Depression in Amyotrophic Lateral Sclerosis: Screening Using Attention Bias Assessment

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Abstract

Introduction. *Depression is highly prevalent in amyotrophic lateral sclerosis (ALS) [9]. Its detection can be challenging, particularly in advanced disease when many patients develop bulbar dysfunction and upper limb muscle weakness. This necessitates objective methods for diagnosing affective disorders in ALS.*

The study aimed *to evaluate the potential utility of eye-tracking technology for detecting depression in ALS patients using an attention bias assessment.*

Materials and methods. *The study enrolled ALS patients meeting Gold Coast criteria. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). During eye-tracking sessions, patients viewed a screen displaying pairs of faces – one emotional (sad or happy) and one neutral.*

Results. *Data from 33 participants were analyzed. Comparative analysis of mean gaze fixation duration showed that ALS patients with depressive symptoms had significantly longer fixation times on sad faces compared to non-depressed patients. HADS depression scores correlated with mean fixation duration on sad ($r = 0.421$; $p = 0.018$) and neutral ($r = 0.36$; $p = 0.047$) faces. To analyze the interaction of sensitivity and specificity of mean fixation time on sad faces for detecting depressive disorders, ROC analysis was performed. An area under the curve was 0.722 (acceptable value).*

Conclusion. *Eye tracking-based attention bias screening assessment shows potential utility for depression detection in ALS. This method may be particularly valuable in advanced disease when patients become immobilized and lose capacity for verbal communication or questionnaire completion [9].*

Keywords: *amyotrophic lateral sclerosis; motor neuron disease; depression; diagnosis; eye tracking*

Ethics approval. All patients provided their written informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of Bashkir State Medical University, Ufa, Russia (protocol No. 6, June 24, 2024).

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Депрессия при боковом амиотрофическом склерозе: скрининг методом оценки предвзятости внимания

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Аннотация

Введение. *Депрессия широко распространена при боковом амиотрофическом склерозе (БАС). Её выявление может представлять сложности, особенно на развёрнутых стадиях болезни, когда у многих пациентов развиваются бульбарные нарушения, слабость в мышцах рук. В связи с этим целесообразна разработка объективных методов диагностики аффективных нарушений при БАС.*

Цель *работы – оценить потенциальную информативность метода трекинга глаз для выявления депрессии у пациентов с БАС на основе парадигмы предвзятости внимания.*

Материал и методы. *В исследование включались пациенты с БАС по критериям Gold Cost. Для оценки депрессивных жалоб использовалась Госпитальная шкала тревоги и депрессии (HADS). При проведении трекинга глаз пациентам показывали экран, на котором демонстрировали изображения пар лиц, одно из которых было эмоциональным (грустным или радостным), второе – нейтральным.*

Результаты. *Проанализированы данные 33 человек. Сравнительный анализ средней длительности фиксации взора на лицах с различными эмоциями показал, что у пациентов с БАС с симптомами депрессии среднее время фиксации на грустных лицах было значимо более длительным, чем у пациентов без депрессии. Выраженность депрессии по HADS коррелировала со средней длительностью фиксации взора на грустных ($r = 0,421$; $p = 0,018$) и нейтральных ($r = 0,36$; $p = 0,047$) лицах. С целью анализа взаимодействия чувствительности и специфичности среднего времени фиксации на грустном лице для выявления депрессивных нарушений был проведён ROC-анализ. Площадь под кривой составила 0,722 (приемлемое значение).*

Заключение. *Скрининг с использованием трекинга глаз, основанный на парадигме предвзятости внимания, потенциально информативен для выявления депрессии у пациентов с БАС. Использование данной методики будет особенно актуально на развёрнутой стадии болезни, когда пациент обездвижен и не может поддерживать речевой контакт или заполнять бумажные бланки опросников.*

Ключевые слова: *боковой амиотрофический склероз; болезнь двигательного нейрона; депрессия; диагностика; трекинг глаз*

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Introduction

Depressive disorders are highly prevalent among patients with neurological diseases [1]. These disorders may stem from both organic mechanisms and psychogenic factors related to emotional responses to neurological symptoms. Organic mechanisms are associated with the pathogenesis of the underlying disease and include neurotransmitter imbalances, focal lesions in emotion-related brain regions, aseptic inflammatory responses, and neuroendocrine disturbances [2]. Depression significantly reduces patients' quality of life and worsens the prognosis of the underlying disease [3].

Amyotrophic lateral sclerosis (ALS) is a severe neurological disorder causing motor neuron degeneration and progressive

muscle weakness. Current pathogenetic therapies for ALS are limited to a few agents with minimal therapeutic efficacy [4]. The average life expectancy after symptom onset in ALS is 2–3 years, necessitating improved approaches to palliative care as a key component of medical management [5].

Depression develops in up to 75% of ALS patients, complicating care and potentially reducing life expetancy through mechanisms including low treatment adherence. It is assumed that depression in ALS results from emotional stress associated with the progression of motor deficits and the patient's awareness of the poor disease prognosis. There is also evidence that neurodegeneration in ALS extends beyond the motor centers of the nervous system and involves adjacent structures, such as the prefrontal cortex, which may be considered a predisposing factor for depression [6, 7].

In neurological practice, depressive symptoms are primarily identified using various diagnostic scales. The most widely used scales include the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Montgomery–Asberg Depression Rating Scale (MADRS), among others. Completing them typically takes 10–20 minutes, requiring patient cooperation and demanding specific expertise from the clinician [1].

Speech and motor impairments typical for ALS often compromise communication. In such cases, detecting depressive symptoms becomes particularly challenging, prompting the search for alternative depression biomarkers. One approach for depression detection utilizes the phenomenon of attentional bias. Studies have demonstrated that patients with depression exhibit attentional bias toward images of sad facial expressions [8]. This approach has been previously investigated in psychiatric practice [8], but its applicability in ALS remains unexplored.

Aim: To evaluate the potential utility of attention bias assessment using eye tracking for detecting depression in ALS patients.

Materials and methods

The study enrolled ALS patients meeting Gold Coast criteria [9]. Exclusion criteria were chronic eye diseases, other severe neurological disorders, comorbid ALS with frontotemporal dementia, and use of psychotropic medications.

During eye tracking, patients were positioned in a quiet room with constant illumination in front of a computer screen displaying pairs of facial images: one emotional (sad or happy) and one neutral. The experiment included 20 happy/neutral pairs and 20 sad/neutral pairs (featuring the same actor in each pair). Facial images were selected from a database of professional actors displaying various emotions [10]. Each image measured 506 × 650 pixels, with non-informative elements (e.g., earrings) removed by cropping within an elliptical shape of 280 × 360 pixels. Each pair was displayed twice (80 trials total). The sequence began with a 500 ms black screen, followed by a 1000 ms white fixation cross. Image presentation duration was 3500 ms [11].

Eye tracking was performed using the stationary Gazepoint GP3 device at approximately the same time of day. The study began with a standard calibration procedure of the eye tracker, followed by data recording. Patients were informed that different faces would be displayed on the screen and instructed to continuously look at the screen without further clarification. The following parameters were assessed: direction of the first gaze (toward emotional or neutral faces), mean time to first fixation on faces, mean duration of first fixation, number of revisits to different faces, and mean fixation duration.

Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). A physician read aloud the questions and possible responses, and the patient selected an answer either verbally or by head nod. Scores of 0–7 indicated no depression, 8–10 indicated subclinical depression, and 11 or higher indicated clinically significant depression [12]. Patients scoring 11 points or higher were referred for consultation of a psychiatrist.

The severity of neurological deficit was assessed using the ALS Functional Rating Scale-Revised (ALSFRS-R) [13], and disease staging was performed using the King's College system [14]. Cognitive functions were evaluated with the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [15], while asthenia was assessed using the Multidimensional Fatigue Inventory (MFI-20) [16].

Statistical analysis was performed using SPSS Statistics v. 26 software (IBM). Non-parametric statistical methods were applied. Data are presented as median and interquartile range (IQR). Comparative analysis was conducted using the χ^2 test and Mann-Whitney U test. Spearman's correlation analysis was used to identify relationships between parameters. ROC analysis evaluated the diagnostic value of the method. A p-value < 0.05 was considered statistically significant.

Results

Data from 33 ALS patients were analyzed. All patients successfully completed the calibration and eye tracking registration procedure. The main characteristics of the study participants are presented in Table 1. Nine patients (27%) showed signs of clinically significant depression (HADS $\geqslant$ 11) and were diagnosed with a depressive episode through clinical interview.

Comparative analysis revealed that ALS patients with depression had longer mean fixation times on all face types compared to non-depressed ALS patients, which may be explained by the cognitive inhibition characteristic of depression [1, 2]. However, these differences reached statistical significance only for sad facial expressions (Table 2). Figure 1 presents heatmaps illustrating the focus of attention on sad and neutral faces in 2 patients with clinically evident depression and without it. Analysis of other eye-tracking parameters did not reveal significant differences between ALS patients with and without depressive symptoms.

Correlation analysis revealed a significant association between depression severity on the HADS [2] and mean fixation duration

Table 1. Social and demographic characteristics of ALS patients

Parameter	Value
Age, years, Me [Q_1; Q_3]	63.0 [52.0; 67.0]
Sex (male/female), *n* (%)	14 (42.4%)/19 (57.6%)
Disease onsetn (bulbar/spinal), *n* (%)	6 (18.2%)/27 (81.8%)
King's College stage, *n* (%)	
I	1 (3.0%)
II	10 (30.3%)
III	10 (30.3%)
IV	12 (36.4%)
Education (higher/secondary), *n* (%)	11(33.3%)/22(66.7%)
Marital status (married/single), *n* (%)	27(81.8%)/6(18.2%)
HADS depression symptoms, Me [Q_1; Q_3]	7 [3; 11]
HADS anxiety symptoms, Me [Q_1; Q_3]	7 [5; 11]
ALSFRS-R disease severity, Me [Q_1; Q_3]	39 [35.0; 43.5]
ECAS cognitive impairment:	
specific Me [Q_1; Q_3]	63 [51.5; 73.5]
non-specific Me [Q_1; Q_3]	25 [20.5; 28.0]
total score Me [Q_1; Q_3]	86 [76.5; 99.0]

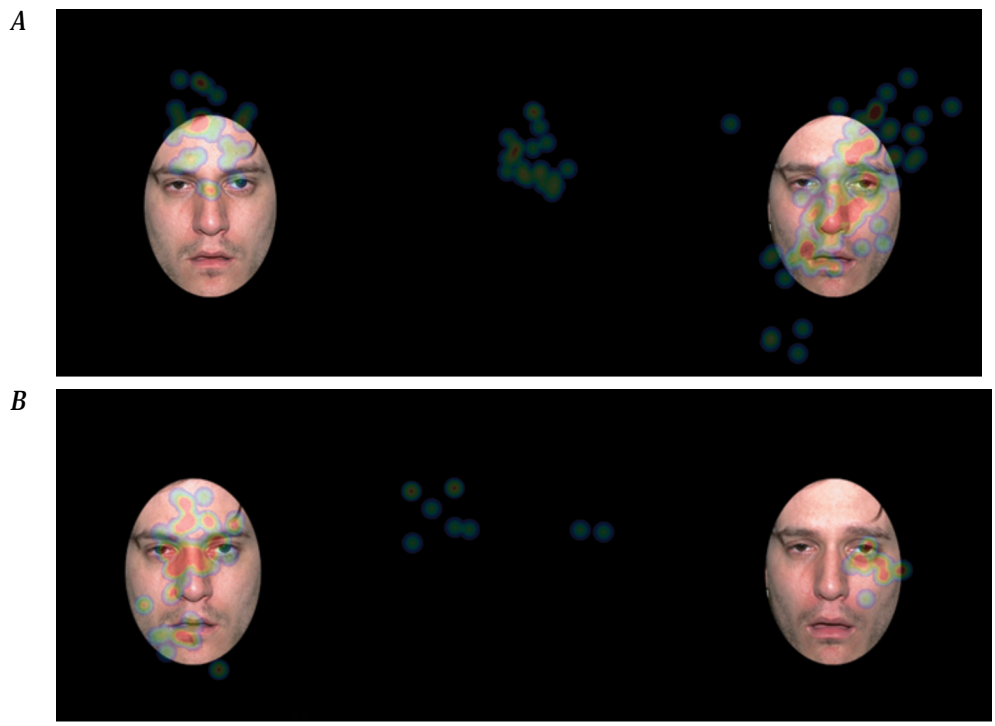

Fig. 1. Heatmaps.
A – patient V. with ALS and clinically significant depression exhibited longer visual fixation on sad faces compared to neutral ones; *B* – patient N. with ALS without depression showed longer fixation on neutral faces than sad ones.

on sad (r = 0.421; p = 0.018) and neutral (r = 0.36; p = 0.047) faces. No significant correlations were found between mean fixation duration on faces with various emotions and HADS anxiety scores, ECAS [3] cognitive decline, MFI-20 asthenia, or ALSFRS-R neurological deficit severity.

To analyze the interaction of sensitivity and specificity of mean fixation time on sad faces for detecting depressive disorders, ROC analysis was performed. The area under the curve (AUC) was 0.72 (95% CI 0.54–0.90 – acceptable value; Fig. 2).

Table 2. Comparative analysis of median gaze fixation duration in patients with and without depressive symptoms, Me [Q_1; Q_3]

Parameter	No depression symptoms (*n* = 26)	Presence of clinically significant depressive symptoms (*n* = 7)	*p*
Mean gaze fixation duration on neutral faces, sec	0.42 [0.08; 1.04]	0.61 [0.32; 1.32]	0.199
Mean gaze fixation duration on happy faces, sec	0.48 [0.05; 0.87]	0.65 [0.32; 1.32]	0.182
Mean gaze fixation duration on sad faces, sec	0.36 [0.12; 0.92]	0.83 [0.44; 1.43]	0.048

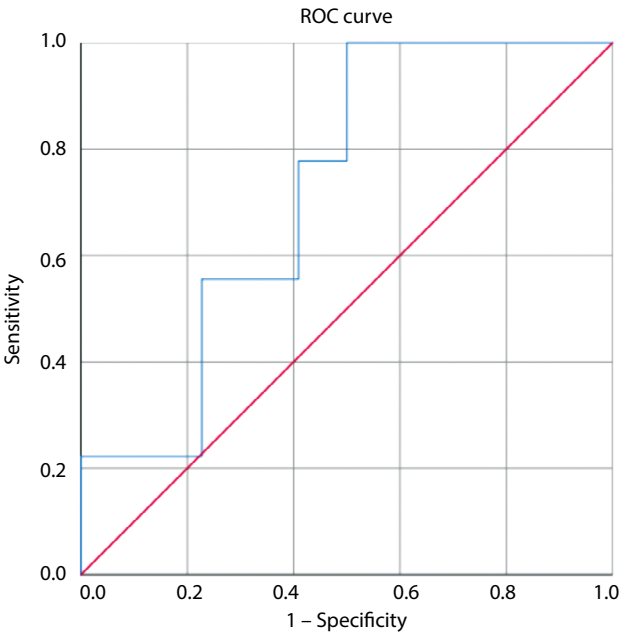

Fig. 2. ROC curve demonstrating the sensitivity and specificity of mean fixation duration on sad faces for detecting depressive symptoms in ALS patients.

The cut-off value for mean fixation duration on sad faces to detect depressive symptoms in ALS patients was determined based on the maximum combined sensitivity and specificity principle. Analysis of the curve coordinates showed that a median average fixation duration on sad face images exceeding 0.37 s indicated depression with 88.8% sensitivity (95% CI 51.75–99.72%) and 50% specificity (95% CI 35.75–82.70%).

Discussion

Analysis of data from a group of 33 ALS patients demonstrated the potential utility of depression symptom screening using eye tracker-based attention bias assessmemt. This approach does not require physician involvement and can be used under the supervision of a trained nurse or technician. No significant correlations between average fixation duration on sad faces and parameters such as severity of asthenia or cognitive impairment suggests that this parameter primarily reflects the presence of depressive disorders. Previous studies have shown that eye-tracking methods can be used in neurological patients with communication deficits, such as post-stroke aphasia [11]. Dysarthria in ALS patients may hinder depression diagnosis through clinical interviews. Paper/electronic questionnaires are also not always feasible due to upper limb muscle weakness progression. Recent studies have revealed that subclinical oculomotor impairments may develop in advanced ALS [17]. However, in this study, the influence of such impairments is unlikely, as the assessment focused on attentional bias rather than visual saccade/antisaccade characteristics.

Digital modalities are increasingly being integrated into the assessment of ALS patients. Most studies in this field focus on evaluating motor deficits. It is hypothesized that technical tools allow for more precise evaluation of neurological impairment severity in ALS and better tracking of disease progression [18]. Significantly fewer studies have explored digital technologies for assessing non-motor manifestations of ALS. Eye-tracking technology is currently successfully employed for alternative communication in advanced ALS, particularly for administering traditional psychometric scales in patients with speech impairment and upper limb paresis [19].

Timely diagnosis of depression remains a critical task in neurological disorders, as depression constitutes an indication for pharmacotherapy. Effective treatment can normalize patients' emotional state, facilitate caregiving, improve compliance, and consequently enhance short-term disease prognosis.

A limitation of this study is the small sample size, the relatively low proportion of patients with symptoms of clinically significant depression, and the absence of patients at the terminal stage of the disease. This research did not perform a detailed evaluation of the diagnostic value of depression screening in ALS using eye tracking.

Future studies should determine the optimal technical parameters of this method and evaluate its sensitivity and specificity compared to standard depression diagnostic tools. The analysis of potential correlations between other parameters and indicators of cognitive and behavioral impairments is also of interest.

Conclusion

Attention bias paradigm-based screening using eye tracking shows potential utility for detecting depression in ALS patients. This method may be particularly valuable in advanced disease when patients become immobilized and lose capacity for verbal communication or questionnaire completion.

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