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Cognitive function in Amyotrophic lateral sclerosis:
Is the ECAS a valid instrument for screening cognitive function in ALS?

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Abstract

The main goal of this study was to validate the Edinburg cognitive and behavioural ALS screen (ECAS) in a Dutch sample. The ECAS is a cognitive instrument developed especially for patients with Amyotrophic lateral sclerosis (ALS) that measures executive function, language, verbal fluency, memory and visuospatial functions (Abrahams et al., 2015). Up to 50% of ALS patients suffer from cognitive impairment, which is associated with a lower quality of life. In order to validate the ECAS, three goals were set. First, normal scores were calculated that were corrected for age and education. The cognitive performance of 298 ALS patients was analysed according to these normal scores. Second, the reliability of the five cognitive domains was assessed. Third, the ECAS was compared with other validated neuropsychological research to obtain construct validity. The hypothesis was that the ALS patients would demonstrate cognitive impairment on the domains executive functions, language and verbal fluency compared with healthy control subjects. A preserved memory and visuospatial functions were expected. Also, a high reliability and construct validity were predicted. In contrast with the hypothesis, the results of the performance in ALS patients on the ECAS deviated from what was expected. Furthermore, reliability and construct validity were not achieved. In conclusion: The ECAS could not be validated in this study due to the limited number of participants with signs of cognitive impairment. Further research with larger sample size is needed to validate the ECAS in the Dutch population.

Introduction

Amyotrophic lateral sclerosis (ALS) is a disease characterized by progressive degeneration of motor neurons, affecting both the upper motor neurons in the brain and lower motor neurons in the spinal cord. ALS leads to muscle atrophy, progressive weakness and spasticity, causing increasing disability and eventually death resulting from respiratory failure. Life expectancy after onset of the first symptoms is three to five years (Rowland & Schneider, 2001). In addition to physical impairment, an estimated 36.5-51% of ALS

patients suffer from cognitive impairment and 10-15% meet the criteria for frontotemporal dementia (FTD) (Goldstein & Abrahams, 2013; Massman, Sims, Cooke, Haverkamp, Appel & Appel, 1996; Ringholz, Appel, Bradshaw, Cooke, Mosnik and Schulz, 2005).

Cognitive impairment in ALS patients results in decreased patient compliance, a lower quality of life and enlarges the burden on caretakers. Therefore, early detection of cognitive problems might improve therapy adherence, quality of life and consequently survival. (Beeldman, Raaphorst, Twennaar, De Visser, Schmand & De Haan, 2015; Irwin, Lippa & Swearer, 2007). However, most conventional neuropsychological measurement tools to assess cognitive impairment are unfit for ALS patients due to problems in speaking and physical movement. This results in exaggeration of performance decrements and overestimation of cognitive impairment (Goldstein & Abrahams, 2013). For that reason, Abrahams, Newton, Niven, Foley & Bak (2014) developed a cognitive behavioural screen especially for ALS patients: the Edinburgh Cognitive and Behavioural ALS screen (ECAS).

The ECAS measures five different cognitive functions, which are divided in two groups: ALS specific functions and ALS non-specific functions. Executive functions, language and verbal fluency are profoundly impaired in comparison to other cognitive domains in ALS patients that show cognitive impairment. (Raaphorst et al., 2010; Phukan et al., 2012; Pukhan et al., 2007; Girardi, MacPherson & Abrahams, 2011; Cobble, 1998; Raaphorst, De Visser, Linssen, De Haan & Schmand, 2010). Therefore, Goldstein and Abrahams (2013) labelled these three domains as specific for ALS. Memory and visuospatial functions are preserved in most ALS patients with cognitive decline (Raaphorst et al., 2010) and therefore are considered as ALS-non-specific functions. The purpose of the ALS non-specific functions is to differentiate cognitive change characteristic of ALS from other disorders common in older adults, like Alzheimer's disease (Abrahams et al., 2014).

The ECAS has been validated in England (Niven, Newton, Foley, Colville, Swingler, Chandran, Bak & Abrahams, 2015) Switzerland and Germany (Lulé, Burkhardt, Abdulla, Boehm, Kollewe, Uttner, Abrahams, Bak, Petri, Weber & Ludolph, 2015) but not yet in the Netherlands. Therefore, the aim of this study is to validate the Dutch version of the ECAS. To this aim, three goals have been set. The first goal is to determine normal scores for the ECAS in healthy control subjects. These normal scores are used to analyse the performance of the ECAS of ALS patients. The second goal is to assess the reliability

of the five cognitive domains measured in the ECAS. The third goal is to compare the performance of the ECAS to the performance of a neuropsychological research that was especially composed for this study.

Methods

Participants

In this study 298 ALS patients were included. All were diagnosed with ALS according to the revised El Escorial criteria, showing both upper and lower motor neuron involvement (Brooks, Miller, Swash & Munsat, 2000). Furthermore, 285 healthy control subjects were included. All participants were selected from an on-going population based epidemiologic study (Huisman, De Jong, Doormaal, Weinreich, Schelhaal, Van der Kooi, De Visser, Veldink & Van den Berg, 2011). From these groups, 17 ALS patients and 17 healthy control subjects were selected to perform an extra neuropsychological research. These participants were matched for age, sex and education.

In order to avoid interference of other disorders during testing, the exclusion criteria were: a history of cerebrovascular disease, stroke, neuromuscular disease, severe head injury or traumatic brain injury, epilepsy, dementia, Parkinson's disease and psychoactive medication usage. Participants were included if they were fluent in Dutch.

This study was approved by the ethics committee of the University medical centre Utrecht with the ethics standards of the revised Helsinki declaration of 1983. Informed consent was obtained prior to the study.

Materials

The ECAS

The Edinburgh Cognitive and behavioural ALS-Screen (ECAS) was used to examine cognitive function in ALS. The ECAS measures executive functions, language, verbal fluency, memory and visuospatial functions (See Table 2 for all subtests per cognitive domain). Participants could respond verbally, which was preferred except for the spelling subtest, or by writing. The method of response could be adapted to the personal physical possibilities of the patient, depending on the severity of the motor and/or speech problems. No time limit was set for the subtests. The raw scores of the subtests were summed, that provided separate outcome measures per cognitive domain. Furthermore, the ALS-specific

score (range: 0-100), the ALS-non-specific score (0-36) and the ECAS total score (0-136) were used as outcome measures (Abrahams, 2013).

Neuropsychological assessment

The neuropsychological assessment was especially composed for this study and therefore consisted of several tests measuring the same five cognitive functions as the ECAS (see Table 2 for the different tests per cognitive domain). All tests were proven to be valid measuring tools (Schmand, Houx, De Koning, Gerritsen, Hoogman, Muslimovic, Saan, Schagen, Schilt, Spikman & Van Tricht, 2012; Lezak, 2004; Elst et al., 2004; Gorissen, 2005; Krabbendam & Kalf, 2000; Zigmond & Snaith 1994; Corcoran, Mercer and Frith, 1994). The tests were selected based on the method of response; most tests did not require physical movement.

Executive functions

Both part A and part B of the Trail Making Task (TMT) were performed, and were analysed in relation to each other (Bowie & Harvey, 2006). The time needed to complete part A was subtracted from the time needed to complete part B (range: 0-300 seconds, Corrigan & Hinkeldey, 1987). Norm scores corrected for sex, age and education defined cognitive impairment (Schmand et. al, 2012).

The spatial span test (backwards) was performed using items of the spatial span and the stimulus of the Corsi block test. One point was granted for each item that was correctly performed (range: 0-32). Impairment was defined according to the results of the healthy control subjects who completed this test in this study (cut-off score: 4).

The rule shift card test is a subtest of the Behavioural assessment of the dysexecutive syndrome (BADS) that measures inhibition. A profile scores was calculated based on the number of errors made by the participant (range: 0-4). Cognitive impairment was defined according to norm scores (Krabbendam & Kalff, 2000), corrected for age and education.

A revised Dutch version of the Reading the mind in the eyes-test (version 2.3) was used to measure social cognition (Gorissen, 2005). One point was granted per correct answer (range: 0-36). The norms scores were provided by Gorissen-van Eenige (2007), corrected for education.

The Hinting task measured social cognition by measuring the ability to filter implicit messages from 10 different stories (Corcoran, Mercer and Frith, 1994). Two points were granted per correct answer (range: 0-20). The norm scores that were used to identify cognitive impairment, were corrected for age and education (Corcoran, Mercer and Frith, 1994).

Verbal fluency

To measure verbal fluency, the letters "K", "O" and "M" were presented to the participants (Elst,Van Boxtel, Van Breukelen & Jolles, 2004). Because the letter "T" was performed in the ECAS, the standard letters "D", "A" and "T" of the verbal fluency test were not used, to eliminate a learning effect. The total score was calculated by counting the number of words named by the participant. The total score was interpreted according to the norm scores corrected for sex, age and education (Schmand et al., 2012).

Language

The short version of the Boston naming test was used to measure language and word finding problems. A maximum of three points could be gained per correct answer (range: 0-90). Impairment was defined by norm scores corrected for age, sex and education (Schmand et al., 2012).

Memory

The Ray auditory verbal learning test (RAVLT) (Dutch version: Kalveboer & Deelman, 1964; Saan & Deelman, 1986) measures immediate memory, delayed recall and recognition. One point was granted for each word that was correctly remembered (range: 0-75), recalled (range: 0-15) or correctly recognized (range: 0-15). An impaired performance was based on norm scores that were corrected for sex, age and education (Schmand et al., 2012; Elst, Boxtel, Van Breukelen and Jolles, 2004).

Visuospatial functions

The spatial span test (forward) was used to measure visuospatial functions. See the methods of the spatial span (backward). The norm scores were determined according to the healthy control subjects in this study (cut-off score: 5).

Table 2

Tests of ECAS and neuropsychological assessment per cognitive domain

Cognitive domain	**ECAS**	**Neuropsychological assessment**
Verbal Fluency	Fluency (letters T and N)	Verbal fluency test (letters K, O and M)
Language	Naming	Boston naming test
	Comprehension	
	Spelling	
Memory	Immediate memory	RAVLT immediate memory
	Recall	RAVLT Recall
	Recognition	RAVLT Recognition
Exective functions	Digit span backwards	TMT A and B
	Alternation	Spatial span backwards
	Sentence completion	Rule shift card test
	Social cognition test	Hinting task
		Reading the mind in the eyes-test
Visuospatial functions	Cube counting	Spatial span forward
	Dot counting	
	Number location	

Assessment of anxiety and depression

The hospital anxiety and depression scale (HADS, Zigmond & Snaith 1994) was used to measure the level of anxiety and depression (Wicks, Abrahams, Hejda-Forde, Leigh & Goldstein, 2007). The presence of depression or anxiety can influence cognitive performance (Beaudreau & O'Hara, 2009).

When a participant was physically unable to fill in the questionnaire, the questions presented verbally and answered verbally. Separate scores were calculated for the depression scale and the anxiety scale. A score of 11-21 indicated the presence of a

depression or anxiety with the participant. A reliability analysis was performed on the HADS, to analyse if all participants filled in the questionnaire correctly. This was confirmed by a high Cronbach's alpha for depression ($\alpha = 0.95$) and anxiety ($\alpha = 0.92$).

Procedure

The ECAS and the neuropsychological assessment were both performed within 12 weeks time. All participants were visited at home, where informed consent was obtained. The tasks were performed in a quiet room and only the examiner and participant were present during testing. The tests of the neuropsychological assessment were carried out in the following order: (1) the Spatial span test, (2) RAVLT (immediate memory), (3) the TMT part A and B, (4) the verbal fluency task, (5) the Boston naming task, (6) the rule shift card test, (7) the RAVLT (recall and recognition), (8) the Hinting task and (9) the Reading the mind in the eyes-test. The HADS was always filled in at the end. Participants were allowed to take a small break between the ECAS and the neuropsychological assessment (15-30 minutes). The duration of the ECAS was 25-30 minutes depending on the method of response. The duration of the neuropsychological assessment was 45-60 minutes and the duration of the HADS was 5 minutes. This resulted in a total time of 75-95 minutes to complete all tests.

Data analysis

All data was analysed with IBM SPSS statistics 22 and $p<0.05$ was considered significant. All data was non-normally distributed, therefore only non-parametric tests were used.

The cut-off scores for the ECAS were calculated based on the performance of the ECAS of the 285 healthy control subjects. A cut-off score was defined as two standard deviations below the average score on a test. Cognitive performance could be influenced by sex, age and education (Van Hooren, Valentijn, Bosma, Ponds, Van Boxtel & Jolles, 2007). Therefore, the cut-off scores were corrected.

Cronbach's alpha (α) was calculated to assess reliability. The five cognitive domains of the ECAS were analysed separately. A Cronbach's alpha coefficient of 0.7 or higher was considered acceptable (George & Mallery, 2003).

Spearman correlation analysis was performed to compare the performance of the ECAS with the neuropsychological assessment. Composite scores were calculated for each cognitive domain of the neuropsychological assessment, so separate analyses could be

performed per cognitive domain. The composite score was the average score of the raw scores of the subtest within one cognitive domain. When a correlation coefficient was above 0.5, it was viewed as a high correlation, which showed constructive validity of the ECAS (Field, 2005).

The sensitivity and specificity of the ECAS were used to assess the ability of the ECAS to correctly identify ALS-patients with cognitive problems. Cognitive impairment was identified according to the results of the neuropsychological assessment (performance below cut-off). Cognitive impairment in a cognitive domain with multiple subtests was determined if half (one out of two) or two thirds (two out of three) of the subtests was impaired (as in Lulé et al., 2015). Based on the sensitivity and specificity, Receiver operator characteristics (ROC) curves were created and the Area under the curve-coefficients (AUC) were examined. An AUC-coefficient of 0.7 or higher was interpreted as acceptable (DeLong, DeLong & Clarke-Pearson, 1988).

Results

Participants

The 285 healthy control subjects and 298 ALS patients did not differ significantly in age, sex, education. See Table 2 for the baseline information. Furthermore, the ALS patients performed significantly lower on the ALS-specific-score, the ALS-non-specific score and the ECAS total score. The performance of two groups differed significantly on the cognitive domains executive functions, language, memory and verbal fluency. Visuospatial functions did not differ significantly between patients and healthy control subjects (see Table 3 and Figure 1).

Table 2

Baseline table

	ALS patients		**Healthy control subjects**		
	Mean/%/median	Range	Mean	Range	*Significance*
N	298	-	285	-	-
Sex, male	63%	-	63%	-	Ns
Age, mean (SD)	63 (10.8)	33-84	63 (10.94)	20-86	Ns
Education*: low	73%	-	59	-	Ns
Education*: high	27%	-	41%	-	Ns
Riluzole use: yes	34%	-	N/A	-	Ns
Antidepressants use: yes	9%	-	3%	-	Ns
NIV: yes	7%	-	N/A	-	-
Site of Onset: bulbar	16% (130 cases missing)	-	N/A	-	-
Familial	7%	-	N/A	-	-
Duration of disease in months	36	5-204	N/A	-	-
C9orf72: extended	3% (181 cases missing)	-	N/A	-	-

*Low education: <17 years of education; high education: ≥17 years of education.

NS: Not significant; SD: Standard devieation.

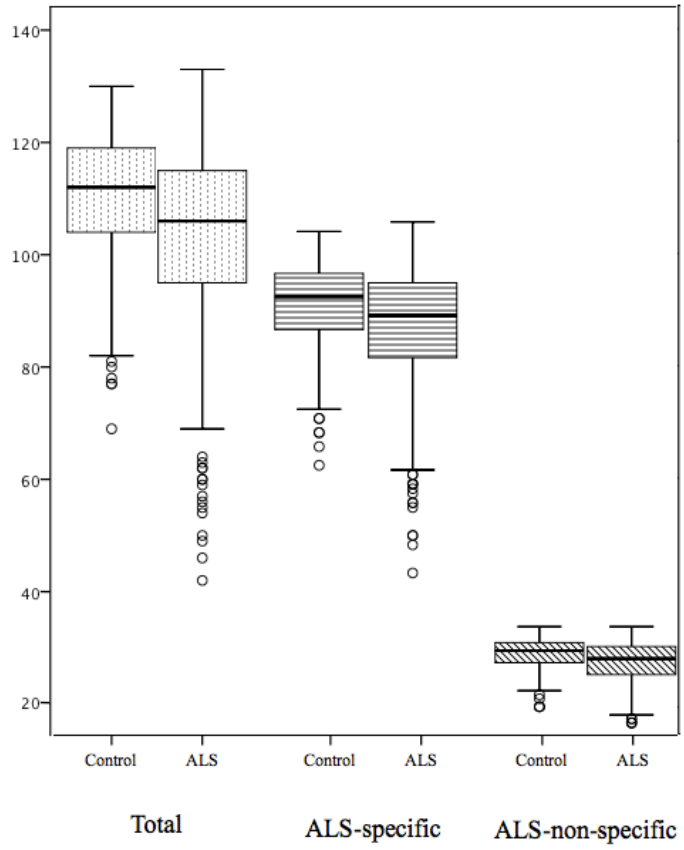
Table 3

Mean, SD and range of the results of ALS patients and healthy control subjects on the ECAS subtests, ALS-specific score and ALS-non-specific score

		ALS patients N=298			**Healthy control subjects N=285**			
	Max	Mean	SD	Range	Mean	SD	Range	*U, p-value*
Executive	48	33.86	8.39	5-48	36.26	6.70	12-48	357, <0.001*
Language	28	25.23	2.63	11-28	26.33	1.69	20-28	306, <0.001*
Fluency	24	17.17	4.79	0-24	18.34	3.57	0-24	327, <0.05*
ALS-specific functions	100	76.27	13.36	24-99	80.93	9.24	47-97	343, <0.001*
Memory	24	15.46	4.91	1-24	17.67	3.62	4-24	308, <0.001*
Visuospatial	12	11.47	1.08	5-12	11.64	0.75	8-12	400, 0.13
ALS-non-specific	36	26.93	5.18	23-36	29.31	3.79	16-36	309, <0.001*
ECAS total score	136	103.19	16.82	42-133	110.24	11.34	69-130	321, <0.001*

Figure 1

Boxplot of the results on the ECAS total score, the ALS-specific score and the ALS-non-specific score compared for ALS and healthy control subjects.



Cut-off scores ECAS adjusted for age and education

Based on the data of 285 healthy control subjects, a positive significant relationship was found between education and the ECAS total score (r_s=0.18, p<0.01), the ECAS ALS-specific score (r_s=0.18, p<0.01) and the ECAS-ALS-non-specific score (r_s=0.12, p<0.01). Furthermore, age was found to influence the ECAS total score significantly (r_s=-0.33, p<*0*.01), as well as the ECAS ALS-specific score (r_s =-0.29, p<0.01) and the ECAS-ALS-not-specific score (r_s=-0.30, p<0.01). Even though patients reported higher levels of anxiety (t(28)=-2.58, p<0.05) and depression (t(28)=-4.42, p<0.05), these factors did not influence the performance on the ECAS (Anxiety: u=24, p=0.28; depression: u=17.5, p=0.12). Based on these results, the cut-off scores were adjusted for age and education (See Table 4). Four subgroups were defined for cut-off scores with regard to years of education and age.

Classification of school years was <17 years and ≥17 years, according to the classification of the International Standard Classification of Education-ISCED. Age is classified in ≤60 years and >60 years.

Tabel 4

Cut-off scores ECAS adjusted for age and education in a Dutch sample

			Low education <17 years		High education ≥17 years	
	Maximum	Total group	Age ≤60 years	Age >60 years	Age ≤60 years	Age >60 years
Executive	48	22	27	19	28	27
Language	28	23	23	22	26	24
Fluency	24	11	7	10	17	14
ALS-specific score	100	63	64	58	74	68
Memory	24	10	12	9	16	10
Visuospatial	12	10	10	9	11	11
ALS-non-specific score	36	22	23	21	28	22
ALS total score	136	88	89	83	104	95

Performance of the ALS patients on the ECAS: Frequencies of cognitive impairment

Sixteen per cent of the ALS-patients performed below the cut-off score on the ECAS total score. Moreover, 14% of the ALS-patients performed below cut-off on both the ALS-specific score and ALS-non-specific score. Memory was found to be impaired in most patients compared to the other cognitive domains. Next, executive functions and verbal fluency were impaired in 10% of the patients. Visuospatial functions (9%) and language (5%) were found to be impaired in a limited number of patients. See table 5 for the percentages and figure 2 for a bar graph.

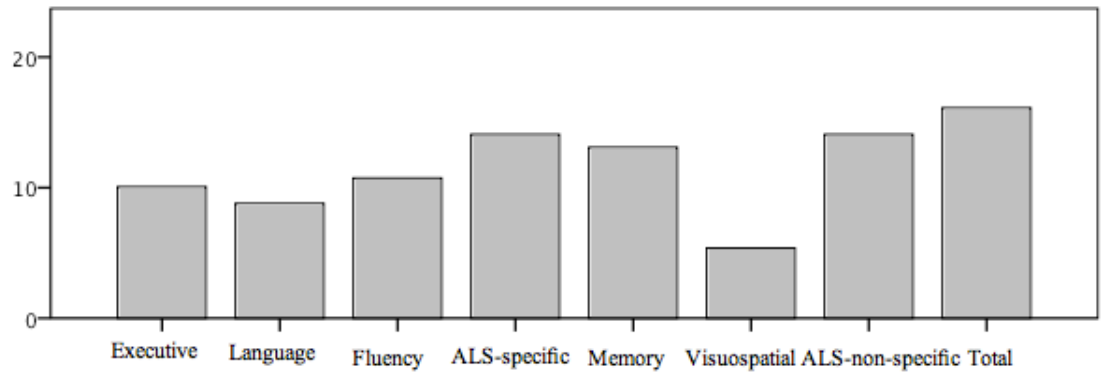
Table 5

Percentages of ALS patients (N=298) that performed below cut-off scores on the ECAS

	Executive	Language	Fluency	ALS-specific	Memory	Visuo-spatial	ALS-non-specific	ECAS total score
N	30	35	32	42	39	16	42	48
% below cut-off	10%	9%	11%	14%	13%	5%	14%	16%

Figure 2.

Bargraph of percentages of ALS patients (N=298) that performed below cut-off scores on the ECAS.



Reliability analysis of the ECAS

Reliability (Cronbach's alpha) was assessed for the subtests within each separate cognitive domain of the ECAS using the results of all participants. Reliability was unacceptable for language (α=0.29), executive functions (α=0.46) and visuospatial functions (α=0.22). Verbal fluency (spoken, α=0,58) and memory (α=0.59) showed a poor Cronbach's alpha. Verbal fluency (written) was considered the only acceptable reliable subtest of the ECAS (α=0.79).

Comparing the ECAS and neuropsychological assessment

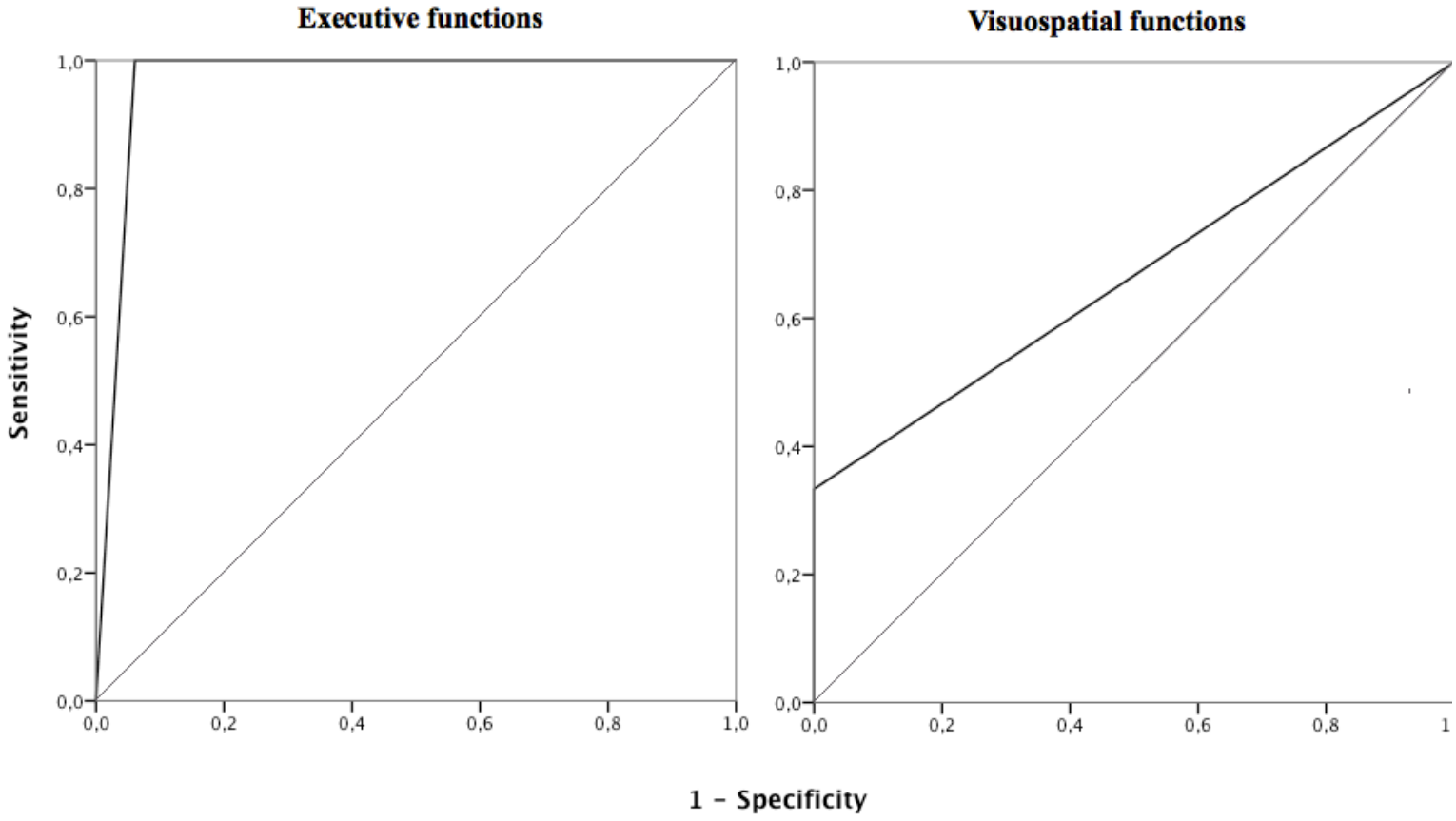
The relationship between the subtests of the ECAS and the neuropsychological assessment was analysed using the data of 17 ALS patients and 17 healthy of both tests. Spearman correlation analysis revealed a significant positive relationship for verbal fluency (r_s=0.64, $p<0.05$) and memory (r_s=0.49, $p<0.05$). However, no relation was found between the ECAS

and neuropsychological assessment for the other cognitive domains (executive functions: r_s=-0.16, p=0.37; language: r_s=0.26, p=0.14; visuospatial functions: r_s=0.28. p=0.11).

The accuracy of the ECAS was examined using specificity and sensitivity analyses. To this aim, the number of participants that performed below the cut-off scores on the subtests of the ECAS was compared with the number of participants that performed below the cut-off scores on the subtests neuropsychological assessment. However, the participants performed above the cut-off scores of most subtests, and therefore the sensitivity and specificity were only calculated for executive functions and visuospatial functions. The ECAS showed one true positive and two false positive participants, revealing a high sensitivity (100%) and specificity (93%). Moreover, the AUC-coefficient was excellent (0.97). One participant was correctly identified with cognitive impairment on visuospatial functions, giving a high sensitivity (100%) en specificity (100%). However, the AUC-coefficient is unacceptable (0.33). See Figure 3 for the ROC-curves.

Figure 3

The ROC-curves of visuospatial functions and executive functions of the ECAS



Discussion

The aim of this study was to validate the ECAS using a Dutch sample. To this aim, three goals were set. First, norm scores for the ECAS, corrected for age and education, were determined using the data of 285 healthy control subjects. The results of the ECAS of 298 ALS patients were analysed according to these norm scores. Second, the reliability was assessed for the subtests of the ECAS. Third, the construct validity was examined by the comparison of the ECAS with a comparable neuropsychological assessment in a smaller group of participants. However, construct validity was not obtained and reliability for the ECAS was low. Therefore, the ECAS could not be validated in this study.

Results

The performance of the ECAS of the ALS patients was analysed in this study according to calculated norm scores, adjusted for age and education. It was expected the ALS-specific functions would be more impaired in ALS patients compared to the ALS-non-specific functions. However, the performance on the ALS-specific functions showed the same number of cognitive impaired patients in comparison to the ALS-non-specific functions. Furthermore, memory was profoundly impaired in the patients compared to executive functions, language and verbal fluency. In conclusion, the results that were expected as described by Abrahams et al. (2014) could not be confirmed.

Next, the reliability was calculated for the ECAS and a high reliability was expected for all five cognitive domains. However, the reliability analyses revealed a high reliability solely for verbal fluency (written method of response). The two subtests together within this domain measure verbal fluency properly. Verbal fluency (spoken method of response), executive functions, language, visuospatial functions and memory showed an unacceptable reliability. These results implied that the subtests of these cognitive domains do not measure one homogeneous construct. The overall reliability of the ECAS was unacceptable in this study.

The ECAS and a neuropsychological assessment were compared using correlational analysis and by calculating the sensitivity and specificity. The correlational analyses showed a significant relationship between the ECAS and the neuropsychological assessment for verbal fluency and memory. An insignificant relationship was found for language, executive functions and visuospatial functions. Therefore, only two of the five cognitive domains showed acceptable construct validity and consequently construct validity

could not be obtained for the complete ECAS. The sensitivity and specificity could only be calculated for executive functions and visuospatial functions due to the limited number of participants with cognitive impairment. The ECAS identified participants with true cognitive impairment correctly on these two domains. However, only cautious conclusions can be drawn from these results because of the limited number of participants with cognitive impairment.

The results compared with other research

The norm scores that were calculated in this study were similar to other international norm scores. These results implied that cognitive impairment is uniformly classified in multiple countries (Lulé et al., 2015; Niven et al., 2015). The ALS patients in this study showed different types of cognitive impairment compared to previous research. Memory was found to be most impaired compared to the other cognitive domains, whereas Abrahams stated memory is preserved in ALS. This study found that executive functions were less impaired compared with the results of other studies (Abrahams et al., 2014; Lulé et al., 2015; Strong et al., 1999). In conclusion, the results in this study contradicted the results from previous research.

The Reliability analysis revealed a low reliability for four of the five subtests for the ECAS. This implied these subtests do not measure one coherent construct. This result was not in agreement with other research, which found high reliability of the ECAS (Lulé et al., 2015; Niven et al., 2015).

The correlational analysis showed insignificant relationships between the ECAS and the neuropsychological assessment for the domains language, executive functions and visuospatial functions. This is in contrast to earlier research, which found significant relationships between the ECAS and other neuropsychological assessments and confirmed construct validity (Niven et al., 2015; Lulé et al., 2015).

The results explained

The performance of the ALS patients on the ECAS was not in agreement with other research (Abrahams et al., 2014; Niven et al., 2015). However, the pattern of cognitive impairment in ALS set by Abrahams et al. (2014) might be premature. A meta-analysis of Beeldman et al. (2015) showed a more severely impaired memory compared to Abrahams et al. (2014). On the contrary, executive functions were less impaired compared with

language and fluency. These results are in line with the findings in this study. In conclusion, cognitive function in ALS is not yet explicit and should be further researched.

The reliability of four of the five cognitive domains was unacceptable. These results were influenced by two factors. First, social cognition is a part of executive functions in the ECAS whereas these two domains are seen as separate constructs in other literature (Lough, Gegory, & Hodgers, 2001). Second, Beeldman et al. (2015) showed a difference in performance on executive functions and social cognition of ALS patients. These results suggest that the two functions should be measured separately. This will lead to an increased reliability for executive functions.

In this study construct validity could not be demonstrated for the ECAS. two aspects contributed to this result. First, the participants showed little variance in the performance on the ECAS and the neuropsychological assessment. To find significant results, the range of performance on the cognitive tests should be larger. Second, in this study the ALS patients performed comparable with healthy controls on the ECAS and neuropsychological assessment. This indicated the sample of ALS patients showed a normal cognitive function. As a result, validation could not be realised.

Limitations

This study has several limitations. First, variance in the data of the smaller groups of participants was limited and therefore construct validity could not be demonstrated. Furthermore, sensitivity and specificity could not be calculated due to the limited number of participants with cognitive impairment. Because of these two factors, the results did not reach statistical significance and the construct validation was inadequate.

Second, neuropsychological assessment consisted of a minimal number of tests, to minimize the number of patients dropping out due to fatigue. The consequence of this method was that the cognitive domains were not extensively researched and thus reliability was diminished.

The third limitation was that visuospatial functions were measured using the Corsi block as stimulus, with the items of the spatial span. Both tests were validated separately, but not in this combination. Therefore the norms determined in previous research could not be used and visuospatial functions might not be measured and interpreted properly.

Recommendations

Further research is needed to validate the ECAS and assess cognitive function in ALS. First, a larger number of participants with signs of cognitive impairment need to be tested, to calculate the specificity, the sensitivity and construct validity reliably. Second, the predictive value of the ECAS should be determined by long-term observation of cognitive function in ALS. Third, the performance on the ECAS could be examined for other diagnoses such as ALS patients with repeat expansions in the *C9orf72* gene and diseases that mimic ALS–like Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS). The cognitive function in these diseases is undefined and needs more researched.

Conclusion

The ECAS could not be validated in a Dutch sample as an appropriate instrument to assess cognitive impairment in ALS. The number of included patients with cognitive impairment was too limited to reach statistical significant results. However, validation in the Dutch population is expected, if the sample size is increased. Validation of the ECAS is needed to detect cognitive impairment at an early stage, as this may improve therapy adherence and quality of life.

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