019;20:123–5.
30. Cui B, Cui LY, Liu MS, Li XG, Ma JF, Fang J, et al. Behavioral symptoms in motor neuron disease and their negative impact on caregiver burden. Chin Med J. 2015; 128:2295–300.
31. Barbagallo G, Nicoletti G, Cherubini A, Trotta M, Bono F, Valentino P, et al. Diffusion tensor MRI changes in gray structures of the frontal-subcortical circuits in amyotrophic lateral sclerosis. Neurol Sci. 2014;35:911–8.
32. Poletti B, Carelli L, Solca F, Lafronza A, Pedroli E, Faini A, et al. An eye-tracker controlled cognitive battery: overcoming verbal-motor limitations in ALS. J Neurol. 2017;264:1136–45.
33. Poletti B, Carelli L, Faini A, Solca F, Meriggi P, Lafronza A, et al. The Arrows and Colors Cognitive Test (ACCT): a new verbal-motor free cognitive measure for executive functions in ALS. PLoS One. 2018;13: e0200953.

34. Pupillo E, The Eurals Consortium, Bianchi E, Messina P, Chiveri L, Lunetta C, Corbo M, et al. Extrapyramidal and cognitive signs in amyotrophic lateral sclerosis: a population based cross-sectional study. Amyotroph Lateral Scler Front Degener. 2015;16:324–30.
35. Gordon PH, Wang Y, Doorish C, Lewis M, Mitsumoto H, Marder K, et al. A screening assessment of cognitive impairment in patients with ALS A screening assessment of cognitive impairment in patients with ALS. Amyotroph Lateral Scler. 2009;8:2968.
36. Pilotto A, Rossi F, Rinaldi F, Compostella S, Cosseddu M, Borroni B, et al. Exploring olfactory function and its relation with behavioral and cognitive impairment in amyotrophic lateral sclerosis patients: a cross-sectional study. Neurodegener Dis. 2016;16:411–6.
37. Spinelli EG, Federica A, Ferraro P, Riva N, Lunetta C, Falzone YM, et al. Brain MR imaging in patients with lower motor neuron. Radiology. 2016;280:545–56.
38. Consonni M, Iannaccone S, Cerami C, Frasson P, Lacerenza M. The cognitive and behavioural pro fi le of amyotrophic lateral sclerosis: application of the consensus criteria. Behav Neurol. 2013;27:143–53.
39. Consonni M, Catrical E, Dalla Bella E, Gessa VCC, Lauria G, Cappa SFF. Beyond the consensus criteria: multiple cognitive profiles in amyotrophic lateral sclerosis? Cortex. 2016;81:162–7.
40. Cui B, Cui L, Liu M, Li X, Ma J, Fang J, et al. Neuropsychological investigation in Chinese patients with progressive muscular atrophy. PLoS One. 2015;10: e0128883.
41. Kasper E, Schuster C, Machts J, Kaufmann J. Microstructural white matter changes underlying cognitive and behavioural impairment in ALS – an in vivo study using DTI. PLoS One. 2014;9:e114543.
42. Wicks P, Abrahams S, Papps B, Shaw CE, Leigh PN, Goldstein LH. SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. J Neurol. 2009;256: 234–41.
43. Agarwal S, Williamson EH, Caga J, Matamala JM, Dharmadasa T, Howells J, et al. Primary lateral sclerosis and the amyotrophic lateral sclerosis – frontotemporal dementia spectrum. J Neurol. 2018;265:1819–28.
44. Schönecker S, Hell F, Bötzel K, Wlasich E, Ackl N, Süßmair C, et al.; German FTLD Consortium. The applause sign in frontotemporal lobar degeneration and related conditions. J Neurol. 2019;266:330–8.
45. Beeldman E, Raaphorst J, Twennaar MK, Govaarts R, Pijnenburg YAL, Haan RD, et al. The cognitive profile of behavioural variant FTD and its similarities with ALS: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2018;89:995–1002.
46. Marjanovíc IV, Selak-djokíc B, Periíc S, Jankoviíc M, Arsenijevíc V, Basta I, et al. Comparison of the clinical and cognitive features of genetically positive ALS patients from the largest tertiary center in Serbia. J Neurol. 2017; 264:1091–8.
47. Heimrath J, Gorges M, Kassubek J, Müller H, Ludolph AC, Lulé D, et al. Additional resources and the default mode network: evidence of increased connectivity and decreased white matter integrity in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:537–45.
48. Zimmerman EK, Eslinger PJ, Simmons Z, Barrett AM. Emotional perception deficits in amyotrophic lateral sclerosis. Cogn Behav Neurol. 2007;20:79–82.
49. Murphy J, Henry RGG, Langmore S, Kramer JHH, Miller BLL, Lomen-Hoerth C. Continuum of frontal lobe impairment in amyotrophic lateral sclerosis. Arch Neurol. 2007;64:530–4.
50. Hervieu-Bègue M, Rouaud O, Graule Petot A, Catteau A, Giroud M. Semantic memory assessment in 15 patients with amyotrophic lateral sclerosis. Rev Neurol (Paris). 2016;2:307–12.
51. Palmieri A, Sorarù G, Ascenzo CD, Balestreri S, Ermani M, Pegoraro E, et al. Specific numerical processing impairment in ALS patients. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:6–12.
52. Mantovan MC, Baggio L, Barba GD, Smith P, Pegoraro E, Soraru G. Memory deficits and retrieval processes in ALS 1. PLoS ONE. 2003;9:e114543.
53. Hanagasi HA, Gurvit IH, Ermutlu N, Kaptanoglu G, Karamursel S, Idrisoglu HA, et al. Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. Cogn Brain Res. 2002;14:234–44.
54. Tomik B, Adamek D, Lechwacka A, Orłowiejska-Gillert M, Bała-Słodowska M, Głodzik-Sobańska L, et al. ALS-Plus syndrome. Pol J Pathol. 2000;51:191–6.
55. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005; 65:586–90.
56. Fu X, Zhu W, Guo Z, Shu G, Cui F, Yang F, et al. 18F-fallypride PET-CT of dopamine D2/D3 receptors in patients with sporadic amyotrophic lateral sclerosis. J Neurol Sci. 2017;377:79–84.
57. Ohta Y, Sato K, Takemoto M, Takahashi Y, Morihara R, Nakano Y, et al. Behavioral and affective features of amyotrophic lateral sclerosis patients. J Neurol Sci. 2017; 381:119–25.
58. Gillingham SMM, Yunusova Y, Ganda A, Rogaeva E, Black SEE, Stuss DTT, et al. Assessing cognitive functioning in ALS: a focus on frontal lobe processes. Amyotroph Lateral Scler Front Degener. 2017;18: 182–92.
59. Benbrika S, Doidy F, Carluer L, Mondou A, Buhour M, Eustache F, et al. Alexithymia in amyotrophic lateral sclerosis and its neural correlates. Front Neurol. 2018;9: 566.
60. Ferraro PM, Jester C, Olm CA, Placek K, Agosta F, Elman L, et al. Perfusion alterations converge with patterns of pathological spread in transactive response DNA-binding protein 43 proteinopathies. Neurobiol Aging. 2018;68:85–92.
61. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriat Psychiatry. 2006;21:1078–85.
62. Hu WT, Shelnutt M, Wilson A, Yarab N, Kelly C, Grossman M, et al. Behavior matters-cognitive predictors of survival in amyotrophic lateral sclerosis. PLoS One. 2013;8: e57584.
63. Woolley SC, York MK, Moore DH, Strutt AM, Murphy J, Schulz PE, et al. Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS^{TM}). Amyotroph Lateral Scler. 2010;11: 303–11.
64. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Front Degener. 2014;15:9–14.
65. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB A frontal assessment battery at bedside. Neurology. 2000; 55:1621–6.
66. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12: 189–98.
67. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.

68. Flaherty-Craig C, Brothers A, Dearman B, Eslinger P, Simmons Z. Penn State screen exam for the detection of frontal and temporal dysfunction syndromes: application to ALS. Amyotroph Lateral Scler. 2009;10:107–12.
69. Murphy J, Ahmed F, Lomen-Hoerth C, Murphy J, Ahmed F, Lomen-Hoerth C. The UCSF screening exam effectively screens cognitive and behavioral impairment in patients with ALS. Amyotroph Lateral Scler Front Degener. 2015;16:24–30.
70. Libon DJ, Rascovsky K, Gross RG, White MT, Xie SX, Dreyfuss M, et al. Validated screening measure for dementia. Clin Neuropsychol. 2011;25:1314–30.
71. Raaphorst J, Beeldman E, Schmand BA, Berkhout J, Linssen W, Berg Van Den LH, et al. The ALS-FTD-Q: a new screening tool for behavioral disturbances in ALS. Neurology 2012; 79:1377–83.
72. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res. 1991;38:143–62.
73. Elamin M, Pinto-grau M, Burke TOM, Bede P, Rooney J, Sullivan MO, et al. Identifying behavioural changes in ALS: validation of the Beaumont Behavioural Inventory (BBI). Amyotroph Lateral Scler Front Degener. 2017;18: 68–73.
74. Radakovic R, Abrahams S. Developing a new apathy measurement scale: dimensional apathy scale. Psychiatry Res. 2014;219:658–63.
75. Kertesz A, Davidson W, Fox H. Frontal behavioral inventory: diagnostic criteria for frontal lobe dementi. Can J Neurol Sci. 1997;24:29–36.
76. Grace J, Malloy P. Frontal Systems Behavioural Scale (FrSBe): Professional Manual. Lutz, FL: Psychological Assessment Resources; 2001.
77. Mioshi E, Hsieh S, Caga J, Ramsey E, Chen K, Lillo P, et al. A novel tool to detect behavioural symptoms in ALS. Amyotroph Lateral Scler Front Degener. 2014;15: 298–304.
78. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.
79. Wedderburn C, Wear H, Brown J, Mason SJ, Barker RA, Hodges J, et al. The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. J Neurol Neurosurg Psychiatry. 2008;79:500–3.
80. Barrash J, Anderson SW, Hathaway-Nepple J, Jones RD, Tranel D, et al. The Iowa Scales of Personality Change. Iowa City: University of Iowa College of Medicine, Department of Neurology; 1997.
81. Santangelo G, Siciliano M, Trojano L, Femiano C, Monsurrò R, Tedeschi G, et al. Apathy in amyotrophic lateral sclerosis: insights from Dimensional Apathy Scale. Amyotroph Lateral Scler Front Degener. 2017; 18: 434–42.
82. Turon-Sans J, Gascon-Bayarri J, Reñé R, Rico I, Paipa A, Povedano M, et al. Cognitive impairment in ALS patients and validation of the Spanish version of the ALS-CBS test. Amyotroph Lateral Scler Front Degener. 2016;17:221–7.
83. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76: 1006–14.
84. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999;169:13–21.
85. Crockford C, Newton J, Lonergan K, Chiwera T, Booth T, Chandran S, et al. ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS. Neurology. 2018;91:E1370–80.
86. Trojsi F, Santangelo G, Caiazzo G, Siciliano M, Ferrantino T, Piccirillo G, et al. Neuropsychological assessment in different King's clinical stages of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2016;17:228–35.
87. Balendra R, Jones A, Jivraj N, Steen IN, Young CA, Shaw PJ, et al.; UK-MND LiCALS Study Group; Mito Target ALS Study Group. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry. 2015;86:45–9.
88. Burkhardt C, Neuwirth C, Weber M. Longitudinal assessment of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): lack of practice effect in ALS patients?. Amyotroph Lateral Scler Front Degener. 2017;18:202–9.
89. Raaphorst J, Visser d. M, Tol v. M-J, Linssen W, Kooi, Van, der AJ, Haan d. R, et al. Cognitive dysfunction in lower motor neuron disease: executive and memory deficits in progressive muscular atrophy. J Neurol Neurosurg Psychiatry. 2011;82:170–5.
90. Watanabe Y, Beeldman E, Raaphorst J, Izumi Y, Yoshino H, Masuda M, et al. Japanese version of the ALS-FTD-Questionnaire (ALS-FTD-Q-J). J Neurol Sci. 2016;367:51–5.
91. Raaphorst J, Beeldman E, Jaeger B, Schmand BA, Van Den Berg LH, Weikamp JG, et al. Is the frontal assessment battery reliable in ALS patients? Amyotroph Lateral Scler Front Degener. 2013;14:73–4.
92. Raaphorst J, Beeldman E, Schmand BA, Van Den Berg LH, De Visser M, De Haan RJ. Response to 'Exploring limits of neuropsychological screening in ALS: The FAB problem.' Amyotroph Lateral Scler Front Degener. 2013; 14:159–60.
93. Tremolizzo L, Ferrarese C, Appollonio I. Exploring limits of neuropsychological screening in ALS: the FAB problem. Amyotroph Lateral Scler Front Degener. 2013; 14:157–8.
94. Wei Q, Chen X, Zheng Z, Huang R, Guo X, Cao B, et al. Screening for cognitive impairment in a Chinese ALS population. Amyotroph Lateral Scler Front Degener. 2015;16:40–5.
95. Xu Z, Alruwaili ARS, Henderson RD, McCombe PA. Screening for cognitive and behavioural impairment in amyotrophic lateral sclerosis: frequency of abnormality and effect on survival. J Neurol Sci. 2017;376:16–23.
96. Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: a behavioural and cognitive continuum. Amyotroph Lateral Scler. 2012;13:102–9.
97. Branco LMT, Zanao T, Rezende TD, Casseb RF, Balthazar MF, Woolley SC, et al. Transcultural validation of the ALS-CBS Cognitive Section for the Brazilian population. Amyotroph Lateral Scler Front Degener. 2017;18:60–7.
98. Rabkin J, Goetz R, Murphy J, Factor-Litvak P, Mitsumoto H. Cognitive impairment, behavioral impairment, depression, and wish to die in an ALS cohort. Neurology 2016;87:1320–8.
99. Ye S, Rosenbohm A, Böhm S, Uttner I, Ji Y, Albert C, et al. Cognitive and behavioral impairments in German and Chinese ALS populations – a post-hoc comparison of national study data. Amyotroph Lateral Scler Front Degener. 2019;20:28–36.
100. Bakker LA, Schröder CD, Spreij LA, Verhaegen M, De Vocht J, Van Damme P, et al. Derivation of norms for the Dutch version of the Edinburgh cognitive and behavioral ALS screen. Amyotroph Lateral Scler Front Degener. 2019;20:19–27.
101. Gorges M, Müller HP, Lulé D, Tredici KD, Del Tredici K, Brettschneider J, et al. Eye movement deficits are consistent with a staging model of pTDP-43 pathology in

amyotrophic lateral sclerosis. PLoS One. 2015;10: e0142546.
102. Lulé D, Burkhardt C, Abdulla S, Böhm S, Kollewe K, Uttner I, et al. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Front Degener. 2015;16:16–23.
103. Mora JS, Salas T, Fernández MC, Rodríguez V, Marín S, Chaverri D, et al. Spanish adaptation of the Edinburgh cognitive and behavioral amyotrophic lateral sclerosis screen. Amyotroph Lateral Scler Front Degener 2018;19:74–9.
104. Niven E, Newton J, Foley J, Colville S, Swingler R, Chandran S, et al. Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): a cognitive tool for motor disorders. Amyotroph Lateral Scler Front Degener. 2015;16:172–9.
105. Poletti B, Solca F, Carelli L, Faini A, Lafronza A, Monti A, et al. Cognitive-behavioral longitudinal assessment in ALS: the Italian Edinburgh Cognitive and Behavioral ALS screen (ECAS). Amyotroph Lateral Scler Front Degener. 2018;19:387–95.
106. Ye S, Ji Y, Li C, He J, Liu X, Fan D. The Edinburgh cognitive and behavioural ALS screen in a Chinese amyotrophic lateral sclerosis population. PLoS One. 2016;11:e0155496.
107. Yoshizawa K, Yasuda N, Fukuda M, Yukimoto Y, Ogino M, Hata W, et al. Syntactic comprehension in patients with amyotrophic lateral sclerosis. Behav Neurol. 2014; 2014. Article ID 230578.
108. Barulli MR, Fontana A, Panza F, Copetti M, Bruno S, Tursi M, et al. Frontal assessment battery for detecting executive dysfunction in amyotrophic lateral sclerosis without dementia: a retrospective observational study. BMJ Open. 2015;5:e007069.
109. Ahn S, Kim S-H, Kim J, Kim S-M, Kim SH, Sung J-J, et al. Frontal assessment battery to evaluate frontal lobe dysfunction in ALS patients. Can J Neurol Sci. 2011;38: 242–6.
110. Floris G, Borghero G, Chi A, Secchi L, Cannas A, Sardu C, et al. Cognitive screening in patients with amyotrophic lateral sclerosis in early stages. Amyotroph Lateral Scler. 2012;13:95–101.
111. Osborne RA, Sekhon R, Johnston W, Kalra S. Screening for frontal lobe and general cognitive impairment in patients with amyotrophic lateral sclerosis. J Neurol Sci. 2014;336:191–6.
112. Oskarsson B, Quan D, Rollins YD, Neville HE, Ringel SP, Arciniegas DB. Using the Frontal Assessment Battery to identify executive function impairments in amyotrophic lateral sclerosis: a preliminary experience. Amyotroph Lateral Scler. 2010;11:244–7.
113. Terada T, Miyata J, Obi T, Kubota M, Yoshizumi M, Yamazaki K, et al. Frontal assessment battery and frontal atrophy in amyotrophic lateral sclerosis. Brain Behav. 2017;7:e00707.
114. Ji Y, Wei L, Chui D, Wang K, Fan D. Prospective memory tasks: a more sensitive method for screening cognitive impairment in early-phase amyotrophic lateral sclerosis? BMC Neurol. 2012;12:142.
115. Ogawa T, Tanaka H, Hirata K. Clinical neurophysiology cognitive deficits in amyotrophic lateral sclerosis evaluated by event-related potentials. Clin Neurophysiol. 2009;120:659–64.
116. Stojkovic T, Stefanova E, Pekmezovic T, Peric S, Stevic Z. Executive dysfunction and survival in patients with amyotrophic lateral sclerosis: preliminary report from a Serbian centre for motor neuron disease. Amyotroph Lateral Scler Front Degener. 2016;17:543–7.
117. Zhu W, Fu X, Cui F, Yang F, Ren Y, Zhang X, et al. ALFF value in right parahippocampal gyrus acts as a potential marker monitoring amyotrophic lateral sclerosis progression: a neuropsychological, voxel-based morphometry, and resting-state functional MRI study. J Mol Neurosci. 2015;57:106–13.
118. Tremolizzo L, Pellegrini A, Conti E, Arosio A, Gerardi F, Lunetta C, et al. BDNF serum levels with respect to multidimensional assessment in amyotrophic lateral sclerosis. Neurodegener Dis. 2016;16:192–8.
119. Flaherty-Craig C, Brothers A, McFalls A, Yang C, Simmons Z. VALUES: a national multicenter study of regional and gender differences in frontotemporal disease in amyotrophic lateral sclerosis. Neurodegener Dis Manag. 2012;2:325–36.
120. Pinto-grau M, Burke T, Lonergan K, Mchugh C, Mays I, Madden C, et al. Screening for cognitive dysfunction in ALS: validation of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) using age and education adjusted normative data. Amyotroph Lateral Scler Front Degener. 2017;18:99–106.
121. Radakovic R, Stephenson L, Colville S, Swingler R, Chandran S, Abrahams S. Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale. J Neurol Neurosurg Psychiatry. 2016;87:663–9.
122. Chiò A, Vignola A, Mastro E, Giudici AD, Iazzolino B, Calvo A, et al. Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. Eur J Neurol. 2010;17:1298–303.
123. Van der Hulst EJ, Bak TH, Abrahams S. Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2015;86:1208–15.
124. Witgert M, Salamone AR, Strutt AM, Jawaid A, Massman PJ, Bradshaw M, et al. Frontal-lobe mediated behavioral dysfunction in amyotrophic lateral sclerosis. Eur J Neurol. 2010;17:103–10.
125. Pinto-Grau M, Costello E, O'Connor S, Elamin M, Burke T, Heverin M, et al. Assessing behavioural changes in ALS: cross-validation of ALS-specific measures. J Neurol. 2017;264:1397–401.
126. Wei Q, Chen XP, Zheng ZZ, Huang R, Guo XY, Cao B, et al. Frontal lobe function and behavioral changes in amyotrophic lateral sclerosis: a study from Southwest China. J Neurol. 2014;261:2393–400.
127. Oh SI, Park A, Kim H, Oh K, Choi H, Kwon M, et al. Spectrum of cognitive impairment in Korean ALS patients without known genetic mutations. PLoS One. 2014;9: e87163.
128. Wei Q, Chen X, Cao B, Ou R, Zhao B, Wu Y, et al. Associations between neuropsychiatric symptoms and cognition in Chinese patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2016;17: 358–65.
129. Glenn, M. B., Burke, D. T., O'Neil-Pirozzi, T., Goldstein, R., Jacob, L., & Kettell, J. (2002). Cutoff score on the apathy evaluation scale in subjects with traumatic brain injury. Brain Injury, 16(6), 509–516. https://doi.org/10.1080/02699050110119132

Appendix. Available language per screening instrument[a]

Cognitive screeners	
ACE-R	Czech; English; Farsi; Flemish; French; German; Greek; Hindi; Italian; Japanese; Mandarin; Polish; Portuguese; Spanish; Swedish; Telugu; and Turkish
ALS-BCA	English
ALS-CBS	English; Portuguese; and Spanish
ECAS	American; Belgium; Chinese; Croatian; Czech; Dutch; English; French; German; Swiss-German; Greek; Hebrew; Italian; Japanese; Norwegian; Polish; Portuguese; Russian; Slovak; Slovenian; Spanish; Swedish; and Welsh
FAB	Dutch; English; French; German; Italian; Persian; Portuguese (Brazilian); and Spanish
MMSE	Afrikaans; Albanian; Arabic; Argentinean Spanish; Armenian; Austrian German; Basque; Belgian Dutch; Belgian French; Bengali; Bosnian; Bulgarian; Catalan; Chilean Spanish; Chinese (Hong Kong/Malaysia/ Singapore/Taiwan); Croatian; Czech; Danish; Dutch; English; Estonian; Farsi; Filipino; Finnish; French (Canadian); Georgian; German; Greek; Gujarati; Hebrew; Hindi; Hungarian; Icelandic; Indian English; Israeli English; Italian; Japanese; Kannada; Korean; Latvian; Lithuanian; Macedonian; Malay; Malayalam; Marathi; Norwegian; Polish; Portuguese (Brazilian); Punjabi; Romanian; Russian; Serbian; Slovak; Slovene; Sotho; South African English; Spanish (USA); Swedish; Tamil; Telugu; Thai; Turkish; Ukrainian; Urdu; Vietnamese; and Zulu
MoCA[b]	English (Singapore); Afrikaans; Arabic; Bengali; Bulgarian; Chinese (Beijing/ Cantonese/Changsha/Hong Kong/Maderian/Mandarin/Minnan/Singapore); Creole (Cape Verdean); Croatian; Czech; Danish; Dutch; Estonian; Filipino; Finnish; French; Georgian; German; Greek; Gujarati; Hebrew; Hindi; Hungarian; Italian; Japanese; Kannada; Korean; Korean (K2-Chuncheon); Latvian; Lithuanian; Malay (Bahasa-Malaysia); Malay (Singapore); Malayalam; Marathi; Myanmar; Norwegian; Persian; Polish; Portuguese; Portuguese (Brazilian); Punjabi; Romanian; Russian; Serbian; Sinhalese; Slovak; Slovenian; Spanish; Swahili; Swedish; Taiwan; Tamil; Telugu; Thai; Turkish; Ukrainian; Urdu; Uyghur; Vietnamese; and Welsh
PSSFTS	English
UCSF-SB	English
Behavioral screeners	
ALS-FTD-Q	Danish; Dutch; English; French; German; Italian; Japanese; Serbian; and Spanish.
AES	Arabic; Dutch; English; Italian; Japanese; Portuguese; Russian; Spanish; Swedish; and Taiwanese
BBI	English
DAS	English; French; Greek; and Italian
FBI	English; French; Italian; Korean; and Portuguese (Brazilian)
FrSBe	Afrikaans; Chinese; Czech; Dutch; French; German; Icelandic; Italian; Japanese; Polish; Romanian; Spanish; Swedish; and Portuguese (Brazilian)
MiND-B	English
NPI	English (USA); Afrikaans; Bengali; Bulgarian; Cantonese (China/Hong-Kong); Chinese (Hong-Kong(Cantonese or Mandarin)/Singapore/Taiwan); Croatian; Czech; Danish; Dutch (Belgium); English (Australia/Canada/Hong-Kong/India/ Israel/Malaysia/New Zealand/ Philippines/Singapore/South Africa/UK/USA); Estonian; Finnish; French (Belgium/Canada); German; German (Switzerland); Greek; Gujarati; Hebrew; Hindi; Hungarian; Italian; Japanese; Kannada; Korean; Malay; Malayalam; Mandarin (China/Malaysia/Singapore); Marathi; Norwegian; Polish; Portuguese (Brazilian); Punjabi Romanian; Russian (Estonia/ Israel/Ukraine); Serbian; Slovak; Slovenian; Spanish (Argentina/Chile/ Mexico/Peru/USA); Swedish; Tagalog; Tamil (Malaysia); Telugu; Turkish; Ukrainian; and Urdu

[a]There is no certainty of mentioning all translations, since there is often no consensus on the number of available translations.

[b]MoCA test's official website states that the test is available in nearly 100 languages. 67 languages are registered in the current overview based on their website.