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Prevalence and determinants of anxiety in amyotrophic lateral sclerosis

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Background

Clinically relevant anxiety can be detected in patients with amyotrophic lateral sclerosis (ALS), but its prevalence and determinants have not yet been fully assessed.

Aims

This study aimed at assessing the prevalence and clinical underpinnings of anxiety in ALS.

Method

Non-demented ALS patients ($N = 433$) and healthy controls ($N = 313$) were administered the State- and Trait-Anxiety Inventory – Form Y (STAI-Y1 for state-anxiety and STAI-Y2 for trait-anxiety) and the Beck Depression Inventory (BDI). Patients were further assessed for cognition (Edinburgh Cognitive and Behavioural ALS Screen), behaviour (Frontal Behavioural Inventory) and motor status (disease duration, ALS Functional Rating Scale-Revised and progression rate). The prevalence of clinically significant state- and trait-anxiety were estimated by applying age-stratified cut-offs to STAI-Y1/-Y2 *t*-scores. Linear and logistic regressions were run to test the determinants of STAI-Y1/-Y2 scores.

Results

STAI-Y1 and -Y2 scores above cut-off were detected in 18.2 and 13.9% of patients, respectively – with proportions being higher in cases versus controls ($ps < 0.001$). BDI, but neither cognitive/behavioural nor motor variables, was identified as a significant predictor of STAI-Y1/-Y2 scores ($ps < 0.003$). The cognitive–affective subscale of BDI was the sole predictor of scores above cut-off on both STAI-Y1 and STAI-Y2 ($ps < 0.001$).

Conclusions

Clinically significant levels of state- and trait-anxiety occur in ~18 and ~14% of non-demented ALS patients, respectively, mostly driven by cognitive and affective facets of depression, and are independent of motor and cognitive/behavioural features.

Keywords

Amyotrophic lateral sclerosis; anxiety; psychiatry; depression.

Clinically significant anxiety may be detected in patients with amyotrophic lateral sclerosis (ALS)[1] and may even precede the onset of motor symptoms.[2]

Current prevalence estimates for such a psychopathological feature in this population are highly heterogeneous – possibly due to the lack of large-scale studies on the topic and variability in the employment of psychometric outcome measures.[1,3] In fact, previous reviews on the topic[1,3] have pointed out that, within the relevant literature, the prevalence estimates of anxiety in ALS patients range from 0 to ~63% – depending on the characteristics of the tools employed to assess these symptoms and the disease stage taken into consideration. Moreover, in this respect, evidence is conflicting on whether the rates of clinically significant anxiety are higher in ALS patients than in the general population.[4–6]

Furthermore, it is currently under debate whether anxiety in ALS patients is of a psychogenic/reactive aetiology and thus possibly related to depressive symptoms, or falls within the spectrum of behavioural changes resulting from extra-motor, frontotemporal involvement.[1,6–9] For instance, Lillo et al[7] found that anxiety levels proved not be predictive of frontotemporal-spectrum behavioural changes in this population; by contrast, Siciliano et al[8] detected a significant association between measures of anxiety and apathetic features. More recently, Faltracco et al[9] replicated the findings of Siciliano et al[8] by detecting significant correlations between anxiety levels and both depression and frontotemporal-spectrum behavioural changes in a fairly large cohort of ALS patients ($N = 249$).

In this respect, evidence on the association between anxiety and cognitive features in this population is likewise inconclusive.[8,10,11] In fact, Carelli et al[10] failed to report any significant association between state- and trait-anxiety and a comprehensive measure of cognition, whereas Siciliano et al[8] detected mild, albeit significant, associations between worse cognitive outcomes and higher state- and trait-anxiety levels. Moreover, Palumbo et al[11] showed that emotional disturbances (including anxiety) tend to become disentangled from social–cognitive deficits by being clustering together with behavioural changes – and, in particular, with apathetic features.

A further clinical domain whose association with anxiety has yet to be fully elucidated in ALS is the motor domain.[6,8,9,12] For instance, Siciliano et al[8] found that a greater degree of bulbar involvement was associated with higher state- and trait-anxiety levels, with Benbrika et al[6] replicating these findings with specific regard to trait-anxiety. Furthermore, Larsson et al[12] and Faltracco et al[9] failed to report any significant association between measures of anxiety and motor-functional outcomes in their cohorts.

Taken together, the above research suggests that a comprehensive examination of the determinants of such a psychopathological feature in ALS should include measures of depression, cognition, behaviour and motor status.

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Shedding further light on the above-mentioned matters is relevant to the care management of ALS patients: in fact, anxiety has been identified as a negative prognostic factor in this population by exerting a detrimental effect on both patients' and carers' quality of life.[8,13,14] Accordingly, its pharmacological and non-pharmacological treatment is a recognised clinical need.[15]

Given the above proposals, this study aimed to (a) provide generalisable prevalence estimates of clinically significant anxiety levels from a large, retrospective cohort of ALS patients; (b) explore their motor, cognitive, behavioural and psychological underpinnings; and (c) compare anxiety levels between ALS patients and healthy controls.

Method

Participants

Data that were originally collected for clinical purposes on $N = 433$ ALS patients[16] and consecutively referred to IRCCS Istituto Auxologico Italiano, Milano, Italy between 2016 and 2024, and having been administered the State- and Trait-Anxiety Inventory-Form Y (STAI-Y),[17] were retrospectively retrieved. Patients did not present with comorbid frontotemporal dementia (FTD) according to current nosographic systems,[18,19] or with previously diagnosed psychiatric disorders traceable in medical history records. ALS patients with comorbid, full-blown FTD were not addressed within this study, in order to prevent the study sample from being phenotypically heterogeneous given that these patients, when compared with those without FTD, often display markedly distinct clinical features possibly rooted in different underlying neural vulnerabilities.[20–22]

Moreover, data on $N = 313$ healthy controls with available STAI-Y scores and no history of (a) neurological/psychiatric disorders, (b) active psychotropic medications or (c) severe, uncompensated general medical conditions were retrieved from the database of the above-mentioned institution. All healthy controls had a normal performance on Montreal Cognitive Assessment as per current Italian norms.[23]

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, and with the Helsinki Declaration of 1975 as revised in 2013. All procedures involving human subjects/patients were approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (no. 2013_06_25).

Instruments

Both patients and healthy controls were administered STAI-Y – a 40-item, Likert-scaled, self-report questionnaire assessing both state- (STAI-Y1) and trait-anxiety (STAI-Y2)[17] – and the Beck Depression Inventory (BDI)[24] – a 21-item, Likert-scaled, self-report questionnaire assessing cognitive–affective (BDI-CA) and somatic performance (BDI-SP) facets of depression.

Patients were further assessed for cognition via the cognitive section of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS),[25] a performance-based battery (score range 0–136) including 5 subscales assessing language (ECAS-L, range 0–28); fluency (ECAS-F, range 0–24); executive functioning (ECAS-EF, range 0–48); memory (ECAS-M, range 0–24); and visuospatial abilities (ECAS-VS, range 0–12); as well as for behaviour via the Frontal Behavioural Inventory (FBI)[26] – a 24-item, Likert-scaled, caregiver-reported questionnaire assessing 'negative' (FBI-A) and 'positive' (FBI-B) behavioural dysfunction of a dysexecutive nature.

With regard to motor status, disease severity was assessed via the ALS Functional Rating Scale Revised (ALSFRS-R),[27] progression rate (ΔFS) was computed according to Kimura et al's[28] formula and disease staging was retrieved via King's staging system.[29]

Procedure

Within the clinical assessment session, patients were first assessed at our Institution for their motor functional status by a neurologist using ALSFRS-R, and subsequently assessed using ECAS for cognition by a psychologist with expertise in neuropsychology. Patients then completed STAI-Y and BDI so that their self-reported psychological status could be evaluated. During patients' cognitive/psychological evaluation or at a separate juncture, a psychologist administered FBI to patients' caregivers to enquire about behavioural changes. The multidimensional assessment of patients' status could be subdivided into two or more sessions in the event of fatigue or distress.

Statistics

Prevalence of anxiety

The prevalence of clinically significant state- and trait-anxiety in both cohorts was determined by applying age-stratified, Italian cut-offs to *t*-scores on STAI-Y1 and -Y2, respectively.[30]

Determinants of anxiety

Because STAI-Y scores proved to be distributed normally (skewness and kurtosis values $< |1|$ and $|3|$, respectively[31] (STAI-Y1: skewness 0.54, kurtosis −0.13; STAI-Y2: skewness 0.45, kurtosis −0.03)), the correlates of trait- and state-anxiety levels were explored via two linear models separately addressing STAI-Y1 and -Y2 scores as the outcomes and, as predictors, motor (i.e. disease duration in months, ALSFRS-R scores and ΔFS values), cognitive (i.e. ECAS-L/-EF/-F/-M and -VS scores), behavioural (i.e. FBI-A and -B scores) and depression (i.e. BDI-CA and -SP scores) measures. Within these models, age, education and gender were entered as covariates.

Similarly, two separate logistic models encompassing the same set of predictors and covariates were run on a below- versus above-cut-off score on STAI-Y1 and -Y2, in order to examine the determinants of clinically significant state- and trait-anxiety, respectively.

Within all models, collinearity was diagnosed in the presence of both a variance inflation factor (VIF) >10 and a tolerance index <0.10;[32] a Bonferroni-adjusted significance threshold was addressed when selecting significant predictors (i.e. $\alpha_{adjusted} = 0.05$/numbers of target predictors (i.e. excluding covariates).

Between-group comparisons

Finally, in order to determine whether the prevalence of clinically significant state- and trait-anxiety differed between ALS patients and healthy controls, two separate logistic models were run by addressing group membership as the predictor and a below- versus above-cut-off score on STAI-Y1 and -Y2, respectively. Age, education and gender were entered as covariates within this mode, because the two groups were unmatched for these variables (age: $t(744) = -7.78$, $p < 0.001$; education: $t(744) = 6.15$, $p < 0.001$; gender: $\chi^2(1) = 32.42$, $p < 0.001$).

Analyses were run using jamovi 2.3 (the jamovi project, Sydney, Australia; https://www.jamovi.org/). Missing data were excluded listwise within the regression models.

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Table 1 Participants' background and clinical measures

Variables	ALS	HCs	*p*	Cohen's *d*
N	433	313	–	–
Age, years	63.4 ± 11.2 (20–88)	57.1 ± 10.8 (24–86)	<0.001[a]	–
Gender (male/female)	267/166	127/186	<0.001[b]	–
Education, years	11.8 ± 4.2 (5–24)	13.8 ± 4.5 (5–24)	<0.001[a]	–
Disease duration, months	18.6 ± 21.1 (1–264)	–	–	–
ALSFRS-R	38.7 ± 6.6 (4–48)	–	–	–
NIV, %	3.5	–	–	–
PEG, %	0.2	–	–	–
ΔFS	0.8 ± 0.9 (0–6)	–	–	–
King's, %				
Stage 1/2/3/4	39.6/32.4/21.6/6.4	–	–	–
MoCA	–	26.9 ± 2.2 (18–30)	–	–
ECAS				
Total	100.7 ± 17.5 (34–129)	–	–	–
Impaired, %	31.2	–	–	–
ALS-specific	74.5 ± 14.4 (22–97)	–	–	–
Impaired, %	30	–	–	–
ALS-non-specific	26.2 ± 4.7 (9–34)	–	–	–
Impaired, %	21.5	–	–	–
Language	23.8 ± 3.7 (10–28)	–	–	–
Impaired, %	20.3	–	–	–
Fluency	16.6 ± 5.4 (0–24)	–	–	–
Impaired, %	19.4	–	–	–
Executive	34 ± 7.6 (9–48)	–	–	–
Impaired, %	21.5	–	–	–
Memory	14.8 ± 4.3 (1–22)	–	–	–
Impaired, %	19.2	–	–	–
Visuospatial	11.4 ± 1.1 (6–12)	–	–	–
Impaired, %	7.2	–	–	–
FBI				
Total	2.9 ± 3.6 (0–21)	–	–	–
A	1.9 ± 2.6 (0–15)	–	–	–
B	1 ± 1.5 (0–12)	–	–	–
STAI-Y1	51.7 ± 10.4 (23–87)	41.9 ± 7.3 (22–70)	<0.001[a]	−1.06
Above cut-off, %	18.2	1.6	<0.001[b]	–
STAI-Y2	49.7 ± 9.6 (20–80)	45.6 ± 8.7 (26–75)	<0.001[a]	−0.44
Above cut-off, %	13.9	7	0.003[b]	–
BDI				
Total	13.3 ± 8.4 (0–58)	6.5 ± 5.8 (0–34)	<0.001[c]	−0.91
Cognitive–affective	6.2 ± 5.3 (0–41)	3.3 ± 3.9 (0–22)	<0.001[c]	−0.59
Somatic performance	7.1 ± 4.1 (0–22)	3.2 ± 2.7 (0–14)	<0.001[a]	−1.10
BDI classification, %			<0.001[b]	–
No depression	36.4	77.6	–	–
Mild depression	35.7	16.3	–	–
Moderate depression	23.5	5.4	–	–
Severe depression	4.5	0.6	–	–

ALS, amyotrophic lateral sclerosis; HCs, healthy controls; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; ΔFS, progression rate; King's, King's College Staging System; MoCA, Montreal Cognitive Assessment; ECAS, Edinburgh Cognitive and Behavioural ALS Screen; FBI, Frontal Behavioural Inventory (A, negative subscale of the FBI; B, positive subscale of the FBI); STAI-Y1, State and Trait Anxiety Inventory Form Y – State-Anxiety; STAI-Y2, State and Trait Anxiety Inventory Form Y – Trait-Anxiety; BDI, Beck Depression Inventory. a.-statistic. b. χ^2-statistic. c. Mann–Whitney *U*-statistic. Continuous variables are reported as *M* ± s.d.; values within parentheses are empirical range; categorical variables are reported as either percentages or frequencies.

Results

Prevalence of anxiety

Table 1 summarises participants' background and clinical features. The prevalence of clinically significant state-anxiety, as indicated by a STAI-Y1 score above cut-off, was 18.2% (79 of 433 patients), whereas that of trait-anxiety was 13.9% (60 of 433 patients). Moreover, patients exhibited higher levels of anxiety and depression than healthy controls, as reflected in continuous STAI-Y and BDI scores and clinical classification.

Determinants of anxiety

Tables 2 and 3 report the full results of linear and logistic models, respectively – which were run on $N = 330$ patients following the removal of missing data. No collinearity was recorded for any of the predictors of each model (VIF $\leq$ 2.72, tolerance index $\geq$ 0.37).

The linear model for STAI-Y1 scores explained 26.5% of variance ($F(15, 314) = 7.54$, $p < 0.001$), with only BDI-CA positively predicting these at $\alpha_{adjusted} = 0.004$ ($\beta = 0.44$, $t(314) = 7.04$, $p < 0.001$, $\eta^2 = 0.12$; Fig. 1). No other predictors indicated significance except for a marginally significant positive effect of ALSFRS-R scores ($\beta = 0.21$, $t(314) = 2.78$, $p = 0.006$, $\eta^2 = 0.02$). Analogous findings were derived from the logistic model on STAI-Y1 – with a higher score on BDI-CA predicting, at $\alpha_{adjusted} = 0.004$, a higher probability of a score above cut-off on this subscale (odds ratio 1.19, 95% CI [1.11, 1.28], $z = 4.71$, $p < 0.001$; Fig. 1).

The second linear model, addressing STAI-Y2, accounted for 45.4% of variance of the outcome ($F(15, 314) = 17.44$, $p < 0.001$), with BDI-CA and -SP as the only positive predictors at $\alpha_{adjusted} = 0.004$ (BDI-CA: $\beta = 0.55$, $t(314) = 10.11$, $p < 0.001$, $\eta^2 = 0.18$; BDI-SP: $\beta = 0.17$, $t(314) = 3.05$, $p = 0.003$, $\eta^2 = 0.02$). Similarly, within the logistic model addressing this STAI-Y subscale,

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Table 2 Effects of motor, cognitive, behavioural and depression measures on STAI-Y1 and STAI-Y2 as shown by multiple linear regression models

Outcome	Predictors	*b*	95% CI	*t*	*p*
STAI-Y1	Age	−0.03	[−0.13, 0.07]	−0.67	0.506
	Education	0.13	[−0.16, 0.42]	0.88	0.382
	Gender (F versus M)	−0.68	[−2.79, 1.44]	−0.63	0.528
	Disease duration	−0	[0.07, 0.07]	0.09	0.932
	ALSFRS	0.32	[0.09, 0.55]	2.78	0.006
	ΔFS	0.87	[0.88, 2.61]	0.98	0.328
	ECAS-L	0.15	[0.21, 0.51]	0.83	0.407
	ECAS-F	−0.19	[0.43, 0.06]	1.50	0.134
	ECAS-EF	0.02	[0.19, 0.22]	0.18	0.855
	ECAS-M	−0.18	[0.45, 0.10]	1.26	0.207
	ECAS-VS	−0.20	[1.18, 0.79]	0.39	0.694
	FBI-A	0.07	[0.40, 0.55]	0.30	0.766
	FBI-B	−0.12	[0.86, 0.62]	0.32	0.749
	BDI-CA	0.82	[0.59, 1.04]	7.04	<0.001*
	BDI-SP	0.34	[0.03, 0.65]	2.17	0.031
STAI-Y2	Age	0.01	[−0.07, 0.09]	0.35	0.730
	Education	0.01	[−0.22, 0.25]	0.11	0.914
	Gender (F versus M)	1.60	[−0.09, 3.29]	1.86	0.064
	Disease duration	0.02	[0.03, 0.08]	0.74	0.462
	ALSFRS	0.08	[0.10, 0.26]	0.86	0.391
	ΔFS	0.08	[1.31, 1.48]	0.11	0.909
	ECAS-L	−0.02	[0.31, 0.26]	−0.15	0.877
	ECAS-F	0.04	[0.16, 0.23]	0.40	0.688
	ECAS-EF	0.02	[0.15, 0.18]	0.18	0.854
	ECAS-M	0.04	[0.18, 0.26]	0.34	0.734
	ECAS-VS	−0.27	[1.06, 0.52]	−0.67	0.502
	FBI-A	−0.07	[0.45, 0.31]	−0.40	0.705
	FBI-B	0.54	[0.05, 1.13]	1.81	0.071
	BDI-CA	0.94	[0.75, 1.12]	10.11	<0.001*
	BDI-SP	0.38	[0.14, 0.63]	3.05	0.003*

STAI-Y1, State and Trait Anxiety Inventory Form Y – State-Anxiety; STAI-Y2, State and Trait Anxiety Inventory Form Y – Trait-Anxiety; ALSFRS-R, ALS Functional Rating Scale-Revised; ΔFS, progression rate; ECAS, Edinburgh Cognitive and Behavioural ALS Screen (L, language; F, fluency; EF, executive functioning; M, memory; VS, visuospatial); FBI, Frontal Behavioural Inventory (A, negative subscale of the FBI; B, positive subscale of the FBI); BDI, Beck Depression Inventory (CA, Cognitive–Affective; SP, Somatic Performance). Age, education and gender were entered as covariates within these models. *Significant coefficient at $\alpha_{adjusted} = 0.004$.

only BDI-CA proved to be a positive predictor of clinically significant trait-anxiety at $\alpha_{adjusted} = 0.004$ (odds ratio 1.17, 95% CI [1.08, 1.28], $z = 3.84$, $p < 0.001$), with a marginally significant effect being found for BDI-SP (odds ratio 1.17, 95% CI [1.04, 1.32], $z = 2.59$, $p = 0.009$).

Between-group comparisons

Finally, net of age, education and gender, the probability of an abnormal score on both STAI-Y1 (odds ratio 12.80, 95% CI [5.52, 37.34], $z = 5.34$, $p < 0.001$) and STAI-Y2 (odds ratio 2.59, 95% CI [1.51, 4.59], $z = 3.38$, $p < 0.001$) was higher for ALS patients (STAI-Y1: $M = 0.18$, s.e. = 0.02; STAI-Y2: $M = 0.14$, s.e. = 0.02) when compared with healthy controls (STAI-Y1: $M = 0.02$, s.e. = 0.01; STAI-Y2: $M = 0.06$, s.e. = 0.01).

Discussion

This study provides clinicians and researchers with generalisable information on the prevalence and clinical correlates of state- and trait-anxiety in ALS from a retrospective cohort of non-demented patients. To the best of the authors' knowledge, this is the largest report on the topic that employed a gold-standard, second-level questionnaire (i.e. STAI-Y) as the outcome measure, providing a sufficient degree of external validity to the current findings while also taking into account the crude prevalence estimate of ALS in the country where the study took place (Italy), which corresponds to 10.54 per 100 000 population (as evidenced by one of the largest epidemiological studies of ALS in Italy to date).[33]

Clinically significant state- and trait-anxiety levels (as assessed by STAI-Y1 and -Y2, respectively) proved not to be a ubiquitous finding in this population (≈18 and ≈14%, respectively). Such a finding substantially aligns with a previous report on a relatively large sample ($N = 159$),[8] in which 19% of patients met the clinical criteria for anxiety-spectrum disorders; and with two studies on $N = 631$[12] and 249[9] patients, respectively, completing a screening questionnaire – the Hospital Anxiety and Depression Scale,[34] with both reporting a 14% prevalence of clinically relevant anxiety. Of relevance, the current report indicates that the rate of clinically relevant anxiety levels is higher in ALS patients than in healthy controls.[5]

This study also sheds further light on the determinants of anxiety in ALS patients, showing that, in this population, such a psychopathological feature is solely driven by depressive symptoms and does not relate to cognitive and/or behavioural features. Although the close interplay between anxiety and depression is widely acknowledged and merely reflects the 'physiological' overlap between these two psychopathological clusters,[35] the present report thus aligns with those having previously forwarded the hypothesis of anxiety not falling within the spectrum of frontotemporal disorders in this population[1] – by, at variance, hinting at the fact that a psychogenic/reactive aetiology underlies this clinical manifestation. This complies with the finding of BDI-CA (assessing emotional and thinking pattern-related facets of depression) being the sole, systematic predictor of STAI-Y scores and classifications – at variance with BDI-SP (assessing neurovegetative components of depression), which showed either non-significant or smaller associations with STAI-Y. A further finding indirectly supporting the hypothesis of a psychogenic/reactive aetiology is the fact that a substantial degree of variance in STAI-Y scores was not accounted for by the present models – suggesting that individual, psychological determinants besides those herewith addressed play a non-negligible role in determining the emergence of anxiety.

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Table 3 Effects of motor, cognitive, behavioural and depression measures on abnormal scores on STAI-Y1 and STAI-Y2 as shown by logistic regression models

Outcome	Predictors	*b*	Odds ratio (95% CI)	*z*	*p*
STAI-Y1	Age	0	1.00 [0.97, 1.04]	0.20	0.843
	Education	0.05	1.05 [0.95, 1.16]	0.96	0.339
	Gender (F versus M)	−0.12	0.89 [0.44, 1.77]	−0.33	0.743
	Disease duration	0	1.00 [0.97, 1.02]	0.09	0.933
	ALSFRS	0.11	1.12 [1.02, 1.23]	2.37	0.018
	ΔFS	0.30	1.35 [0.68, 2.44]	0.93	0.354
	ECAS-L	0.07	1.08 [0.96, 1.21]	1.21	0.226
	ECAS-F	−0.05	0.95 [0.88, 1.03]	1.23	0.219
	ECAS-EF	0.04	1.04 [0.97, 1.12]	1.17	0.241
	ECAS-M	−0.06	0.95 [0.86, 1.04]	1.23	0.218
	ECAS-VS	−0.20	0.82 [0.59, 1.17]	1.16	0.246
	FBI-A	0.07	1.07 [0.92, 1.23]	0.88	0.380
	FBI-B	0.09	1.10 [0.86, 1.37]	0.80	0.427
	BDI-CA	0.17	1.19 [1.11, 1.28]	4.71	<0.001*
	BDI-SP	0.11	1.12 [1.01, 1.24]	2.18	0.029
STAI-Y2	Age	0	1.00 [0.96, 1.04]	0.07	0.942
	Education	0	1.00 [0.89, 1.13]	0.03	0.980
	Gender (F versus M)	0.92	2.50 [1.11, 5.79]	2.19	0.029
	Disease duration	0.01	1.02 [1.00, 1.04]	1.25	0.211
	ALSFRS	−0.01	1.00 [0.90, 1.09]	0.18	0.859
	ΔFS	−0.04	0.96 [0.41, 1.97]	0.10	0.917
	ECAS-L	−0.01	0.99 [0.86, 1.14]	0.18	0.816
	ECAS-F	0.09	1.09 [0.98, 1.22]	1.56	0.118
	ECAS-EF	−0.05	0.95 [0.87, 1.04]	1.18	0.239
	ECAS-M	−0.01	0.99 [0.89, 1.11]	0.14	0.893
	ECAS-VS	0.03	1.03 [0.67, 1.68]	0.14	0.886
	FBI-A	0.07	1.08 [0.90, 1.28]	0.85	0.398
	FBI-B	0.11	1.12 [0.83, 1.46]	0.80	0.425
	BDI-CA	0.16	1.17 [1.08, 1.28]	3.84	<0.001*
	BDI-SP	0.15	1.17 [1.04, 1.32]	2.59	0.009

STAI-Y1, State and Trait Anxiety Inventory Form Y – State-Anxiety; STAI-Y2, State and Trait Anxiety Inventory Form Y – Trait-Anxiety; ALSFRS-R, ALS Functional Rating Scale-Revised; ΔFS, progression rate; ECAS, Edinburgh Cognitive and Behavioural ALS Screen (L, language; F, fluency; EF, executive functioning; M, memory; VS, visuospatial); FBI, Frontal Behavioural Inventory (A, negative subscale of the FBI; B, positive subscale of the FBI); BDI, Beck Depression Inventory (CA, Cognitive–Affective; SP, Somatic Performance). Age, education and gender were entered as covariates within these models. *Significant coefficient at $\alpha_{adjusted} = 0.004$.

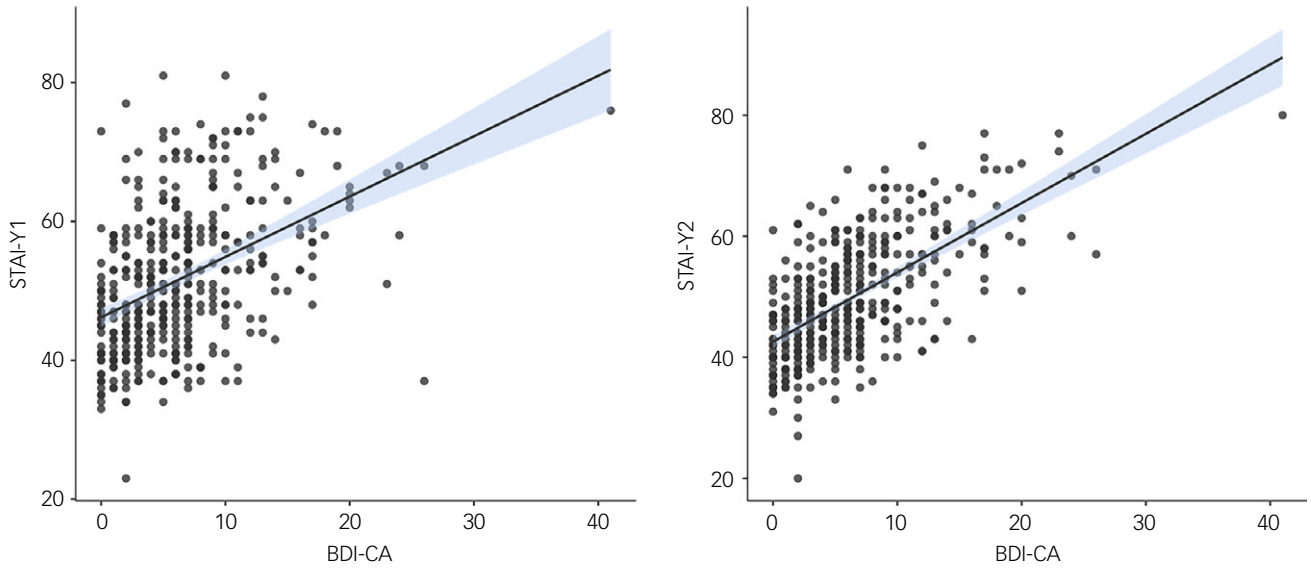

Fig. 1 Scatterplots for the association between STAI-Y1 (left) and STAI-Y2 (right) scores and BDI-CA. STAI-Y1, State and Trait Anxiety Inventory Form Y – State-Anxiety; STAI-Y2, State and Trait Anxiety Inventory Form Y – Trait-Anxiety. BDI-CA, Beck Depression Inventory Cognitive–Affective. The regression line is depicted along with its s.e. area.

Among these putative variables, coping strategies towards the challenges faced when adjusting to the disease have been shown to significantly contribute to ALS patients' psychological status.[36]

Moreover, this investigation did not report substantial associations between STAI-Y scores and motor-functional outcomes (i.e. disease duration, severity and progression rate). With regard to disease severity, this report is in agreement with previous investigations that likewise failed to link such a facet of motor status to anxiety levels in ALS.[9,12] At the same time, the marginally significant positive association between ALSFRS-R and

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STAI-Y1 scores detected in the present study deserves a potential explanation. Such a counterintuitive finding – enhanced motor status relating to higher levels of state-anxiety – might be accounted for by the fact that patients at the earlier stages of the disease (i.e. with high ALSFRS-R scores) are still within a phase of 'emotional adjustment'.[37] This hypothesis appears to be supported by a previous study showing that, in ALS patients, levels of psychological distress are higher during the diagnostic phase and decrease thereafter,[14] as well as by a recent longitudinal investigation showing that patients' anxiety levels decrease soon after diagnosis.[12]

The above findings on the underpinnings of anxiety in this population may convey useful information regarding patients' psychological well-being management. Indeed, assuming that patients' anxiety is mostly driven by their depression levels, therapeutic approaches that target both these clusters would be appropriate for improving their well-being. Such a stance appears to be supported by a recent systematic review suggesting that interventions based on cognitive–behavioural and mindfulness might improve patients' quality of life and psychological well-being, by also decreasing anxiety and depression levels.[38] It would thus be advisable that all ALS patients be screened for anxiety and depression using disease-specific scales,[9,34] so that those showing a clinically relevant level of psychological distress could be referred for further psychodiagnostic evaluation and, eventually, for possible psychological interventions tailored to their specific needs.[1] Such a diagnostic work-up appears to be even more relevant in light of the fact that, in the present cohort, the frequency of clinically significant anxiety levels was higher in ALS patients when compared with healthy controls from the general population.

This study is not free from limitations. First, as previously mentioned, no measures of coping strategies have been addressed – with the only psychological predictor taken into account being mood (i.e. BDI). Hence, further studies are needed aimed at replicating the current findings by the inclusion of measures of patients' coping strategies within the context of disease adjustment. Second, depression in this study was measured by BDI, which includes certain items that do not account for motor disabilities. Future investigations should thus consider the employment of ALS-specific scales for depression.[9,31,39] Third, this report did not include study-specific reliability measures for the instruments employed; hence, it cannot be ruled out that discrepancies between the present investigation and previous ones could be attributed, at least to some extent, to the varying degree of measurement error affecting test/questionnaire scores. Finally, this study did not include patients with comorbid FTD – thus not allowing inferences to be to drawn on the prevalence and determinants of anxiety in ALS patients with such a condition. This granted, at least to some extent, however, a greater level of phenotypic homogeneity in the sample – given that ALS patients with comorbid FTD display distinct clinical features when compared with both neuropsychologically unimpaired and cognitively and/or behaviourally impaired ALS patients.[20–22] Future research is needed to explore the prevalence and correlates of anxiety in this specific population.

In conclusion, clinically significant levels of state- and trait-anxiety occurring in ≈18 and ≈14% of non-demented ALS patients, respectively, were mostly driven by cognitive and affective facets of depression, and were independent of motor and cognitive/behavioural features.

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Data availability

Data-sets associated with the present study cannot be made publicly available on ethical–legal grounds but have been stored on an online repository (https://doi.org/10.5281/zenodo.19454469) and can be made available upon reasonable request of interested researchers to the corresponding author, B.P., who will forward a request for a data transfer agreement to the relevant Ethical Committee(s).

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Author contributions

E.N.A.: conceptualisation, analyses, drafting, revision; B.C., G.D.L.: analyses, drafting, revision; S.T., C.G., A.C., E.C., A.M.: data collection, revision; C.M., S.M., A.D., F.V., V.S.: resources, revision; A.D.S., D.M., R.F., S.B.: revision; B.P., N.T.: resources, drafting, revision.

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Declaration of interest

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, and with the Helsinki Declaration of 1975 as revised in 2013. All procedures involving human subjects/patients were approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (no. 2013_06_25).

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