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Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): a cognitive tool for motor disorders

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ABSTRACT (max 200 words)

OBJECTIVES

To assess the validity of the Edinburgh Cognitive and Behaviour ALS Screen (ECAS), a multi-domain screen designed to detect cognitive deficits in patients with motor disorders.

METHODS

40 ALS patients (without pre-diagnosed dementia) and 40, age, gender and education matched healthy controls were recruited. All participants underwent extensive neuropsychological assessment and the ECAS. Performance at neuropsychological assessment across five domains (fluency, executive function, language, memory and visuospatial function) was compared to the ECAS ALS-Specific (fluency; executive functions and social cognition; language), ALS Non-specific (memory; visuospatial functions), and total scores.

RESULTS

Data from the healthy controls produced population-based abnormality cut-offs: composite score performance $\leq$ 2 SD in any domain classified impairment at neuropsychological assessment. 33% of patients were impaired, most commonly in a single domain (executive or language dysfunction). Receiver Operator Curve (ROC) analyses using ECAS total scores and ALS-Specific scores revealed 85% sensitivity and 85% specificity in the detection of cognitive impairment characteristic of ALS (fluency, executive function, language). A five point borderline range produced optimal values (ALS-Specific Score 77-82 and ECAS-Total Score 105-110)

CONCLUSIONS

Validation against gold standard extensive neuropsychology demonstrated that the ECAS is a screening tool with high sensitivity and specificity to impairment characteristic of ALS.

EDINBURGH COGNITIVE & BEHAVIOURAL ALS SCREEN: VALIDATION

Key words: Cognition, Screen, Executive Functions, Language, Fluency,

INTRODUCTION

Cognitive and behavioural changes in ALS are well recognized as integral to the disease. Recent research has demonstrated that such changes are heterogeneous with impairments not only in letter fluency and executive functions, but also in language and social cognition (see (1) for review). However extensive neuropsychology testing may not be appropriate for all patients due to increasing physical disability or not feasible due to limited time and resources. The challenge for neuropsychology has been to develop an appropriate screening test, which is quick and easy to perform and can be undertaken by health care professionals within the clinic or at home. Effective screening should identify who has cognitive impairment, what type of impairment is present, and how severe that impairment is (2). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (3) was launched as a rapid screening test to provide the early identification of these cognitive and behavioural changes in ALS. The screen has been validated against other generic screening measures (4). Here the test is validated against gold standard extensive neuropsychology.

MATERIALS AND METHODS

Participants

Healthy Volunteers: Forty (26 male) healthy volunteers were recruited from spouses or friends of ALS patients, and through local voluntary organisations. The age and education levels of healthy volunteers were selected to closely match the patient comparison group. All participants were native English speakers, and scored above the cut-off for abnormality (82/100) in the Addenbrooke's Cognitive Examination III (5) (mean 93.90, SD 4.44; range 85-100). No participant had a documented neurological or psychiatric history.

ALS Patients: Recruitment took place through local ALS clinics and through the Scottish MND Register, a population based database of patients with MND living in Scotland. 40 (26 male) patients with ALS (38 sporadic, 2 familial – patients with a history of ALS in a first degree relative) were assessed. All patients had clinical and electrophysiological evidence of combined upper and lower motor neurone involvement and fulfilled the revised El Escorial criteria for clinically definite or probable ALS (6). Six patients had bulbar onset of symptoms. Exclusion criteria included terminal stages of disease or major comorbid medical, neurological or psychiatric history including severe diabetes, epilepsy, alcohol/substance-related disorders, severe head injury or traumatic brain injury cerebrovascular disease or stroke. Disability was assessed using the *ALS Functional Rating Scale-Revised* (ALSFRS-R; 7); mean ALS-FRS was 35.68 (range 11-47), and median duration of illness was 25.5 months (range 5-221). Twenty three of 34 ALS patients had a Sniff Nasal Inspiratory Pressure (SNIP) score of lower than 40cmH(2)O (mean 32.5, SD 15.24, range 10-74) indicating respiratory dysfunction; this data was not available for six patients. Six patients were receiving non-invasive ventilation and three patients had a radiologically inserted gastrostomy. Dementia was not noted in the clinical files of any patient.

Participants and, where appropriate patient carers were provided with a detailed explanation of the research aims and requirements, and informed consent was obtained; recruitment and testing procedures adhered to the tenets of the Declaration of Helsinki. This study was approved by the South East Scotland Research Ethics Committee and the University of Edinburgh's Department of Psychology Ethics Committee.

Procedure

All patients and controls underwent both extensive neuropsychological assessment and, at a separate appointment completed within 12 weeks of assessment, the ECAS (time between appointments in days: mean 26.08, SD 22.25); all participants were assessed either in their own home or in a purpose-made clinic-based appointment. Order of completion of tests during neuropsychological assessment sessions followed a schedule counterbalanced across participants and testing was divided across multiple sessions per patient, where required, in order to minimise effects of fatigue. The ECAS screening data of a subset of these patients has been published previously (3).

Materials

ECAS: The ECAS (3) is a brief 15-20 minute screen that includes assessment of the following domains; Fluency (Free and Fixed); Executive Functions (Reverse Digit Span, Alternation, Inhibitory Sentence Completion, Social Cognition); Language (Naming, Comprehension, Spelling); Memory (Immediate Recall, Delayed Percentage Retention, Delayed Recognition); Visuospatial Functions (Dot Counting, Cube Counting, Number Location). The ECAS has been carefully designed to include tasks that have been shown to be particularly sensitive to changes in ALS. The measures of these domains (fluency; executive functions and social cognition; language) combine to produce an ALS-Specific

score, and those domains that are not normally affected in ALS (memory; visuospatial functions) are combined to produce an ALS Non-specific score. An ECAS total score (performance across all tasks) is also calculated. Previously published normative data (3) classified abnormality of performance on each of these sub-scores that were $\leq$ 2SD below the healthy control mean: scores of less than or equal to 77 for ALS-Specific scores (max 100), 24 for ALS Non-specific scores (max 36) and 105 for ECAS total scores (max 136).

Full Neuropsychological Assessment: Within an extensive battery of tests, five cognitive domains (fluency, executive function, language, memory and visuospatial function) were addressed, each via multiple tests (Table 1). In addition, premorbid IQ was measured using the Test of Premorbid Functioning (TOPF) (21) with those participants who were able to provide verbal responses (n = 30). Individual physical difficulties and abilities within ALS presentation meant that certain tests were not completed by all patients (Test of Premorbid Functioning; Name Recognition - The Doors and People Test; Written Verbal Fluency; Spoken Verbal fluency), while others were adapted where required such that, verbal, written or pointing responses were accepted. For tests of spelling (Graded Difficulty Spelling Test; Psycholinguistic Assessment of Language Processing in Aphasia) participants who spoke their answers were given the option of seeing their responses written down and participants who wrote their answers were given the option of having their letters read aloud to them before stating their answer as final. Moreover, scoring of performance for certain tests deviated from standard practice (as detailed in Table 1) to accommodate use in a patient population with motor difficulties, for example timing in the Hayling Sentence Completion Test performance was implemented as a latency measurement of the difference between the two component conditions rather than as a measurement of only the second of these components. In addition affective screening was undertaken using the Hospital Anxiety and Depression Scale (HADS) (22).

The data from healthy controls were used to create standardized Z scores for each measure. Patients were judged to be impaired overall if they showed a deficit on any of the targeted five domains; determination of a deficit in a domain is detailed below.

Composite scores were produced for some cognitive domains and subdomains. For each composite score performance $\leq$ 2SD classified impairment. Where subdomains were present (for example, executive functions) impairment was classified where deficit was exhibited in 2 out of 3 subdomains; where multiple tests were used to index a subdomain (for example, shifting), or directly a domain (for example, memory), performance $\leq$2 SD in 1 of 2, or 2 of 3 task performances, or a single composite was used to determine impairment (see Table 1).

Statistical Analyses

Demographic and cognitive data were characterised and compared using SPSS V.20. Between-group comparisons were made via t-tests, and Pearson's and Spearman's correlations were used to detail relationships between measures. Receiver operating characteristics (ROC) curve analyses and area under the curve (AUC) was used to evaluate the ability of the ECAS screen to detect cognitive change in an ALS population (statistics carried out in MedCalc V. 14.10.2).

RESULTS

Demographic characteristics

Patient and healthy control groups displayed no significant differences in age, years of education, full scale (premorbid) IQ as measured through the TOPF (21), or gender distribution. While the two groups were comparable on mean anxiety scores, as measured through the HADS (22), patients as a group reported higher depression scores in the HADS than did controls (see Table 2). Further investigation of demographic details through correlations in the patient group demonstrated no relation between ECAS Total scores and ALSFRS or SNIP or Anxiety measures, however a negative correlation with age ($r = -0.44$, $p<0.01$) and a positive correlation with education ($rho = 0.41$, $p< 0.01$) emerged.

Neuropsychological Assessment

Analyses of the neuropsychological assessment revealed that 13 of the 40 ALS patients were classified as impaired in domains known to be affected in ALS (fluency, executive, language, or any combination of these domains), giving a prevalence of 33% (95% CI 18-48). Of the pattern of ALS impairment in these patients, 9 showed single domain impairment (1 fluency, 4 executive, 4 language) while 4 showed a mixed profile. Of those with a multidomain profile 2 showed two domain impairment (1 displayed both fluency and executive deficits and 1 displayed both executive and language deficits) and 2 showed deficits in the fluency, executive, and the language domain. Three of the above 13 patients were also impaired in the memory or the visuospatial domain; a further one patient showed impairment solely in the visuospatial domain (see Table 3).

ECAS ALS-Specific impairment:

The main aim of the analysis was to assess the ability of the ECAS to identify ALS specific impairment in an ALS population. Two main scores are used for this purpose in the ECAS: the ALS-Specific score and the ECAS-Total score. Of the 13 patients who were categorized with ALS specific forms of impairment at neuropsychological testing, 11 were identified using the ECAS ALS-Specific score or the ECAS-Total score measures. The two patients who were not identified by the ECAS as impaired showed sole language or executive deficits only (see Table 3, patients 19 and 11 respectively). Overall, combined use of ECAS ALS-Specific scores and total scores revealed 85% sensitivity and 85% specificity (PPV 0.73, NPV 0.92) in the detection of cognitive impairment characteristic of ALS (fluency, executive function, language). Separately the ECAS's ALS-Specific score displayed 77% sensitivity and 89% specificity (PPV 0.77, NPV 0.89), and the ECAS-Total score displayed 69% sensitivity and 89% specificity (PPV 0.75, NPV 0.86) to ALS specific impairment.

ROC curves allow further consideration of the ECAS ALS-Specific and Total measures by, rather than considering only the sensitivity and specificity of pre-defined cut-off scores, plotting the trade-off that would occur between sensitivity (true positive rate) and 1-specificity (false positive rate) at each *possible* cut-off score on these measures (see Figure 1). This analysis also indicated that sensitivity could be increased (by raising cut-off scores) without much compromise on specificity (see Table 4). Analysis of the area under the ROC curve provides a single value to represent the discriminatory capacity of the measures: the closer the AUC value is to 1 (perfect discrimination capacity) and hence the further the AUC is from 0.5 (chance performance), the better the measure is in accurately classifying patients. The ALS-Specific score produced an AUC of 0.93 (95% CI 0.80 to 0.99), while separately ROC analysis of the ECAS-total score produced an AUC of 0.91 (95% CI 0.77 to 0.98), indicating both measures have a high sensitivity over a range of specificities.

ECAS ALS Non-specific impairment:

The two patients demonstrating memory impairment at neuropsychological testing were identified via the ECAS ALS-Nonspecific score (see Table 3). Of the 2 patients who presented with a visuospatial deficit, one was identified at screening via the ECAS-Total score, but not the ALS Non-specific score.

ECAS –Cognitive Domains

The ability of the ECAS screen to indicate impairment in each of the five domains using published cut-off scores (3) and when compared against the neuropsychological assessment is detailed in Table 5. Analyses were also undertaken to determine which individual subtests had the greatest sensitivity and specificity to detect the presence of an ALS-Specific impairment at neuropsychological testing. The highest sensitivity of individual tests within the ECAS was for Alternation (54% sensitivity and 85% specificity) Spelling (44% sensitivity and 78% specificity), Fixed Fluency (46% sensitivity and 88% specificity) and Social Cognition (38% sensitivity and 100% specificity) for overall impairment. The Executive domain score on its own had 57% sensitivity and 85% specificity, the language domain had 85% sensitivity and 74 % specificity, and fluency 46% and 75% to detect overall impairment. The findings suggest that the each domain has high sensitivity and specificity against neuropsychological assessment, but should be used as a whole test to increase sensitivity and specificity overall.

DISCUSSION

The findings of this study demonstrate that the ECAS is an effective method for detecting the range of cognitive impairment present in ALS. The patients sampled here showed a typical profile of cognitive impairment on extensive neuropsychological assessment with 33% of the patients displaying a combination of deficits in fluency, language and executive functions. This frequency is similar to that found in other larger studies (23, 24). The most typical impairment (23% of all patients) was in a single cognitive domain with either executive or language dysfunction, the latter is consistent with recent reports demonstrating the prevalence of language dysfunction in ALS (25, 26, 27, 28). The independence of these deficits highlights the need for comprehensive screening covering both domains.

The ECAS demonstrated high sensitivity and specificity in detecting overall impairment (85% sensitivity and 85% specificity) and an inspection of the ROC analyses indicated that a borderline range of Total Scores 105-110 and ALS-Specific scores 77-82 may optimize usage. However the significant correlations with age and education should also be taken into consideration, for example a borderline score may be considered as a possible impairment in a younger well educated individual in comparison with an older less educated person. Future normative data should accommodate for these parameters. Individual domain scores also demonstrated good sensitivity and specificity against detailed neuropsychology and may therefore be used to detect the subtleties of the cognitive profile. However the findings demonstrated that the effectiveness of domain or individual tests at detecting overall impairment (outside of that domain) was reduced and as such it is suggested that the test be used as a whole with overall scores indicating cognitive impairment.

Some patients did not meet criteria for cognitive impairment on the neuropsychological battery but showed an impairment on a single test/domain. The current criteria for impairment was based on other classification methods (29) with the aim of reducing false positives. However follow up

investigation would be of interest to determine the relevance, persistence or progression of these isolated deficits.

The ECAS elicited a false positive result in four cases on either the ECAS-Total score and/or ALS-Specific score. In three of the four cases the scores were very close to the cut-off for abnormality differing by only 1 or 2 points (patient 35, ALS-Specific 78 Borderline, ECAS Total 104; patient 32, ALS-Specific 75, ECAS Total 104; patient 29 ALS-Specific 77, ECAS Total 106). As such these three cases are falling on the margins of abnormality and follow up full neuropsychological assessment would have demonstrated intact functions. It is of interest that one of the patients (patient 29) is impaired on Inhibition, but given the strict criteria employed here for measuring impairment they do not classify as impaired. Similarly the remaining patient (patient 26) has more evidence of impairment on the ECAS (ALS-Specific 67, ECAS Total 97), but they are impaired only on the Test of Reception of Grammar at neuropsychological assessment. Long term follow up of these patients may be of interest to determine whether there is further progression of these impairments.

In conclusion, validation against gold standard extensive neuropsychology demonstrated that the ECAS is a screening tool with high sensitivity and specificity to impairment characteristic of ALS. The ECAS is an effective within clinic assessment for ALS that determines the presence, severity and type of cognitive change, an essential first step to managing these symptoms.

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REFERENCES

1. 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.

2. Abrahams S. ALS, cognition and the clinic. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14: 3-5.

3. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler. 2014; 15: 9-14.

4. 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. In press.

5. Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive examination III in frontotemporal dementia and Alzheimer's diseas e. Dement Geriatr Cogn Disord. 2013; 36: 242-250.

6. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2000; 1: 293–9.

7. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169: 13–21.

8. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grisé D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia. 2000; 38: 734-47

9. Burgess P, Shallice T. The hayling and brixton tests. Bury St Edmonds: Thames Valley Company, 1997.

10. Delis D, Kaplan E, Kramer J. Delis-Kaplan executive function system. San Antonio: Psychological Corporation, 2001.

11. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "reading the mind in the eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001; 42: 241-51.

12. Girardi A, MacPherson S, Abrahams S. Deficits in emotional and social cognition in amyotrophic lateral sclerosis. Neuropsychology. 2011; 25: 53-65.

13. Kaplan E, Goodglass H, Weintrab S. Boston naming test. Philadelphia: Lee & Febiger, 1983.

14. McKenna P, Warrington EK. The Graded Naming Test. Windsor: NFER-Nelson, 1983.

15. Baxter D, Warrington EK. Measuring dysgraphia: A graded-difficulty spelling test. Behav Neurol. 1994; 7: 101-7.

16. Kay J, Lesser R, Coltheart M. Psycholinguistic assessments of language processing in Aphasia (PALPA). East Sussex: Lawrence Erlbaum Associates, 1992.

17. Bishop DV. Test for the reception of grammar (TROG-2). London: Harcourt Assessment, 2003.

18. Coughlan AK, Oddy MJ, Crawford JR. BIRT Memory and information processing battery (BMIPB). London: Brain Injury Rehabilitation Trust, 2007.

19. Baddeley AD, Emslie H, Nimmo-Smith I. Doors and people: a test of visual and verbal recall and recognition. Bury St. Edmunds: Thames Valley Test Co., 1994.

20. Warrington EK, James M. The visual object and space perception battery. Bury St Edmunds: Thames Valley Test Co., 1991.

21. Wechsler, D. Test of Premorbid Functioning – UK Edition. London: Pearson Assessment, 2011.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67: 361-70.

23. 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

24. 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.

25. Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, et al. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? J Neurol Neurosurg Psychiatry. 2013; 84: 494-8.

26. Abrahams S. Executive dysfunction in ALS is not the whole story. J Neurol Neurosurg Psychiatry. (Editorial Commentary). 2013; 84: 474-5.

27. Bak TH, Hodges JR. The effects of Motor Neurone Disease on language: Further evidence. Brain Lang. 2004; 89: 354-61.

28. Bak TH, Chandran S. What wires together, fires together: Verbs, actions and neurodegeneration in Motor Neuron Disease. Cortex. 2012; 48: 936-44.

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29. Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2009; 10: 131–46.

EDINBURGH COGNITIVE & BEHAVIOURAL ALS SCREEN: VALIDATION

TABLES AND FIGURES

Table 1: Neuropsychological Assessment

Domain	**Subdomain:**	**Measures contributing to domain or subdomain**
Fluency		
	Written	Phonemic verbal fluency index (VFI) (8); words beginning with 'S'* and 4-letter words beginning with 'C'*
	Spoken	Phonemic verbal fluency index (VFI) (8) ; words beginning with 'P'*, 'R'*, 'W'*
Executive		
	Inhibition	Hayling Sentence Completion Test (9): total unconnected errors (converted but not scaled); latency score (time taken to complete unconnected sentences minus time taken to complete connected sentences)
	Shifting & rule detection	Brixton Spatial Anticipation test (9): total number correct Card Sorting test from Delis-Kaplan Executive Function System (10): sorting score (scaled for age)
	Social	Reading the mind in the Eyes – revised version (11): total number correct Judgment of Preference (12): total score (graded scoring, recognising correct answers, random responses and egocentric responses separately)
Language		
	Naming	Boston naming test (13): total number correct * Graded Naming test (14): total number correct*
	Spelling	Graded Difficulty Spelling Test (15): (Form A) total number correct* Psycholinguistic Assessment of Language Processing in Aphasia (16): (subtest Grammatical Class Spelling: nouns and verbs) total number correct*
	Comprehension	Test of Reception of Grammar version 1 (17): number of blocks passed
Memory		BIRT Memory and Information Processing Battery (18): immediate story recall; delayed story recall (percent retained). The Doors and People Test (19): name recognition score (scaled for age)
Visuospatial function		The Visual Object and Space Perception Battery (20): Dot Count subtest*; Cube Analysis*; Number Location*.

*** Measures provide a composite score prior to Z score transformation**

Table 2: Demographics of Participants

	Patients		Controls		t (df)/ χ^2(df)	Significance (p<0.05)
		Range		Range		
Age, mean (SD)	64.45 (10.24)	38-86	62.70 (10.48)	39-88	0.76 (78)	ns
Gender, female	14	-	14	-	0.00	ns
Education, mean years (SD)	11.15 (1.97)	9-18	12.26 (3.38)	9-25	-1.80 (62.68)	ns
FSIQ (TOPF)	104.57 (9.64)	90-123	105.35 (9.07)	91-123	-0.35	ns
HADS Depression	5.30 (3.67)	0-15	2.40 (1.81)	0-6	4.48 (56.86)	<0.001
HADS Anxiety	6.00 (4.27)	0-20	4.83 (2.75)	0-11	1.47 (66.56)	ns

TOPF: Test of Premorbid Function, FSIQ: Full Scale IQ, HADS: Hospital Anxiety and Depression Scale.
ns = non significant.

Table 3. Impairment in Neuropsychological Domains and ECAS in 40 MND patients

	Fluency	Executive	Language	Memory	VSP	ECAS - Specific	ECAS-nSpec	ECAS-Total
1		X - I S SC				X		B
2		S				B		
3								
4	X	X - I S SC	X - N T	X		X	X	X
5								
6								
7	X	S				X		X
8		I						
9		I						
10		SC	X - N T	X		X	X	X
11		X - I SC	Sp			B		B
12		I						
13								
14								
15								
16		SC	X – N T			X		X
17								
18		X - I S SC	X - N T		X	B		X
19		SC	X - T Sp					
20		S			X			
21								
22		S						
23		X - I S				X		B
24								
25			X - T Sp			X		X
26			T			X		X
27								
28		X - I S SC				X		X
29		I				X		B
30		SC						
31	X	X - I S SC	T			X		X
32						X		X
33						B		B
34								
35						B		X
36								
37								
38		I						
39		S						
40	X	X – I S SC	X- N T S			X		X

VSP: Visuospatial functions, nSpec: non-specific. I: Inhibition, S: Shifting, SC: Social Cognition, N: Naming, T: Test of Reception of Grammar, Sp: Spelling, B: Borderline. X marks overall impairment classification.

Table 4: Sensitivity, specificity and predictive values of current and alternative cut-off values for ALS-Specific and ECACS-Total measures

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
ALS-Specific score cut-off				
≤77	**0.77**	**0.89**	**0.77**	**0.89**
≤78	0.85	0.81	0.69	0.92
≤80	0.92	0.81	0.71	0.92
≤ 82	0.92	0.74	0.63	0.95
≤83	1.00	0.74	0.65	1.00
ECAS Total Score cut-off				
≤105	**0.69**	**0.89**	**0.75**	**0.86**
≤107	0.77	0.81	0.67	0.88
≤108	0.85	0.81	0.69	0.92
≤110	0.92	0.81	0.71	0.96
≤115	1.00	0.52	0.50	1.00

Note: current cut-off values in bold; cut-offs with duplicated sensitivity values are omitted

Table 5: Sensitivity, specificity and predictive values of individual domain cut-off scores to detect analogous domain impairment at neuropsychological assessment

Domain	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Fluency (14/24)	1.00	0.83	0.40	1.00
Executive (33/48)	0.63	0.78	0.42	0.89
Language (26/28)	0.86	0.64	0.33	0.95
Memory (13/24)	1.00	1.00	1.00	1.00
Visuospatial (10/12)	0.50	1.00	1.00	0.97

Figures in parentheses are previously published cut-off scores and maximum scores per domain (3)

Figure Legends:

Figure 1: ROC curve for ECAS ALS-Specific (Panel A) and ECAS total scores (Panel B) as detecting ALS Specific cognitive impairment.