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## Anosognosia in amyotrophic lateral sclerosis: a cross-sectional study of 85 individuals and their relatives

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Anosognosia in amyotrophic lateral sclerosis: a cross-sectional study of 85 individuals and their relatives

**Background.** Amyotrophic lateral sclerosis (ALS) has long been considered a pure motor neurodegenerative disease. However, now, extra-motor manifestations such as cognitive-behavioral disorders are considered not rare and are even a severity factor of the disease. Experiencing anosognosia (i.e., the inability to recognize neurological symptoms) might affect care and treatment compliance in ALS. Regardless, this pivotal feature has been little investigated.

**Objectives.** By comparing patients' and caregivers' reports, we analysed whether patients with ALS would experience a lack of awareness about their executive disorders and their apathy symptoms.

**Methods.** From the ALS reference center in Paris, we included 85 patients (47 men, mean [SD] age 60.5 [12] years and ALS-Functional Rating Scale-revised score 8 to 46) and their primary family caregivers who all completed the Dysexecutive Questionnaire (DEX) and the Apathy Evaluation Scale (AES). Overall scores and answers were compared by agreement/disagreement statistical methods.

**Results.** Caregivers reported higher levels of cognitive-behavioral disorders than did patients, but reports matched when cognitive-behavioral disorders were absent or mild. With published DEX and AES cutoffs, 32% and 51% of patients had executive disorders and apathy, respectively. In these patients with significant impairment, Bland-Altman plots (i.e., visual display agreement that represents the difference between the patient's and caregiver's scores as a function of their average) showed a strong discrepancy between joint reports: patients underestimated their symptoms by a mean bias of -6.81 DEX points (95% confidence interval

-11.88, -1.75) and -8.85 AES points (95% confidence interval -11.72, -5.98). We found no clear relationship between bulbar or spinal ALS subtypes and anosognosia.

**Conclusions.** ALS patients with a cognitive-behavioral phenotype show anosognosia by a mismatch between self and proxy reports, which warrants further investigation in neuroimaging. Systematic longitudinal screening of anosognosia is needed to propose targeted psychoeducation in patient–caregiver dyads showing disagreement.

**Keywords:** amyotrophic lateral sclerosis, ALS, anosognosia, apathy, dysexecutive disorders

## **Introduction**

Although amyotrophic lateral sclerosis (ALS) has long been considered a pure motor neurodegenerative disease, extra-motor symptoms, including cognitive-behavioral impairment, have been explored over the past 20 years [1]. Cognitive and behavioral dysfunction are not rare in ALS, with an estimated prevalence ranging from 30% to 50% and including frequent apathy and dysexecutive syndrome [2]. In addition, these extra-motor manifestations have been described as a severity factor of the disease because of both their association with short survival and an accelerated course of ALS [3,4].

Anosognosia (i.e., the inability to recognize neurological symptoms) has been little explored in ALS [5]. Investigating anosognosia related to cognitive-behavioral disorders in ALS is complex: first, we lack specific tools enabling an assessment of awareness and loss of insight about symptoms in ALS as well as a recommended methodology in the field. Also, the neurodegenerative course of ALS results in patients living longer and experiencing increasing cognitive-behavioral disorders as the disease progresses [6]. Yet, assessing apathy and executive dysfunction in advancing disease stages may become difficult because of increasing motor impairment: patients might have difficulty performing daily life activities because of

motor impairment or lack of motivation (apathy) to initiate these activities; also, patients might be unable to meet their communication needs using natural speech to report their symptoms [7].

Depicting anosognosia over the therapeutic course of ALS remains important for patient care and quality of life: awareness of symptoms will make it easier for patients to participate in rehabilitation programs, anticipate end-of-life decisions or be compliant in the use of compensation aids (such as non-invasive ventilation). Identification of anosognosia might also enable psychoeducation in caregivers and perhaps lower anxiety and burden with better information [8].

To our knowledge, the extent to which patients and caregivers would report similar or distinct narratives regarding patients' cognitive-behavioral symptoms has been little explored in ALS. Neuropsychological deficits in ALS fall along a heterogeneous spectrum that overlaps with frontotemporal dementia (FTD) [9]. In the present study, we did not include patients with a formal diagnosis of ALS-FTD. We aimed to analyze executive disorders and apathy as reported by primary caregivers and patients with ALS at different possible stages of the disease. To study whether patients' and caregivers' reports would match, we used two published scales that both had a patient and a proxy version (the Dysexecutive Questionnaire [DEX] and the Apathy Evaluation Scale [AES]) and agreement/disagreement methods.

## **Methods**

The reporting of the study was according to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement (Equator network, <https://www.equator-network.org/reporting-guidelines/record/>) and is accessible as supplementary material.

Patients with ALS and their primary caregivers were followed up on a regular basis in the ALS reference center in the Neurological Department of La Pitié-Salpêtrière Hospital,

Paris, France [10]. Patients with a formal diagnosis of ALS-FTD were excluded. During their multidisciplinary day care visits, patients and their primary caregivers are asked to report symptoms, deficiencies and incapacities in a standardized manner, including the cognitive-behavioral disorders of the patients. The primary caregiver is defined as the family member or friend who is most responsible for decision-making and care of the patient [11]. We analysed patient and caregiver assessments that had been reported between February 1 and April 30, 2018.

Cognitive-behavioral evaluation included the DEX [12] (evaluating executive dysfunction) and the AES [13] (evaluating apathy disorders). Both questionnaires assess dysfunction in everyday life and have a self and a proxy version that includes the same set of questions, thus enabling the assessment of inter-rater reporting consistency between patients and caregivers. With a set of 20 questions, the score for the DEX ranges from 0 (normal) to 80 (maximum of disorders); a clinical cut-off of 19 has been used to depict moderate dysexecutive functioning and a score  $> 28$  is considered a high degree of dysexecutive disorder [14]. With 18 questions, the score for the AES (scoring details in [15]) ranges from 0 to 72 (most apathy) and a clinical cut-off of 38 has been identified to depict significant apathy [16].

In addition to the DEX and AES scores, other data that are routinely collected in hospital day care were analyzed: patient's socio-demographic information; relationship to the caregiver; severity of the disease as assessed by the reference ALS Functional Rating Scale Revised (ALS-FRS-R) [17], a 12-domain global functioning and disability measure specifically designed for ALS, the total score ranging from 0 (maximum disability) and 48 (normality); and mood disorders as reported by the patient with the Hospital Anxiety and Depression scale (HAD) [18], with both anxiety and depression subscores ranging from 0 (no disorder) to 21 (abnormal). A clinical cutoff of 8 on the HAD is considered to identify

individuals with significant depression [18]. The ALS form for patients was classified as follows: “spinal form” for patients with ALS onset with a limb deficiency and/or symptoms related to focal muscle weakness and wasting (with onset distally or proximally in the upper or lower limbs) and “bulbar form” for those with an ALS onset with dysarthria and dysphagia for solid or liquids and those whose limb symptoms developed in parallel or followed bulbar symptoms [19]. According to this classification, the published distribution of ALS forms is 70% spinal, 25% bulbar and 5% other forms [20].

### **Statistical analysis**

Data are described with number (%) and mean (SD) (range). DEX and AES evaluations (overall scores for both caregivers’ and patients’ ratings) were displayed with scatter plots with fitted values and 95% confidence intervals (CIs). Spearman correlation coefficients and Lin’s concordance correlation coefficients (CCC; measures the strength of agreement between raters) were computed on overall DEX and AES scores to further explain scatter plots. A CCC close to 0 indicates that ratings are not similar and a CCC close to 1 indicates excellent agreement. The interpretation of CCC (and, accordingly, choices of cutoffs) depends on the nature of the rated phenomenon (i.e., interpretation thresholds differ for survey reports vs standardized normed biomarkers). Spearman correlations were computed to assess the correlation between DEX and AES scores and ALS duration since diagnosis and ALS-FRS-R and HAD scores. Bland-Altman plots representing the difference between the patient’s and caregiver’s scores as a function of their average were used to represent inter-rater agreements regarding DEX and AES scores. The Bland-Altman plots enable evaluation of a bias between the mean differences and estimate an agreement interval within which 95% of the difference between ratings fall (the limit of agreement) [21,22]. Finally, the kappa statistic was computed to identify DEX and AES questions with the lowest percentages of agreement among patients who showed a significant overall level of cognitive-behavioral disorders

[23,22]. Statistical analyses were performed with STATA (Stata Statistical Software: Release 15, StataCorp. LLC 2017) and R (R Core Team 2013 <http://www.R-project.org/>).

The study was approved by the local ethics committee Comité de Protection des Personnes–Ile de France VI, Pitié-Salpêtrière hospital. Patients were informed about the purpose of the study, the protocol, data collection and the possibility to decline participation. They received oral and written information and gave their informed written consent before inclusion in the study.

## **Results**

Data for 85 patient–caregiver pairs that had been consecutively followed up in the Paris ALS reference center over 3 months were analyzed. The mean (SD) age of patients was 60.5 (12) years and the ALS duration was wide, with an average of 2.4 years since diagnosis (Table 1). The relationship to the primary caregiver was as follows: 68 caregivers (80%) were from same generation (mostly spouse), 11 (12.9%) were from a lower generation (mostly children), and 4 (4.7%) were from the upper generation (mostly parents); these data for 2 pairs were missing (2.4%).

Patients had moderate mean DEX and AES scores as reported by both patients and caregivers (Table 1). In the whole sample, caregivers reported higher scores than patients regarding the AES ( $p=0.03$ ) but not the DEX ( $p=0.17$ ). In the whole sample, the bulbar ALS form was not associated with significantly higher scores than the bulbar form regarding both AES and DEX scores.

Using caregivers' ratings and published cutoffs allowed for defining 2 subsamples of patients with behavioral, cognitive and emotional symptoms, one with “moderate to severe executive dysfunction” and one with “significant apathy”: whatever the ALS form, 31.8% (27/85) of the sample had a DEX score  $> 19$ , and 51.2% (43/84) had an AES score  $> 38$ .



Caregivers ratings chosen to identify those 2 subsamples revealed that patients' ratings would identify 27/85 patients with a DEX score > 19 and a lower number of 32/84 with an AES score > 38. The mean depression score on the HAD-depression scale was 6.6 (3.5) (range 1–17) and 29% (23/78) had depression (i.e., with HAD-depression score  $\geq$  8). Patients with and without apathy differed in depression score (mean 8.0 vs 5.2,  $p < 0.001$ ). Patients' and caregiver's AES scores were correlated with HAD-depression scores ( $\rho = 0.57$ , and  $\rho = 0.48$  respectively;  $p < 0.001$ ). We found no correlation between ALS characteristics (ALS duration since diagnosis, ALS-FRS-R score) and higher DEX or AES scores, even in the 2 cognitive subsamples and no significant difference between spinal and bulbar forms regarding ALS characteristics (ALS duration since diagnosis, ALS-FRS-R) and HAD scores.

Figure 1 shows scatter plots for the whole sample with sparse distribution of caregivers' ratings as a function of patients' ratings for DEX (Fig. 1a) and AES scores (Fig. 1b). As shown by the fitted value of this figure (plain line), patient and caregiver evaluations were correlated on DEX and AES scores ( $\rho = 0.60$  and  $\rho = 0.48$ , both  $p < 0.001$ ). However, these plots and their associated fitted values illustrate the strength of relationship between reports, but not inter-rater agreement: indeed, the DEX and AES scatter plots were not tight and deviated from the 45° concordance line (dot line), which would represent excellent agreement between dyads (i.e., a CCC close to 1). Accordingly, for the whole sample, we found a CCC of 0.59 (95% CI 0.46–0.73), suggesting moderate to good agreement for the DEX and a CCC of 0.45 (95% CI 0.28–0.61) suggesting poor to moderate agreement for the AES.

To better study the extent to which patients and caregivers ratings would be concordant, we used Bland-Altman analyses. Bland-Altman plots of the overall sample showed no significant discrepancy between patients and caregivers DEX ratings (Fig. 2a, b, c). For the bulbar ALS form, we found greater difficulties, although not significant, reported

by caregivers, as represented by the plain line below the zero dot line, with a mean bias of -3.19 on DEX scores (but a 95% CI -7.59, 1.22, Fig. 2c). Bland-Altman plots of the overall sample showed a constant negative moderate bias between the 2 AES ratings (Figure 3a, b, c) in favor of greater difficulties reported by caregivers (with a mean bias of -2.63, 95% CI -4.94, -0.32 at the scale of the whole sample, Fig. 3a). Limits of agreement (i.e., mean bias  $\pm$ 1.96 SD) were wide in all Bland-Altman plots (Figs. 2 and 3).

Because of the magnitude of cognitive-behavioral disorders, we computed a second set of Bland-Altman plots on the 2 cognitive subsamples only, which resulted in strong significant discrepancies: for individuals with moderate to severe executive disorders, the negative bias was -6.81 points for the DEX score (95% CI -11.88, -1.75) and was significant because the line of equality (i.e., zero) was not within the confidence interval of the mean differences (Fig. 4). Similarly, for individuals with significant apathy, the negative bias was -8.85 points for the AES scale (95% CI -11.72, -5.98) and was significant (Fig. 4).

Additionally, focus on specific disorders in the 2 cognitive subsamples with significant overall DEX and AES scores allowed for depicting DEX and AES questions for which disagreement was highest. Agreement on DEX questions ranged from 25.8% to 85.2%, with the lowest agreement for questions 8 (25.9% of agreement), 5 (29.6%) and 18 (33.3% (i.e., questions about apathy, euphoria, and distractibility, respectively). Agreement on AES questions ranged from 32.6% to 85.2%, with lowest agreement for questions 9 (32.6%), 7 (41.9%) and 14 (44.2%) (i.e., “spending time on doing things that interest him/her”; “approaching life with intensity”; “getting excited when something good happens”, respectively).

## **Discussion**

At the scale of the whole ALS sample (which included individuals within a large spectrum of disease stages), patients and caregivers reported moderate levels of executive dysfunction (DEX scale) and apathy (AES scale). Although caregivers reported constantly higher levels of cognitive-behavioral disorders than patients, Bland-Altman plots of DEX and AES showed a strong discrepancy between reports from patients with significantly impaired DEX and AES scores: particularly, ALS patients with a cognitive phenotype underestimated their symptoms, which suggests that anosognosia needs to be discussed.

The frequency of executive disorders (32%) and apathy (51%) we report is moderate at the scale of the whole sample and agrees with previous publications in ALS, with frequencies ranging from 30% to 60% [2,3,5,24,25]. Mean overall DEX and AES scores were close and correlated, but agreement visual display (Bland-Altman) was a useful method that did not rely on self-rated anosognosia and allowed for pointing out a discrepancy between patients' and caregivers' reports according to the level of cognitive behavioral impairment. Patients' ratings indicated that they are partially aware of their cognitive status when disorders are absent or mild, with interchangeable reports between patients and caregivers in that case. In contrast, patients with significant cognitive-behavioral impairment (as depicted by our 2 cognitive subsamples) underestimated their executive functioning and apathy (by a mean of 7 and 9 for DEX and AES scores). This finding suggests that patients with cognitive-behavioral symptoms experience anosognosia, which echoes recent publications: cognitively impaired ALS patients that were compared to healthy controls [5,26] had lack of insight about their cognitive performance (on verbal fluency and problem-solving tests [26]). In cognitive-type ALS, anosognosia was found a characteristic cognitive symptom in ALS with dementia [27] and ALS with fronto-temporal dementia [28], with a reported frequency of 10% [29]. Aside from anosognosia, psychological adjustments, including denial and coping (i.e.,

adequate strategies to deal with their deficiencies), could account for symptom underestimation by patients [29].

Radakovic's group reported anosognosia regarding apathy by using the Dimensional Apathy Scale, finding that 28% of patients versus 43% of their caregivers reported abnormal levels of apathy on at least 1 of the 3 apathy subscales (executive, emotional, initiation). The authors were also able to depict specific apathy patterns in ALS with an increase in initiation apathy (i.e., lack of self-generated behavior and cognition) and reduced emotional apathy (which could be related to dysfunction in emotional processing, theory of mind and social cognition [5, 30]). Although apathy is a prominent feature of ALS, these authors stress the importance in differentiating lack of auto-activation due to behavioral disorders from ALS motor dysfunction [5].

The DEX and AES questionnaires used in the present study deal with the impact of executive dysfunction or apathy on motivation to initiate or do activities more than with experiences, which indeed could be influenced by physical limitations: the generic wording of the DEX questions ("do things") and the AES questions ("some activities") do not refer to specific tasks but rather to the intentionality to perform such activities. The discussion about confounding factors that might be associated with apathy (respiratory insufficiency, physical disability [9]) also applies to psychological reactions including depression that vary widely according to the study (from 20% to 64% [5, 31, 32]). Our ALS patients were moderately depressed (29%), in accordance with a recent review [29]. Depression significantly related to apathy can be discussed in terms of concomitant symptomatology or overlapping symptoms: in that apathy and depression share some comparable characteristics (e.g., reduced energy and lack of interest), there might be an overlap between measures, and patients and caregivers might have difficulty disentangling attributable symptoms. Both need to be evaluated longitudinally, including a psychiatric examination when needed, and managed accordingly.

Whether anosognosia regarding executive functioning (DEX) could be stronger in a particular ALS subtype remains unclear: we found a 3-point discrepancy for individuals with the bulbar-type of ALS, which almost reached significance. This finding echoes that cognitive disorders might be more frequent and more severe in the bulbar subtype [24,29,33,34]. However, reverse findings with no significant difference between ALS bulbar and limb subtypes in frontal cognitive assessments have also been reported [28]. Further studies are needed to find neural correlates between anosognosia and ALS subtypes.

Disagreements in specific DEX items about negative (apathy) and positive affects (euphoria, distractibility) [35] and AES items (emotional and auto-activation of apathy) [5] suggest potential for psychoeducation about anosognosia [31,36]. Indeed, specifically monitoring the poor agreement in patient–caregiver dyads might be useful to deliver targeted information about the consequences of cognitive-behavioral disorders in daily living and their impact on the patient–caregiver shared decision-making, relationship and quality of life [31]. This in turn could support better compliance to treatment by patients [37] and lower burden in informal caregivers, which was found associated with cognitive-behavioral manifestations [38]. Finally, anosognosia as screened here, by a significant discrepancy between patient and proxy reports, could help health professionals identify ALS patients in need of a full objective neuropsychological examination [9] with specific ALS tests such as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [39] and the ALS Cognitive Behavioural Screen (ALS-CBS) [40]. Indeed, when cognitive, behavioral, emotional and psychological manifestations are present, they have been reported to occur since disease onset [29]. We examined only a portion of cognitive-behavioral disorders by using reported complaints about executive dysfunction and apathy, which are not as objective as validated cognitive testing. For instance, the ECAS supports further exhaustive cognitive screening: it is a recent multidomain assessment that can be implemented by non-neuropsychology health professionals [39] and

evaluates functions typically affected in ALS (fluency, executive functions, and also language functions and social cognition that have been recently identified as impaired in ALS) and other functions that are not specific to ALS (visuospatial and memory). More neuropsychological screening and longitudinal follow-up on cognitive-behavioral symptoms can now be supported by the refined Strong criteria [9].

### **Limitations and future directions for research**

We performed a cross-sectional evaluation of anosognosia on some cognitive-behavioral disorders in ALS. Longitudinal monitoring of loss of insight into all cognitive-behavioral disorders as well as other motor symptoms would be interesting: indeed, little is known about how anosognosia displays among motor and extra-motor symptoms and how it would change over time [29]. Expert objective cognitive testing was not performed here. Full neuropsychological examination that would include specific dementia scales would usefully complement dyadic evaluations for patients with fronto-temporal dementia and for those who do not fulfill the criteria for fronto-temporal dementia [41] but show a cognitive or behavioral phenotype: the 2017 Strong revised consensus criteria [9] now enable embracing the wide and heterogeneous frontotemporal spectrum disorder of ALS (ALS-FTSD) and support further tuned classification of patients with cognitive and/or behavioral forms associated with ALS. A future study could assess the dyadic (dis-)agreement in patients with a specific diagnosis of ALS-FTD and study whether a gradient in anosognosia could be found according to different cognitive behavioral phenotypes. Structural, metabolic and functional neuroimaging are needed to explore anatomical correlates of these extra-motor deficits: non-dementia ALS patients with cognitive dysfunction have been shown to have an impaired activation in cortical and subcortical regions including the medial prefrontal cortex [42] and temporal lobes [43]. Importantly, self-rated anosognosia in ALS has been found associated with greater

anterior and inferior horn sizes, reflecting fronto-temporal lobar atrophy [44]. The neuropsychological manifestations of fronto-temporal, parietal and basal ganglia involvement in ALS have clinical implications for care needs, treatment compliance and survival [45].

## **Conclusion**

Assessing the frequency of anosognosia seems crucial to provide adequate care and support quality of life and choices (including end-of-life decision-making) for patients with ALS. Our results on executive functioning, apathy and anosognosia along with those of other groups suggest a heterogeneous spectrum of cognitive-behavioral disorders and a lack of insight in the ALS population. We found that the patient's and caregiver's reports do not match when patients have significant cognitive-behavioral impairment. How psychoeducation about anosognosia specifically would benefit patients and the family needs to be further assessed.

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**Conflict of interest.** None declared.

## **Legends**

Figure 1. Scatterplots of caregivers' ratings as a function of amyotrophic lateral sclerosis (ALS) patients' ratings for overall scores of the (a) Dysexecutive Questionnaire (DEX) and (b) Apathy Evaluation Scale (AES). The colored area illustrates fitted values with 95% confidence intervals and the 45° red dot line represents theoretical perfect agreement.

Figure 2. Bland-Altman plots of DEX scores for (a) all ALS patients, (b) those with the spinal form and (c) those with the bulbar form. The plain colored line below the zero dotted line represents the mean bias and the upper and lower lines illustrate the limits of agreements.

Figure 3. Bland-Altman plots of AES scores for (a) all ALS patients, (b) those with the spinal form and (c) those with the bulbar form. The plain colored line below the zero dotted line represents the mean bias and the upper and lower lines illustrate the limits of agreements.

Figure 4. Bland-Altman plots of (a) DEX scores and (b) AES scores for individuals with significant cognitive-behavioral disorders.

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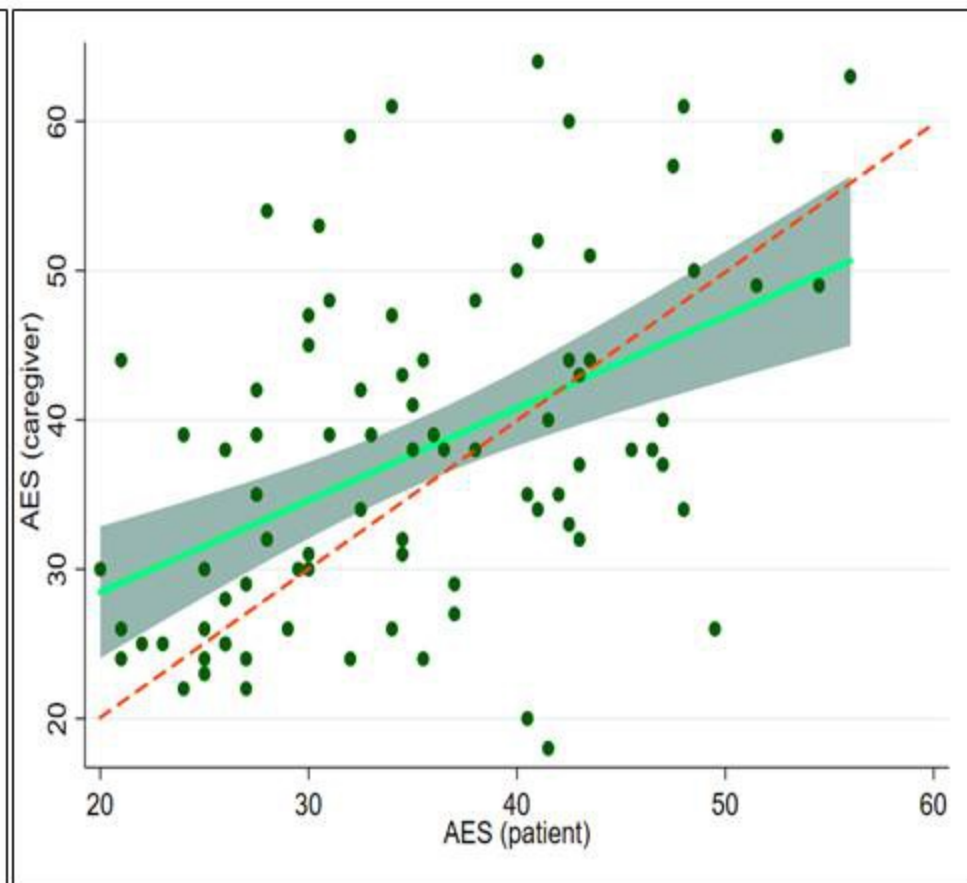
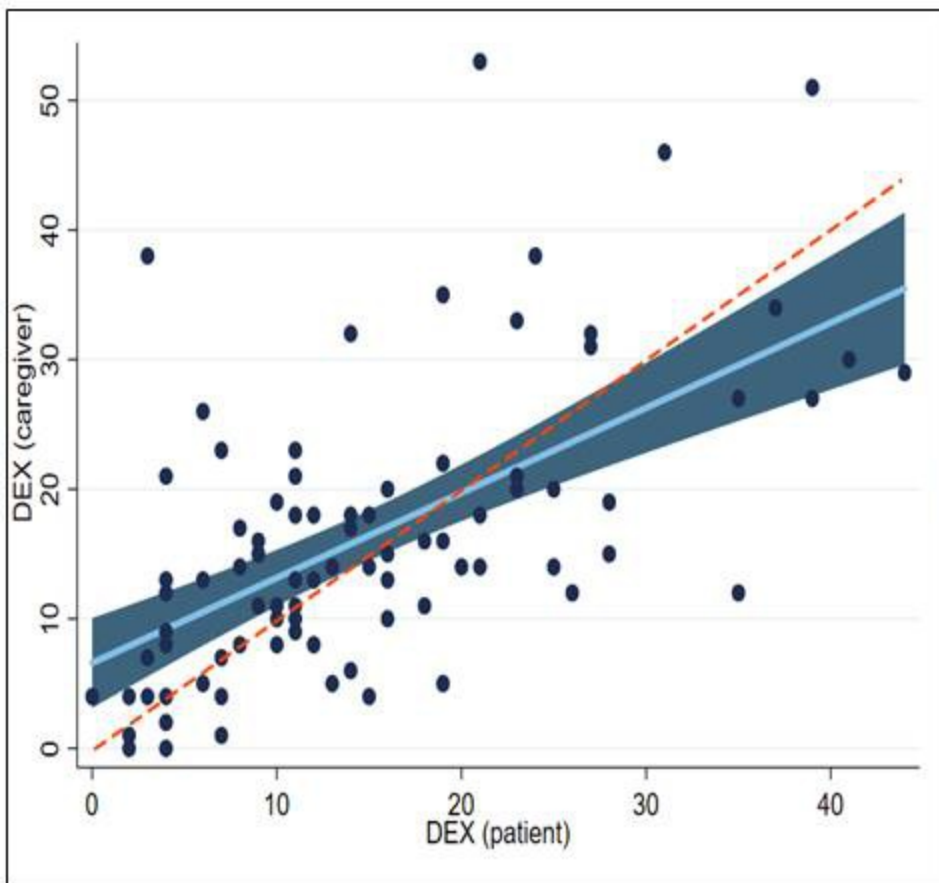
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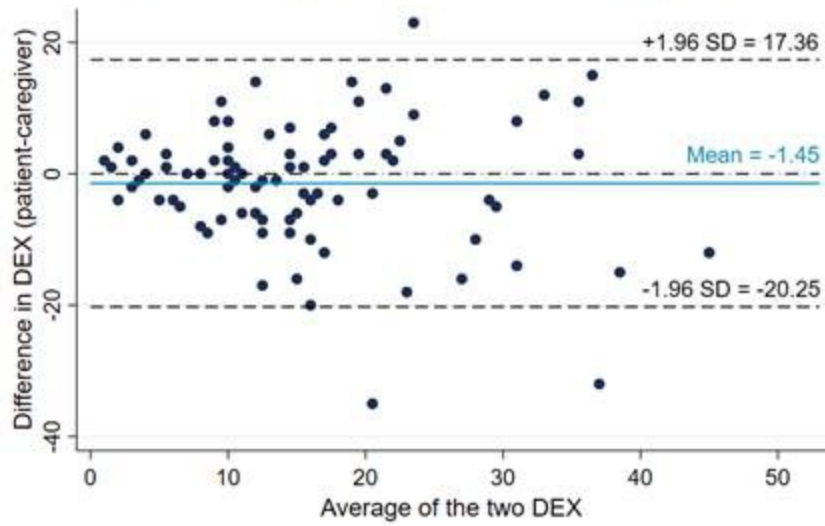
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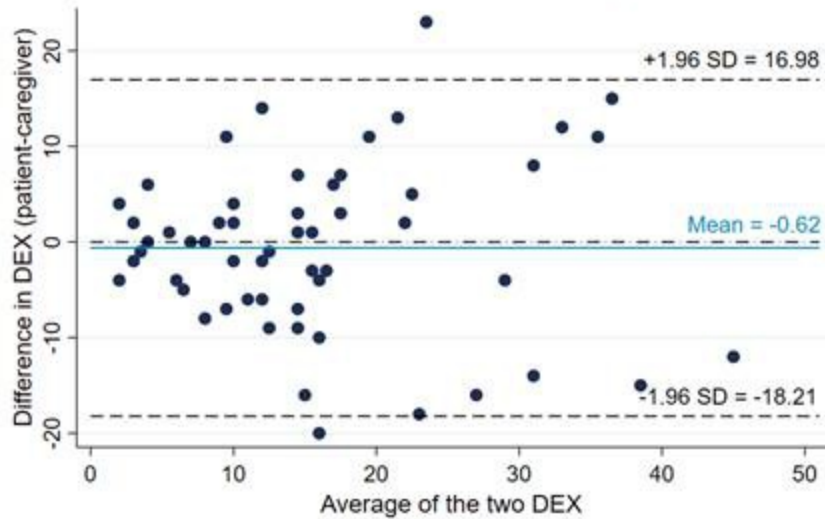
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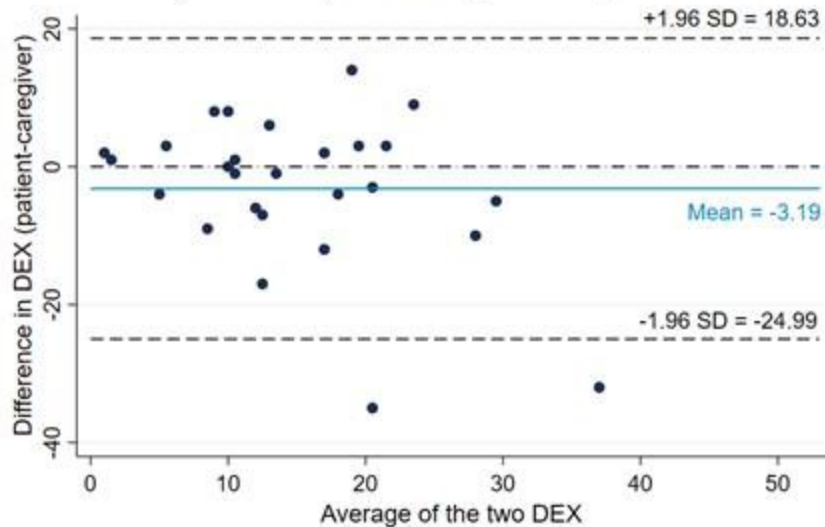
Dysexecutive questionnaire (DEX score), all ALS forms



Dysexecutive questionnaire (DEX score), spinal form

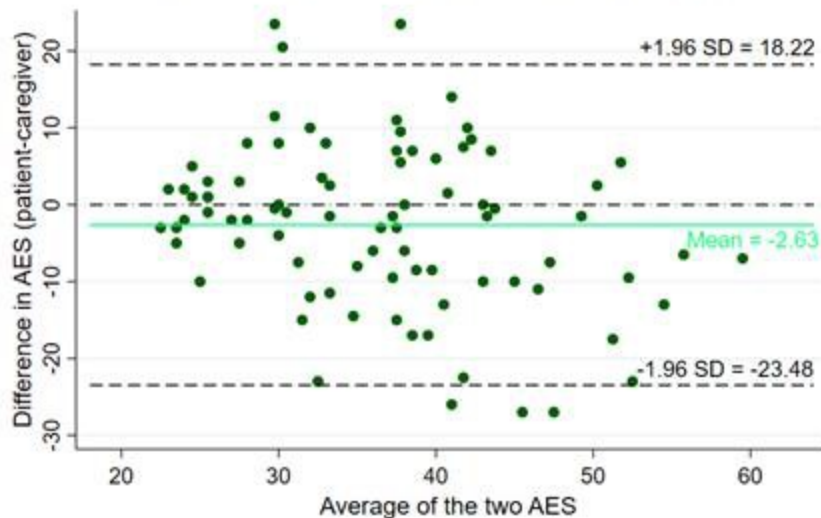


Dysexecutive questionnaire (DEX score), bulbar form

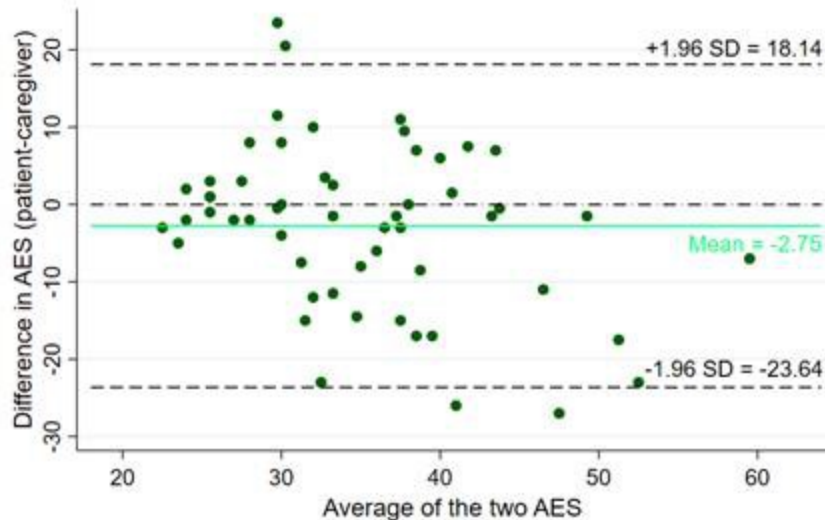




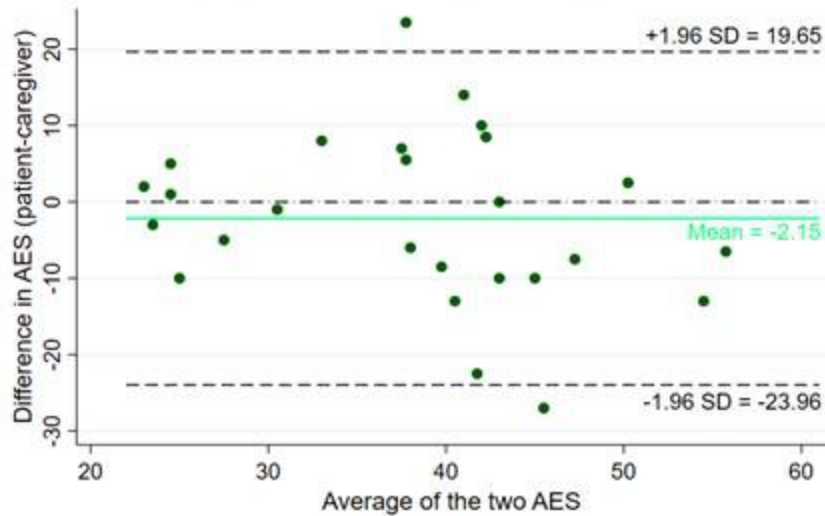
Apathy Evaluation Scale (AES) score), all ALS forms



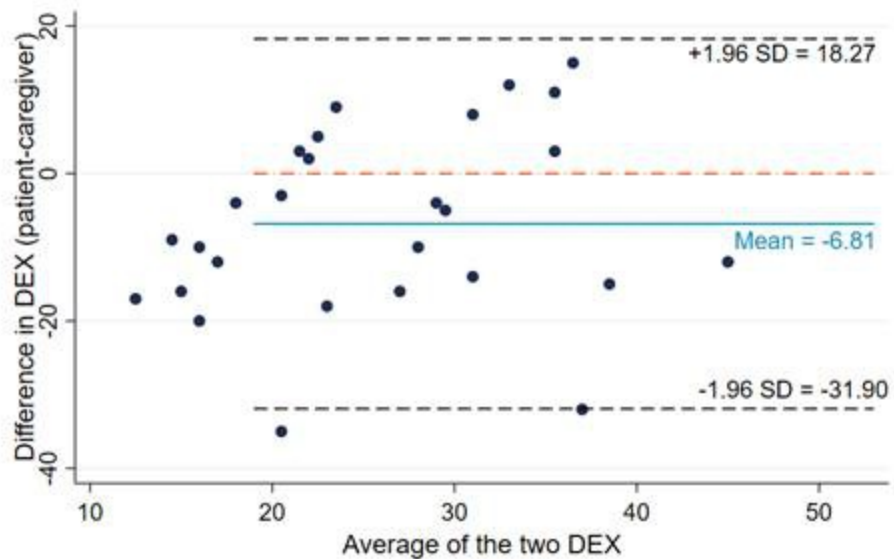
Apathy Evaluation Scale (AES score), spinal form



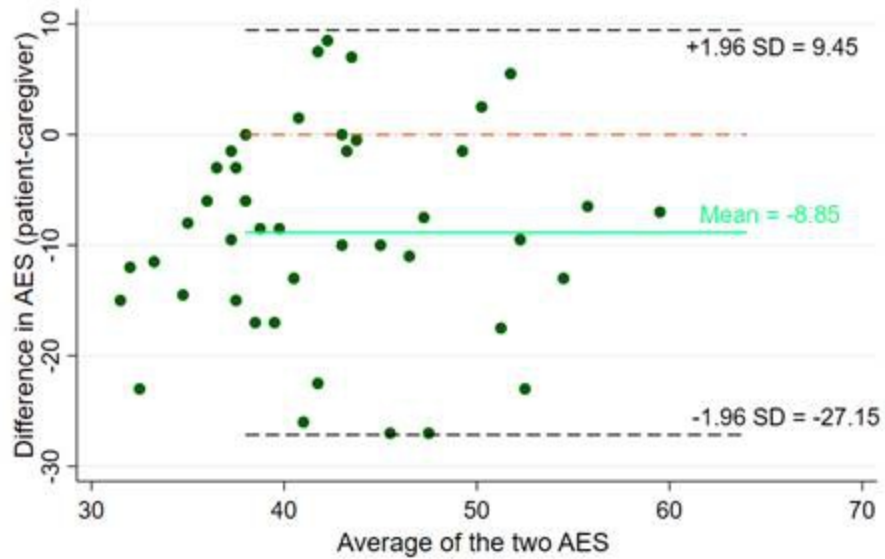
Apathy Evaluation Scale (AES score), bulbar form



Dysexecutive questionnaire, cognitive subsample (caregiver's DEX  $\geq 19$ )



Apathy Evaluation Scale, cognitive subsample (caregiver's AES  $\geq 38$ )



**Table.** Characteristics of patients with amyotrophic lateral sclerosis (ALS) and patients' and caregivers' ratings (n=85 pairs).

Men	47 (55.3%)
Age (years)	60.5 (12) (22–83)
Duration of ALS since diagnosis (months)	28.3 (17.8) (5–94)
Spinal form	55 (64.7%)
Bulbar form	27 (31.8%)
Unknown	3 (3.5%)
ALS-FRS revised	29.7 (10.2) (8–46)
HAD total (n=78, 7 missing)	14.3 (5.7) (4–30)
HAD-anxiety	7.6 (3.3) (1–15)
HAD-depression	6.6 (3.5) (1–17)
DEX-patient (all, n=85)	14.9 (10.2) (0–44)
DEX-patient (spinal form)	15.4 (11.0) (0–44)
DEX-patient (bulbar form)	13.44 (8.06) (2–28)
DEX-caregiver (all, n=85)	16.4 (11.2) (0–53)
DEX-caregiver (spinal form)	16.1 (11.0) (0–51)
DEX-caregiver (bulbar form)	16.6 (11.8) (0–53)
AES-patient (all, n=85)	35.3 (8.8) (20–56)
AES-patient (spinal form)	33.7 (7.9) (21–56)
AES-patient (bulbar form)	36.9 (9.6) (20–52.5)
AES-caregiver (all, n=84, 1 missing)	37.8 (11.5) (18–64)

AES-caregiver (spinal form)	36.5 (11.1) (18–64)
AES-caregiver (bulbar form)	39.3 (11.9) (22–61)

Data are mean (SD) (range) or n (%)

HAD, Hospital Anxiety and Depression; DEX, Dysexecutive Questionnaire; AES, Apathy Evaluation Scale