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1 **Cognitive-behavioural longitudinal assessment in ALS:**

2 **the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS)**

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51 **Running title:** ECAS longitudinal assessment in ALS

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1 **Abstract**

2 **Objective:** The study presents data on the longitudinal administration of the Italian Edinburgh
3 Cognitive and Behavioural ALS Screen (ECAS). We investigated cognitive-behavioural
4 performance in a group of ALS patients over time and the feasibility of repeating the ECAS
5 longitudinally compared to standard neuropsychological tests. Finally, correlations between
6 clinical/genetic and cognitive/behavioural data were considered.

7 **Methods:** 168 ALS patients were tested at baseline (T_0). Among these, 48 patients performed
8 the ECAS after 6 months (T_1), 18 patients performed it at T_2 (12 months) and 5 patients were
9 assessed after 24 months (T_3). Participants were also administered two cognitive test (FAB;
10 MoCA) and psychological questionnaires (BDI; STAI/Y). The FBI was carried out with
11 caregivers.

12 **Results:** No cognitive deterioration was found across follow-ups. In contrast, although scores
13 did not change between T_0 and T_1 , scores improved significantly for ECAS Total/ALS Non-
14 specific and Memory domains when the ECAS was repeated on three occasions (T_0 , T_1 , T_2).
15 Apathy/Inertia was the most common behavioural symptom, but no worsening of behavioural
16 scores was detected over time. After 12–24 months, patients were still able to perform the
17 ECAS in total, in contrast to FAB and MoCA, which were only partially administrable.

18 **Conclusions:** The significant improvement of some ECAS scores over time supports the
19 presence of possible practice effects, particularly in the memory domain, highlighting the
20 need to accommodate for these in longitudinal assessments, through healthy controls groups
21 or alternate versions. This work represents the first Italian ECAS follow-up study and
22 confirms ECAS feasibility in patients with increasing physical disability.

23

24 **Keywords:** *ECAS; longitudinal assessment; Amyotrophic Lateral Sclerosis (ALS); cognition;*
25 *behavioural change; practice effect*

1 **Introduction**

2 Cognitive-behavioural changes in patients with amyotrophic lateral sclerosis (ALS) are now
3 fully recognized as integral elements of the disease, along a spectrum of frontotemporal
4 dysfunctions (1, 2). In recent years, several cognitive screening tools have been developed for
5 ALS (3-8); however, they are not designed to detect a heterogeneous cognitive involvement
6 (9-11), nor to compensate for patients' physical disability (6, 12, 13). In order to overcome
7 such limitations, Abrahams et al. (14) developed a rapid cognitive-behavioural screening tool
8 (Edinburgh Cognitive and Behavioural ALS Screen – ECAS), specifically designed to
9 accommodate for verbal/motor disability. The ECAS has been translated (15, 16, 17) and
10 validated against gold standard neuropsychological measures (15, 16, 18-20), showing high
11 sensitivity and specificity (15, 18).

12 Although the existence of cognitive-behavioural involvement in ALS is now well-established,
13 its longitudinal evolution has been less investigated. Previous follow-up studies revealed
14 conflicting results (21-29); however, due to the lack of verbal-motor adaptations, it is not
15 possible to determine whether any observed deterioration was caused by increasing physical
16 disability affecting performance or by cognitive decline. Similarly, few longitudinal studies
17 are available on behavioural changes along the disease course (30-32). To date, only one
18 study has focused on longitudinal assessment using the ECAS, specifically investigating a
19 possible learning effect on ECAS repeated measurements (33); however, no data were
20 provided about the relationship between cognitive and clinical aspects, including affective or
21 genetic issues. Moreover, the longitudinal validity of the ECAS Behaviour Interview, also
22 with respect to other standard tools, was not considered. The possible progression of
23 cognitive-behavioural alterations over time represents a crucial issue, since such changes are a
24 negative prognostic factor in ALS (34), associated with shorter survival and faster functional
25 decline (24, 35, 36). This study aimed 1) to investigate cognitive-behavioural change in ALS

1 patients longitudinally; 2) to compare the feasibility of undertaking an ECAS over time
2 against standard neuropsychological assessment tools; 3) to analyse the relationship between
3 cognitive, behavioural and psychological aspects and clinical/genetic features.

4

5 **Material and methods**

6 *Participants and procedure*

7 168 ALS patients, who fulfilled the revised El Escorial criteria for possible, probable,
8 probable laboratory-supported or definite ALS (37), were recruited at the Department of
9 Neurology, IRCCS Istituto Auxologico Italiano between May 2013 and February 2017.
10 Patients in terminal stage of disease or with major comorbid medical, neurological,
11 psychiatric or cardio-vascular diseases were excluded. Disease status was evaluated using the
12 ALS Functional Rating Scale-Revised - ALSFRS-R (38). Patients were also screened for
13 mutations in *C9orf72*, *SOD1*, *TARDBP* and *FUS* genes according to standard protocols (39,
14 40). A subset of patients (N=107) was previously included in the Italian ECAS validation
15 study (15).

16 All patients were invited to take part in a longitudinal study from baseline (T₀), with follow-
17 up at 6 (T₁), 12 (T₂) and 24 (T₃) months when possible given the clinical conditions. Of the
18 168 patients who performed the ECAS protocol at T₀, 48 patients performed it at T₁, while 18
19 patients performed it also at T₂. Finally, 5 patients were tested at T₃; however, due to the
20 small proportion of patients who managed to complete this 24-months follow-up, such data
21 were not considered, due to their poor reliability. Further details are reported in Figure 1.
22 Given the rate of attrition, the longitudinal comparison was conducted in the 48 patients who
23 performed the ECAS at T₀ and T₁ and in the 18 patients who performed all the three
24 assessment at T₀, T₁ and T₂.

1 The study protocol was reviewed and approved by the Ethics Committee of our Institution
2 (N° of approval: 2013_06_25) and all eligible subjects received both verbal and written
3 information about the study. All participants signed an informed consent, according to the
4 Declaration of Helsinki.

5

6 *Cognitive and Psychological Assessment*

7 The Italian version of the ECAS was administered (15), assessing different cognitive
8 domains, including ALS-Specific and ALS Non-specific tasks. When possible, the mode of
9 testing (spoken or written) was maintained for the longitudinal screens. Moreover, caregivers
10 longitudinally performed the ECAS Behaviour Interview (see Poletti et al. (15) for further
11 details about the procedure adopted); both the number of behavioural symptoms (ECAS
12 Behaviour Interview-Symptoms) and the global score obtained (ECAS Behaviour Interview-
13 Total score) were recorded.

14 The study protocol also included two widely used screening tools, i.e. the Frontal Assessment
15 Battery (FAB) (41) and the Montreal Cognitive Assessment (MoCA) (42), that were
16 administered at T₀ and at any follow-up, when possible, and the Frontal Behavioural
17 Inventory (FBI), assessing behavioural alterations (43). To explore the relationship between
18 ECAS performance and psychological factors, participants completed the Beck Depression
19 Inventory (BDI) (44) and the State-Trait Anxiety Inventory-Y (STAI-Y) (45), for depressive
20 and anxiety evaluation, respectively.

21

22 *Statistical analyses*

23 To compare the scores between the longitudinal follow-ups, ANOVA for repeated measures
24 were used followed by a posteriori contrasts when applicable. Otherwise the comparison was
25 performed using Friedman's test followed by Wilcoxon signed rank test with continuity

1 correction; for discrete variables McNemar test was applied. Benjamini and Hochberg False
2 Discovery Rate was used as correction for multiple testing. Finally, Pearson's correlation
3 coefficient was used to assess the degree of association between measures. An α level of 0.05
4 was considered for all hypothesis tests. All data analyses were performed using SAS 9.2
5 software (SAS Institute, Cary, NC, USA).

6

7 **Results**

8 Patients' demographic characteristics and reasons for attrition are depicted in Figure 1.
9 Performance of 168 patients at T₀, 48 patients at T₁ and 18 patients at T₂ are summarized in
10 Supplementary Table 1.

11 Nine out of 168 patients (5%) had to use the written version at T₀ due to severe dysarthria and
12 five out of the 48 patients who completed the T₁ evaluation (10%) had to switch to the written
13 version at 6-months follow-up. The proportion of ALS patients for which it was necessary to
14 change to the written version did not increase at 12- and 24-months follow-ups. The
15 cognitive-behavioural performance in the ECAS of patients within the local geographical
16 region who dropped out was analysed (see Supplementary Table 2 for details); results
17 revealed that 38% of them presented with behavioural alterations and met the new revised
18 criteria for ALS with behavioural impairment (ALS_{bi}) (46) basing on ECAS performance at
19 their last evaluation, while 32% could be classified for ALS with cognitive impairment
20 (ALS_{ci}) and 13% as ALS with combined cognitive and behavioural impairment (ALS_{cbi}).

21

22 ***Longitudinal ECAS in ALS patients***

23 No statistically significant difference was found between any ECAS score from T₀ to T₁ in the
24 48 patients who performed the ECAS after 6 months from baseline [Table 1 near here].

1 When considering the subgroup who performed all the three assessments at T₀, T₁ and T₂
2 (N=18), results from ANOVA demonstrated a significant increase in ECAS Total and ALS
3 Non-specific scores among the three follow-ups; in particular, post-hoc analysis revealed a
4 significant increase from T₀ to T₂ (ECAS Total: $p=0.058$; ALS Non-specific: $p=0.004$), as
5 well as from T₁ to T₂ (ECAS Total: $p=0.027$; ALS Non-specific: $p=0.011$). Moreover, the
6 score obtained at the Memory subdomain globally increased among the three assessments, in
7 particular between T₀ and T₁ ($p=0.039$) and between T₀ and T₂ ($p=0.012$), with patients
8 showing a significantly higher score at the Immediate Recall task globally among the three
9 follow-ups and particularly between T₁ and T₂ ($p=0.029$) [Table 2 near here].

10 Of 168 patients, 37% met criteria for ALSci (46) at T₀ and 31% of 48 patients were classified
11 as ALSci at T₁. No patients met criteria for ALS-FTD at any follow-up. When considering the
12 18 patients who performed all the three assessments, 6 (33%) met criteria for ALSci at T₀, 5
13 (28%) were classified as ALSci at T₁ and 6 (33%) at T₂. No significant difference was
14 detected over time in the percentage of patients classified as ALSci.

15

16 ***Behavioural changes***

17 At baseline and at T₁, the majority of patients showed no relevant behavioural impairment or
18 dysfunction detected across only one behavioural domain at the ECAS Behaviour Interview.
19 Between 40-50% of patients showed evidence of behavioural changes meeting criteria for
20 ALSbi at T₀ (41%) and T₁ (50%), while 33% of patients was classified as ALSbi at T₂.
21 Moreover, 12% of ALS patients was classified as ALScbi at T₀, 21% at T₁ and 22% at T₂.
22 Apathy/Inertia was the most represented symptom (34% at T₀, 42% at T₁, 33% at T₂),
23 followed by Loss of Sympathy/Empathy at T₀ and T₁, while at T₂ Loss of
24 Sympathy/Empathy, Behavioural Disinhibition and Change in Eating Behaviour were equally
25 recorded as the most frequent dysfunctions (11%) after Apathy/Inertia. Data about the

1 distribution of behavioural dysfunctions at the ECAS Behaviour Interview across each
2 follow-up are reported in Figure 2. Five patients at T₀ (3%), three at T₁ (6%) and none at T₂
3 had psychotic features; in all cases the only reported symptom was suspiciousness.

4 When considering the subgroup who completed all the three assessments, no significant
5 increase in behavioural symptoms was detected neither at the ECAS Behaviour Interview-
6 Symptoms ($p=0.716$), nor at the global score obtained at the ECAS Behaviour Interview-Total
7 Score ($p=0.065$).

8 Strong correlations were found between both the number of symptoms and the total score at
9 the ECAS Behaviour Interview and FBI-A, FBI-B and FBI Total score at any follow-up
10 [Table 3 near here].

11 In the 48 patients who performed the ECAS twice (i.e. after 6 months from baseline), a
12 significant increase of FBI Total Score and FBI-A was detected between T₀ and T₁ (FBI
13 Total: $p=0.036$; FBI-A: $p=0.056$). Concerning the subgroup that completed all the three
14 assessments, a significant increase of FBI Total Score could be globally detected ($p=0.038$);
15 in particular, higher scores were found at T₂ with respect to T₀, but which did not reach
16 statistical significance ($p=0.075$).

17 Focusing on the relationship between behavioural alterations in the ECAS Behaviour
18 Interview and cognitive performance, the ECAS Behaviour Interview-Symptoms negatively
19 correlated with ECAS Total, ALS-Specific and ALS Non-Specific scores only at T₂ (see
20 Table 4). On the contrary, no correlations were found between the ECAS Behavioural
21 Interview-Total Score and the ECAS subscores nor at T₀, T₁ or T₂. With concern to the FBI,
22 no significant correlations were found at T₀ and T₁ between FBI-A, FBI-B and FBI Total
23 score and any ECAS cognitive subscore, while at T₂ significant negative correlations of FBI-
24 A and FBI Total scores were found with the ECAS Total, ALS-Specific and ALS Non-
25 specific scores [Table 4 near here].

1

2 *Longitudinal FAB and MoCA assessment in ALS patients*

3 All patients were able to complete the ECAS without any difficulties at T₁. Even after 12–24
4 months, the ECAS was still feasible as indicated by completion of the full test by all of the
5 patients bar one who performed these assessments. In contrast, the FAB was administrable
6 only in 71% of patients at T₁ and in 67% of patients at T₂. With the MoCA, only 69% of
7 patients could perform it at T₁ and 72% of patients completed it at T₂. Patients showed neither
8 a significant deterioration nor improvement in the FAB and MoCA scores at T₁ and T₂, when
9 considering the patients' subgroup who completed all the three assessments.

10

11 *Clinical and affective status*

12 No significant correlations were found between ECAS scores and disease duration or
13 ALSFRS-R scores at any follow-up. Similarly, no correlations were found between disease
14 duration and the number of behavioural symptoms or the ECAS Behaviour Interview-Total
15 score at the carer interview.

16 With concern to psychological aspects, of the 154 patients who completed the BDI at T₀, 100
17 (65%) showed scores indicative of clinically significant depression, ranging from mild-to-
18 moderate (66%), moderate-to-severe (26%) and severe (8%). At T₁, 33 out of 47 patients
19 (70%) showed some degree of depression, while at T₂ 11 out of 17 patients (65%) showed
20 depressive symptoms. In the subgroup that completed all the three follow-ups, no significant
21 differences were found between T₀, T₁ and T₂. Patients did not show clinically relevant state
22 and trait anxiety levels neither at T₀, nor at T₁ and T₂; moreover, no significant differences
23 concerning anxiety emerged across the serial follow-ups, when considering the patients'
24 subgroup who completed all the three assessments.

25

1 ***Relationship to genetic profile***

2 At T₀ three (19%) of the 16 patients presenting with *C9orf72* repeat expansions performed
3 abnormally on the ECAS Total, ALS-Specific and ALS Non-specific functions scores, while
4 two (12.5%) were impaired at the ECAS Total and ALS-Specific functions scores. The
5 remaining eleven patients (69%) showed normal cognitive performances. Six of 16 *C9orf72*
6 patients (37,5%) who performed the study at T₀ and one of the two patients who performed it
7 at T₂ met criteria for ALSbi, while none of the five *C9orf72* patients who performed the
8 ECAS at T₁ showed cognitive impairment. Moreover, six of 16 patients at T₀, two of 5 at T₁
9 and one of two at T₂ were classified as ALSbi, while three patients at T₀ and one at T₂ met
10 criteria for ALScbi. None of the *C9orf72* patients showed psychotic abnormalities at any
11 follow-up.

12

13 **Discussion**

14 Longitudinal neuropsychological studies of ALS are plagued by difficulties in assessing
15 patients with progressive physical disability. The lack of use of cognitive tools
16 accommodating for verbal-motor disability is one of the reason for the sparse and often
17 conflicting data. Our work represents the first Italian longitudinal study assessing both
18 cognitive and behavioural performance in ALS patients through the use of a multi-
19 dimensional screening test able to compensate for verbal-motor disability. All patients bar one
20 were able to complete the whole ECAS. In contrast, the FAB was not administrable in about
21 30% of patients at 6 and 12 months; comparable data were also obtained for the MoCA. Such
22 findings are to be explained by the presence of subtasks involving motor and verbal skills and
23 not accommodating for physical disability, thus confirming previous literature data (15, 33,
24 47).

25

1 *Longitudinal cognitive changes*

2 The Italian ALS population showed no significant changes in ECAS scores from baseline to
3 6-months follow-up. After 12 months, our patients' subgroup who performed all the three
4 evaluations achieved a significant improvement in some scores (ECAS Total, ALS Non-
5 specific and Memory subdomain), thus presenting a possible practice effect. In contrast,
6 Burkhard et al. (33) did not find any practice effect in an ALS cohort, although this was found
7 in healthy controls. Such conflicting results could be attributed to our larger sample size,
8 rather than to other factors such as age, education or disease duration. Our results seem to
9 support a well-known phenomenon in neuropsychological assessment underlining the
10 presence of potential practice effects or initial unfamiliarity with test situation when patients
11 are assessed repeatedly (48, 49); such an issue has been poorly investigated in ALS and few
12 results are available (28). Recently, in order to overcome this issue, alternate forms of the
13 ECAS have been developed (ECAS B and C) (50, 51). Repeated serial administration of the
14 ECAS original version over a short time period produced improved scores for ALS-Specific,
15 ALS Non-specific and ECAS Total scores, whereas such effects were not found when ECAS
16 alternate versions were administered serially. The current study demonstrates that these
17 practice effects can last over longer months, particularly in relation to the memory domain.

18

19 *Longitudinal behavioural changes*

20 No increase was observed in the number of behavioural symptoms detected at the ECAS
21 Behaviour Interview, nor at the ECAS Behaviour Interview-Total Score within 12 months. In
22 line with recent literature, Apathy/Inertia and Loss of Sympathy/Empathy were the more
23 frequently observed changes (52, 53); furthermore, at 12 months also Behaviour Disinhibition
24 and Change in Eating Behaviour became prominent in our cohort. Our data are partially in
25 contrast with previous results indicating a slight progression of behavioural alterations at the

1 ECAS over time (33). However, when considering the FBI scores, an increment of
2 behavioural dysfunction was longitudinally found, thus confirming the possible progression
3 of behavioural features in ALS. Such contrasting data about the longitudinal changes detected
4 at ECAS Behaviour Interview and FBI, as well as the relationship with cognitive performance
5 at the ECAS, could be explained by the fact that, unlike the FBI, the ECAS Behaviour
6 Interview has been designed to diagnose ALSbi and/or ALS-FTD and scores the
7 presence/absence of a behavioural dysfunction, not measuring its severity. Behavioural
8 dysfunction also emerged as a prominent feature characterising our dropped-out patients, thus
9 highlighting the need to consider these symptoms in ALS patients' clinical management.
10 The lack of significant correlations of disease duration and ALSFRS-R with ECAS
11 cognitive/behavioural performance is in line with previous literature data (54, 55).
12 Depressive symptoms are prevalent in ALS; however, worsening depression was not observed
13 in our sample during follow-ups, as previously recorded (56, 57). In contrast, no clinically
14 relevant anxiety levels were found at serial investigations, in accordance to previous results
15 (58-60).

16

17 *Longitudinal cognitive-behavioural performance and genetic profile*

18 Despite recent literature having confirmed the high prevalence of cognitive-behavioural
19 impairment in patients with *C9orf72* repeat expansions (39, 30, 61), only a small proportion
20 of our mutated ALS patients showed such alterations. However, our data could possibly be
21 explained by the small number of mutation carriers who completed the follow-up evaluations
22 in our sample cohort.

23 More generally, the high drop-out rate of patients during the serial follow-up and the resulting
24 small sample size, also with regard to genetic data, represent a limitation of our study,

1 together with a bias towards slow progressors and long survivors, thus suggesting the need to
2 enlarge these cohorts in future analyses.

3

4 **Conclusion**

5 In summary, our results support the use of the ECAS also in moderate and advanced stages of
6 the disease, in order to assess cognitive-behavioural progression in ALS. Our ALS Italian
7 population showed no significant cognitive deterioration at ECAS performance between serial
8 evaluations; on the contrary, we detected a significant improvement between baseline and 12-
9 months assessment at some ECAS scores. No increase of behavioural changes over time was
10 recorded at the ECAS Behaviour Interview even if such changes were detected when
11 measured by FBI, thus suggesting a possible progression of behavioural features in ALS.
12 Moreover, behaviour impairment emerged as a prominent issue characterising our drop-outs,
13 further underlining its critical role in clinical management of ALS patients. Despite the above
14 mentioned limitations, the present work represents the first Italian follow-up study performed
15 with the new gold standard for cognitive/behavioural screen in ALS. Accommodating for
16 verbal-motor components represents a crucial issue for ALS longitudinal assessment. The
17 implementation of Italian ECAS alternate forms represents a future challenge, in order to
18 minimize the presence of possible unfamiliarity/practice effect bias and will help to better
19 describe ALS patients' phenotypes along the course of the disease.

20

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25

1 **Disclosure of interest**

2 The authors report no conflict of interest.

3

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8

9 **Supplementary material available online**

10 Supplementary Tables 1-2

11

12 **Tables and Figure Captions**

13 Table 1. Longitudinal performance on the ECAS subdomains and Total score, FAB and
14 MoCA of the 48 ALS patients who completed the ECAS at T0 and T1. Data are expressed as
15 means (standard deviations).

16 Table 2. Longitudinal performance on the ECAS subdomains and Total score, of the ALS
17 patients subgroup (n=18) who completed the three assessments. Data are expressed as means
18 (standard deviations).

19 Table 3. Correlations between ECAS Carer Interview (number of symptoms and total score)
20 and FBI at T₀, T₁ and T₂.

21 Table 4. Correlations between ECAS Carer Interview (number of symptoms and total score)
22 and FBI and cognitive performance at the ECAS at T₀, T₁ and T₂.

23

24 Figure 1. Flowchart and basic demographic characteristics of the ALS cohort

25 Figure 2. Distribution of behavioural changes in ALS patients across each follow-up

1
 2 Supplementary Table 1. Mean performance of ALS patients at T₀, T₁ and T₂ on the ECAS
 3 subdomains and Total score, FAB and MoCA. Number of patients cognitively and/or
 4 behaviourally impaired are also reported

5 Supplementary Table 2. Number of dropped out patients who were classified as cognitively
 6 and/or behaviourally impaired at the last evaluation performed

7

8 **Tables**

9 Table 1. Longitudinal performance on the ECAS subdomains and Total score, FAB and MoCA of the
 10 48 ALS patients who completed the ECAS at T₀ and T₁. Data are expressed as means (standard
 11 deviations).

	Baseline (T ₀) N=48	6 months (T ₁) N = 48	<i>t-test</i> <i>p-value</i>
Executive functions	34.25 (6.25)	34.29 (7.60)	0.952
Language functions	23.54 (3.68)	24.02 (3.36)	0.143
Fluency	17.13 (4.95)	16.92 (5.47)	0.711
Memory functions	14.60 (4.60)	15.42 (4.50)	0.059
Visuospatial functions	11.38 (0.89)	11.40 (1.30)	0.921
ALS-Specific Functions	74.92 (11.79)	75.23 (13.12)	0.753
ALS Non-specific Functions	25.98 (4.75)	26.81 (5.04)	0.053
ECAS Total Score	100.90 (15.11)	102.04 (17.07)	0.286
FAB	15.93 (1.51)	16.13 (1.45)	0.589
MoCA	24.35 (3.09)	24.15 (3.55)	>0.999

12 Bold numbers indicate statistical significance with $p < 0.05$. FAB: Frontal Assessment Battery; MoCA: Montreal
 13 Cognitive Assessment.

14

15 Table 2. Longitudinal performance on the ECAS subdomains and Total score, of the ALS patients
 16 subgroup (n=18) who completed the three assessments. Data are expressed as means (standard
 17 deviations).

	Baseline (T ₀) N=18	6 months (T ₁) N=18	12 months (T ₂) N=18	<i>ANOVA</i> <i>p-value</i>
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Executive functions	36.17 (5.35)	34.61 (8.98)	37.83 (4.55)	0.230
Language functions	23.78 (3.84)	23.72 (3.44)	24.33 (3.50)	0.505
Fluency	17.67 (5.46)	17.89 (5.29)	17.00 (5.58)	0.423
Memory functions	13.72 (5.07)	14.39 (5.50)*	16.39 (4.68)*	0.011
Visuospatial functions	11.28 (0.89)	11.17 (1.72)	11.50 (0.86)	0.289
ALS-Specific Functions	77.83 (12.24)	76.06 (14.55)	79.17 (11.43)	0.125
ALS Non-specific Functions	25.00 (5.18)	25.56 (6.32)	27.89 (4.71)*,§	0.003
ECAS Total Score	102.83 (16.42)	101.61 (20.12)	107.06 (15.76)*,§	0.023

Bold numbers indicate statistical significance with $p < 0.05$. * $p < 0.05$ vs T₀; § $p < 0.05$ vs T₁

Table 3. Correlations between ECAS Carer Interview (number of symptoms and total score) and FBI at T₀, T₁ and T₂.

		T ₀			T ₁			T ₂		
		FBI-A	FBI-B	FBI-TOT	FBI-A	FBI-B	FBI-TOT	FBI-A	FBI-B	FBI-TOT
ECAS	r	0.68	0.52	0.71	0.71	0.74	0.81	0.74	0.78	0.85
Behaviour Interview – Symptoms	<i>p-value</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001
ECAS	r	0.68	0.60	0.75	0.72	0.76	0.82	0.69	0.89	0.87
Behaviour Interview – Total Score	<i>p-value</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	<0.001	<0.001

Bold numbers indicate statistical significance with $p < 0.05$. FBI: Frontal Behaviour Inventory.

1 Table 4. Correlations between ECAS Carer Interview (number of symptoms and total score) and FBI and cognitive performance at the ECAS at T₀, T₁ and T₂.

		T ₀					T ₁					T ₂				
		ECAS Behav Interview- Symptom	ECAS Behav Interview- Tot	FBI-A	FBI-B	FBI-Tot	ECAS Behav Interview- Symptom	ECAS Behav Interview- Tot	FBI-A	FBI-B	FBI-Tot	ECAS Behav Interview- Symptom	ECAS Behav Interview- Tot	FBI-A	FBI-B	FBI-Tot
ALS-Specific Functions	r	-0.09	-0.08	-0.11	-0.09	-0.12	-0.16	-0.16	-0.29	-0.12	-0.27	-0.57	-0.49	-0.72	-0.35	-0.63
	<i>p-value</i>	0.277	0.324	0.193	0.274	0.159	0.287	0.274	0.051	0.431	0.072	0.026	0.065	0.002	0.204	0.011
ALS Non-specific Functions	r	-0.11	-0.09	-0.06	-0.06	-0.07	-0.15	-0.18	-0.24	-0.17	-0.24	-0.54	-0.50	-0.61	-0.43	-0.60
	<i>p-value</i>	0.178	0.274	0.477	0.479	0.414	0.317	0.222	0.112	0.260	0.101	0.036	0.057	0.016	0.105	0.018
ECAS Total Score	r	-0.10	-0.09	-0.10	-0.09	-0.11	-0.17	-0.18	-0.29	-0.14	-0.28	-0.58	-0.51	-0.71	-0.38	-0.64
	<i>p-value</i>	0.217	0.278	0.214	0.284	0.176	0.263	0.228	0.047	0.347	0.060	0.024	0.055	0.003	0.158	0.009

2 Bold numbers indicate statistical significance with $p < 0.05$. ECAS Behav Interview – Symptom: ECAS Behaviour Interview – number of symptoms; ECAS Behav Interview – Tot: ECAS

3 Behaviour Interview – Total Score; FBI: Frontal Behaviour Inventory.

4