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Emotion recognition in amyotrophic lateral sclerosis in a dynamic environment

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ABSTRACT

Objective: The aim of our study was to measure the ability of ALS patients to process dynamic facial expressions as compared to a control group of healthy subjects and to correlate this ability in ALS patients with neuropsychological, clinical and neurological measures of the disease.
Methods: Sixty-three ALS patients and 47 healthy controls were recruited. All the ALS patients also underwent i) the Geneva Emotion Recognition Test (GERT) in which ten actors express 14 types of dynamic emotions in brief video clips with audio, ii) the Edimburgh Cognitive and Behavioral ALS Screen (ECAS) test; iii) the ALS Functional Rating Scale Revised (ALSFRS-R) and iv) the Medical Research Council (MRC) for the evaluation of muscle strength. All the healthy subjects enrolled in the study underwent the GERT.
Results: The recognition of irritation and pleasure was significantly different between ALS patients and the control group. The amusement, despair, irritation, joy, sadness and surprise had been falsely recognized differently between the two groups. Specific ALS cognitive impairment was associated with bulbar-onset phenotype (OR = 14,3889; 95%CI = 3,96-52,16). No association was observed between false emotion recognition and cognitive impairment (F(1,60)=,56,971, p=,45,333). The number of categorical errors was significantly higher in the ALS patients than in the control group (27,66 ± 7,28 vs 17,72 ± 5,29; $t = 8723$; $p = 0.001$).
Conclusions: ALS patients show deficits in the dynamic processing of a wide range of emotions. These deficits are not necessarily associated with a decline in higher cognitive functions: this could therefore lead to an underestimation of the phenomenon.

1. Introduction

ALS is a progressive neurodegenerative disease caused by motor neuron loss, for which there is currently no effective treatment. It relentlessly leads to muscle paralysis and death, usually within 3 years from the symptoms onset.

Depression rates remain low in ALS patients [1] and – despite the devastating motor impairment – a significant number of patients with ALS maintains a relatively good quality of life (QoL) [2–4]. This psychosocial adjustment raises important questions about the coping strategies adopted by patients [5].

Although traditionally characterized as a pure motor system disorder, ALS is now recognized to affect multiple systems, with cognitive impairment representing the most frequent non-motor symptom. Most patients with ALS have mild cognitive impairment with subtle executive deficits or behavioral impairment, and approximately 5–15% met the Neary diagnostic criteria for FTD [6,7]; there is evidence that ALS and FTD overlap clinically, radiologically, pathologically, and genetically [8]. In ALS, the most common recognized form of cognitive impairment is frontal dysexecutive syndrome. Some patients with ALS show more subtle frontal executive deficits that involve verbal fluency, attention, and working memory [9,10]. Cognitive and behavioral impairment appear to be more frequent in bulbar-onset patients than in spinal-onset ones [8].

The construct of social cognition represents the set of cognitive processes used to encode, decode, store, retrieve and use information

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about people in social relationships. A key aspect of social cognition is the ability to infer other people's mental states (i.e. beliefs, preferences and intentions), thoughts and feelings; it is referred to as "theory of mind" (ToM). ToM is a critical ability for adapting to our complex social environment [11].

Research is increasingly focusing on deficits in social cognition in various neurodegenerative disorders and on their impact on everyday life. Alterations in the decoding of facial emotions have been observed in Parkinson's disease (PD), with a deficit in the recognition of anger, fear and sadness [12–14]. Widespread impairments in social cognition, in basic emotion processing and recognition (especially of negative emotions) and in higher emotional abilities have been also found in patients with Huntington disease (HD), Alzheimer's disease (AD), Friedreich Ataxia, FTD, and corticobasal syndrome [15–20].

Previous studies directly investigating ToM abilities in ALS patients have provided heterogeneous results. While ALS patients did not show significant deficits on tasks involving humorous cartoons and stories with mental and physical scenarios [21], they showed were impaired on the Judgement of Preference task, showed a trend towards significantly lower Reading the Mind in the Eyes test accuracy scores [22] and were significantly impaired at identifying social faux pas, recognizing emotions and decision-making [23].

Previous studies investigated the pattern of interaction between social cognition impairment and other cognitive functions, and also showed inconsistent results [24,25]. A recent study assessed emotion processing on ALS patients with or without FTD and concluded that patients with FTD-ALS and FTD showed similar, significant impairments in emotional processing; conversely, ALS patients without dementia exhibited preserved emotion processing [26]. These results are in contrast with recent clinical and radiological researches demonstrating the coexistence of emotional dysregulation and difficulty in recognizing facial and vocal expression of emotions (especially negative ones) also in ALS nondemented patients [22,27–29].

A meta-analysis of 15 studies of emotion recognition in ALS concluded that in ALS patients there was a significant relationship between social cognition impairment and executive dysfunction. [30].

Studies of ToM abilities in ALS patients may have yielded conflicting results because of the heterogeneity of the tasks used, the patients' cognitive status or the co-occurrence of depressive symptoms. To date, no studies investigated dynamic emotional recognition in ALS. Hence, the aim of our study was to measure the ability of ALS patients to process dynamic facial expressions and to correlate this ability with neuropsychological, clinical and neurological measures of the disease.

The primary objective of our study was to investigate the ability to decode dynamic emotions in ALS patients and to compare the results to a control group of healthy subjects. Secondary objectives included: i) to investigate any correlation between anomalies in the emotion recognition and executive function decline as tested by the Edinburgh Cognitive and Behavioral ALS Screen (ECAS), ii) to investigate any correlation between the recognized emotions and clinical variables, such as the clinical phenotype at the onset of disease (bulbar-onset versus limb-onset), the disease duration expressed in months, the muscle strength of the upper and lower limbs as tested by the Medical Research Council (MRC) scale, the functional status of the patient as measured by the revised ALS functional rating scale (ALSFRS-R) and the age of the subject.

2. Materials and methods

This is a single center cross-sectional study conducted in the Rare Neuromuscular Disorders Unit of the Umberto I University Hospital, Sapienza University of Rome, Italy. The study was approved by the institutional review board and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before inclusion in the study.

2.1. Inclusion criteria

1) diagnosis of probable or definite ALS [31,32];
2) absence of ALS non-specific cognitive deficit at the ECAS, to exclude other causes of cognitive impairment not related to the motor neuron disease;
3) absence of comprehension deficit at the subitem Understanding of the ECAS.

2.2. Exclusion criteria

1) use of any pharmacological treatment that could interfere with the neuropsychological results;
2) presence of non ALS-related cognitive disorders;
3) inability to independently move the computer mouse due to severe motor deficits;
4) additional presence of other neurological and/or psychiatric disorders or of significant sensorial impairments.

Healthy controls were related to the ALS patients (spouses) enrolled in the present study, and it was established that none of them had a positive history of neurological and/or psychiatric disorders, or of alcohol or drug abuse.

We recorded the following baseline data: age, disease duration, sex, education level. All the ALS patients enrolled in the study also underwent i) GERT, ii) the ECAS; iii) the ALSFRS-R, a validated rating instrument for monitoring the progression of disability in patients with ALS [33], and iv) the MRC, the best known and most commonly used muscle strength grading system for the evaluation of muscle strength [34]. All the healthy subjects enrolled in the study underwent the GERT.

In the ALS group, a comprehensive genetic testing was performed, including sequencing all exons of the SOD1 gene and testing for hexanucleotide intronic repeat expansions (G4C2) in the C9orf72 gene using fuorescent repeat-primed PCR (RP-PCR). Whole Exome NGS Sequencing (WES) was performed, followed by an in silico multigene panel targeting motor neuron disease.

2.3. Geneva emotion recognition test (GERT)

The GERT consists of 14 emotions including six positive ones and covers a larger spectrum of emotional expressions than previous emotion recognition ability (ERA) tests. The stimuli are dynamic and multimodal (short audio-video clips) using nonverbal hints (facial expressions, prosody, and non-existing language).and are portrayed by 10 actors of different ages, adding to the ecological validity of the test [35].

The GERT, performed on a computer, consists of the administration of 83 short audio-video clips in which actors express the emotions by communicating them with face, spoken language and body language.

After each clip, the 14 emotion labels were presented on the screen, and subjects were asked to choose which of the 14 emotions had been expressed by the actor in the clip (forced-choice format). For each clip, responses were recoded into binary variables (0 = incorrect, 1 = correct).

The correctly recognized emotions in the ALS group were compared to the control group. False recognitions (i.e., the emotion misinterpreted by the patient, regardless of the actual emotion presented in the video) in the ALS group versus control group were also compared.

The decoding was further facilitated by grouping emotions into 4 categories, corresponding to four quadrants (Fig. 1). Categorical errors were considered only when the decoding concerned emotions was erroneously attributed to quadrants different from the one in which the emotion was actually contained.

2.4. Edinburgh cognitive and behavioral ALS screen (ECAS)

The ECAS is a multi-domain brief assessment including tests of

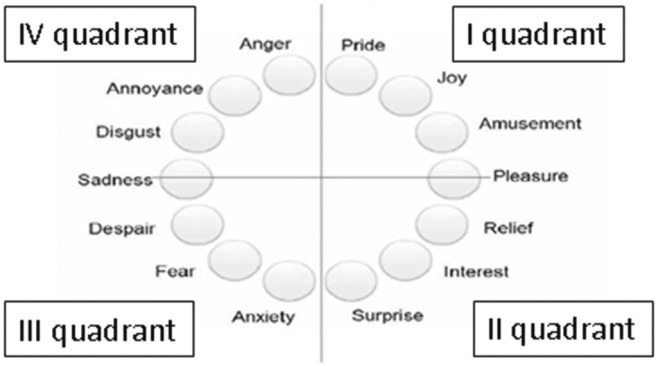

Fig. 1. After each video, 14 emotion words are presented, arranged in a circle that will help to rapidly select the appropriate emotion. These emotions were further divided into quadrants, each of which includes 3,5 different emotions.

executive functions, language, fluency, memory and visuospatial functions. It includes a separate carer/informant interview for behavior abnormalities common in FTD.

The ECAS is an effective method for detecting the range of cognitive impairment present in ALS, showing high sensitivity and specificity in detecting overall impairment (85% sensitivity and 85% specificity) [36,37].

The ECAS has been carefully designed to include tasks that have been shown to be particularly sensitive to changes in ALS. The measures of these domains combine to produce an ALS-Specific score, and those domains that are not normally affected in ALS are combined to produce an ALS Non-specific Score. An ECAS Total Score is also calculated [38].

2.5. Statistical analysis

The data were subjected to statistical analysis with parametric tests (*t*-test, ANOVA, chi square) after evaluation of the distribution normality test. A descriptive and inferential statistical analysis was carried out.

The confidence intervals derived from the study by Schlegel K. et al. were applied [35]. who had identified 55% of the correct answers in multiple samples for a total of 966 healthy subjects. Using this sample, the estimated CI on the population is 0.0460–0.0792.

The percentage of emotions correctly and falsely recognized for each subject affected by the disease and for each control was calculated. The percentages of recognized categorical emotions were also calculated.

Within the ALS group, we measured with the Odds Ratio any correlation between the deficit in the recognition of emotions either for the specific ALS cognitive deficit or for the onset phenotype (limb versus bulbar onset). The cognitive deficit was then related in the same way with the onset phenotype also using the Chi-square test.

We applied ANOVA for evaluating the association between altered emotion recognition and cognitive decline, MRC muscle scale, ALSFRS-R total score.

The association between disease duration expressed in months, specific ALS cognitive disorders and difficulties in the dynamic decoding of emotions was studied with the analysis of the survival curve (Log-Rank test).

Data are expressed as mean ± SD. *P* values <0,05 were considered as statistically significant.

3. Results

Sixty-three ALS patients (mean age 63,65 ± 11,77 years, 43 limb-onset and 20 bulbar-onset) were enrolled in the study and compared to 47 control subjects (mean age 61,22 ± 8,29 years). Genetic testing did not reveal any mutations in the genes strongly associated with ALS. The two groups were well matched for age and level of education (11,46 ± 4,45 years in the ALS group vs 10,88 ± 6,29 years in the control group, $p > 0,05$).

3.1. Recognized emotions

Overall, the percentage of correctly recognized emotion was similar between the two groups (36,47% in ALS patients, range 15,87-60,58%, vs 39,16% in the control group, range 21,18-56,94%).

After a specific evaluation of individual emotions, the recognition of irritation (15,87% in the ALS group versus 25,0% in the control group; $p = 0,003$) and pleasure (37,03% in the ALS group versus 44,44% in the control group; p = 0,04) was significantly different in the two groups (Fig. 2).

3.2. False emotion recognition analysis

The percentage of false emotion recognition was also similar between the two groups (66,00% in ALS patients, range 41,26-95,23%, versus 62,07% in the control group, range 24,3-94,09%).

After a specific evaluation of the individual emotions, what emerged is that amusement (51,85% in the ALS group versus 41,66% in the control group; $p = 0,009$), despair (75,66% in the ALS group versus 46,52% in the control group; $p = 0,001$), irritation (86,24% in the ALS group versus 92,01% in the control group; $p = 0,01$), joy (82,01% in the ALS group versus 68,40% in the control group; $p = 0,001$), pride (40,21% in the ALS group versus 47,91% in the control group; p = 0,04), sadness (95,23% in the ALS group versus 73,26% in the control group; p = 0,001) and surprise (83,06% in the ALS group versus 94,09% in the control group; p = 0,001) were differently falsely recognized in the two groups (Fig. 3).

3.3. Cognitive disorders

Specific ALS cognitive impairment was associated with bulbar-onset phenotype (OR = 14,3889; 95%CI = 3,96-52,16); it was not associated with age (F(1,61) = 22,761, $p = 0,13,672$), disease duration ((F(1,61) = 10,920, p = 0,30,186) or schooling (F(1,61) = 0,35,300, $p = 0,55,481$).

The number of recognition mistakes was related to age (F(1,61) = 11.479; $p = 0,001$). It was not related to the duration of disease (F(1,61) = 2.358; p = 0,131), neither to the MRC muscle scale (F(1,61) = 1868; p = 0,179), neither to the ALSFRS-R total score (F(1,61) = 0,686; p = 0,412), neither to the education level (F(1,61) = 3178; $p = 0,08$). Interestingly, no association was observed between false emotion recognition and cognitive impairment at the ECAS test (F (1,60)=,56,971, p=,45,333) (Fig. 4).

The number of categorical errors was significantly higher in the ALS patients than in the control group (27,66 ± 7,28 vs 16,72 ± 5,29; $t = 8723$; p = 0,0001) (Fig. 5).

Furthermore, in the first months after disease diagnosis, the

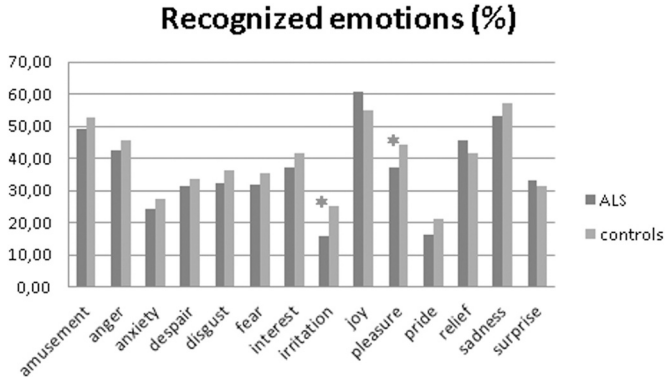

Fig. 2. Correctly recognized emotions in ALS and control groups.

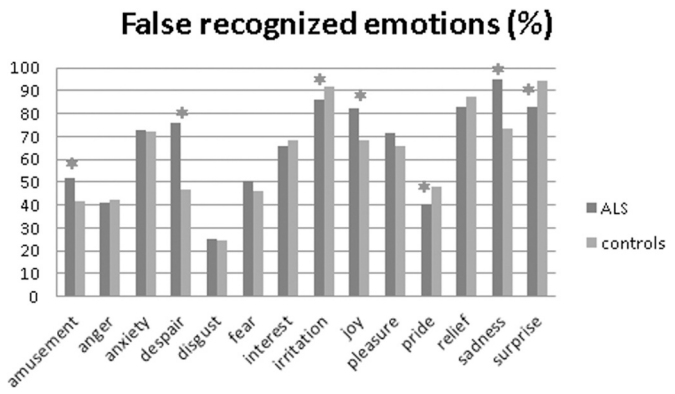

Fig. 3. False recognized emotions in ALS and control groups.

recognition of emotions seems to be independent of the cognitive impairment, while subsequently there is a trend towards the reduction of the recognition of emotions in the cognitively impaired group compared to the cognitively healthy group (Fig. 6).

4. Discussion

Our results – although preliminary due to a relatively small number of patients analyzed – showed that ALS patients have deficits in the dynamic processing of a wide range of emotions; these deficits are not necessarily associated with a decline in higher cognitive functions.

Through social interactions we experience interpersonal emotions that are processed at different levels of the nervous system and condition behavior and cognition, promoting socially appropriate behaviors and discouraging socially inappropriate ones. Impairment of processing social emotions has a significant impact on interpersonal relationships and plays an important role in the manifestation and maintenance of clinical symptoms in several clinical-pathological disorders that affect social behavior [39,40]. Our results showed impairment in social cognition in ALS subjects, regardless of the cognitive status of the patients.

This is in line with previous studies providing evidence that ALS patients show emotional deficits within nonmotor symptoms. Some studies using the classic full displays of the Ekman and Friesen dataset of facial expressions or standardized emotional images in ALS revealed a compromising in anger, sadness and disgust recognition [3,22,26,28,41–44]. Our research is the first study to investigate emotion recognition in ALS using visual and non-verbal auditory hints.

The incorrectly recognized emotions within the ALS group of patients in our study are not only those having a negative value. The different type of test used in our study may justify this discrepancy from previous researches; GERT may be considered a dynamic test which presumably captures ERA more broadly than previous tests, mostly relied on fewer emotions, fewer actors, and less stimuli from only one modality.

Despite the differences from previous findings, it can nevertheless be said with some certainty that in a pathology such as ALS the circuits of emotion recognition are involved; the limbic system and associated regions, such as the prefrontal and sub-cortical cortical regions, are involved in different pathological processes. It is known that subcortical gray-matter structures are involved in the neurodegenerative process of ALS before cognitive impairment becomes evident [45] and neuroimaging studies provided proof about the link between the structures involved in the emotion regulation and motor neuron disease, indicating the presence of early microstructural changes in ventral associative bundles connecting occipital, temporo-limbic and orbitofrontal regions in the right hemisphere [46,47].

Previous studies assessing social cognition in ALS patients according to the cognitive status reported heterogenous results [24–29]; our data showed that the lack of emotion recognition was not associated with executive disorder in the group of patients with ALS. According to our results, the presence of specific ALS cognitive deficit as assessed by the ECAS test does not necessarily imply a difficulty in emotion processing. Executive dysfunction may be present but the subject's social cognition may remain intact. The executive dysfunctions can thus be preparatory to the recognition of emotions, but our study shows that the opposite is not true.

Furthermore, in the first months after disease diagnosis, the recognition of emotions seems to be independent of the cognitive impairment, while subsequently there is a trend towards the reduction of the recognition of emotions in the cognitively impaired group compared to the cognitively healthy group. This is probably because other domains are more easily involved as the disease progresses.

In this study we did not perform a longitudinal assessment of social cognition and cognitive impairment; it would be interesting to evaluate the course of these deficit over time and to study any predictive role of social cognition impairment with regard to motor and non-motor

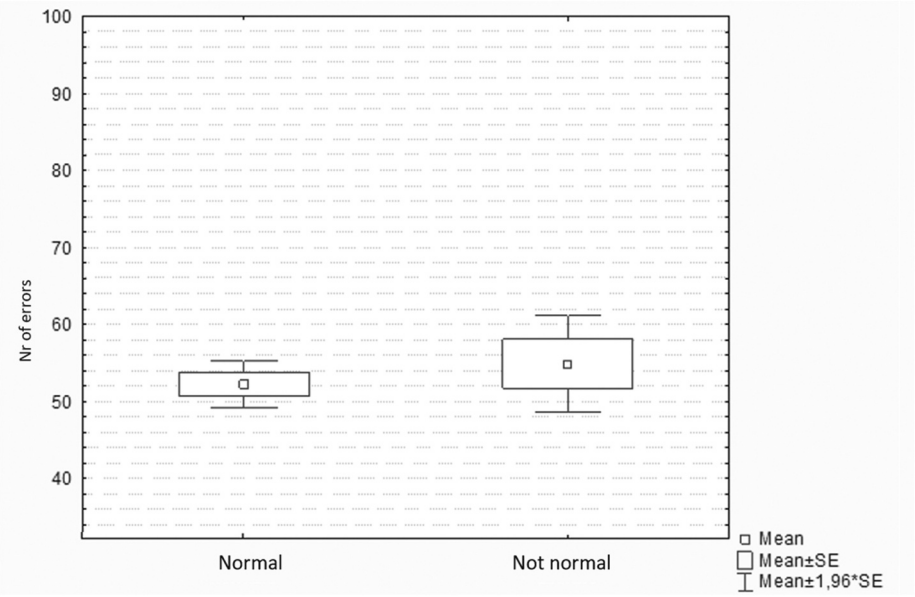

Fig. 4. No association was observed between false emotion recognition and cognitive impairment as assessed by the ECAS test.

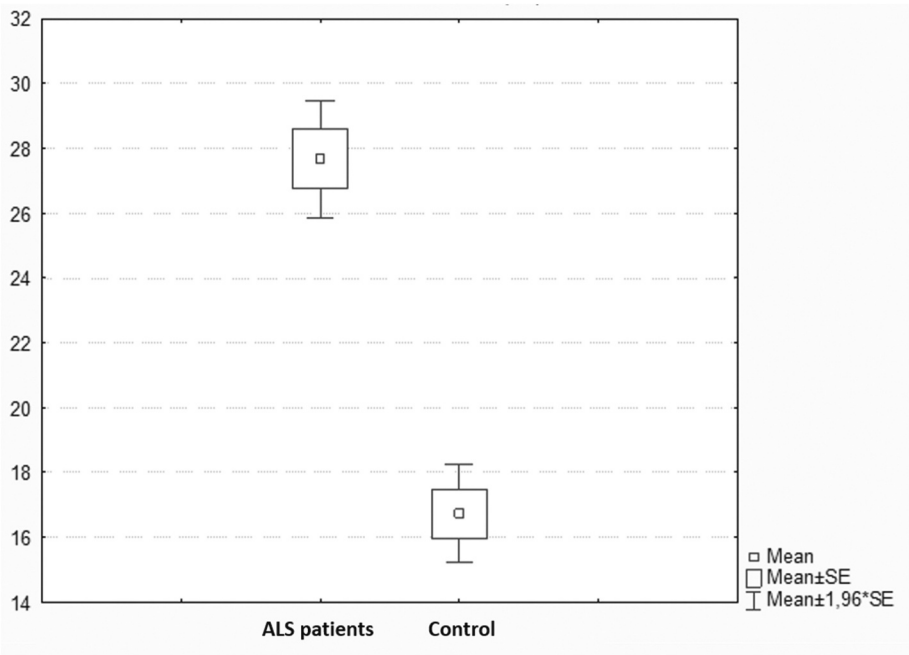

Fig. 5. ALS patients committed a greater number of errors in quadrants different from the macro-categories compared to the control group.

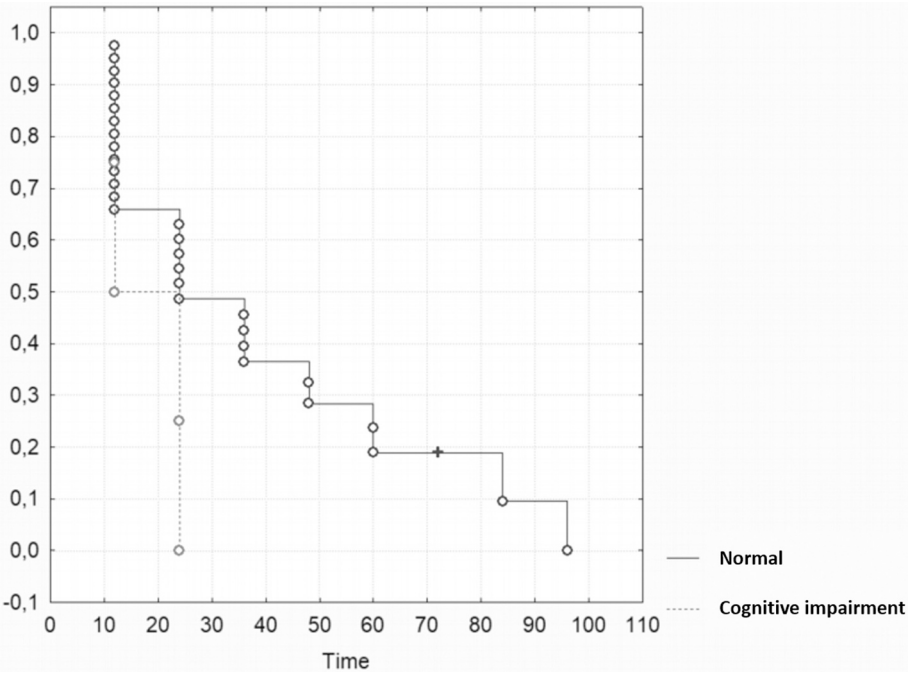

Fig. 6. Percentage of emotions correctly recognized by ALS patients over time, in relation to the presence or absence of ALS-specific deficit at the ECAS test,

manifestations of the disease. Furthermore, investigating quality of life and depression would provide relevant information in the context of social cognition impairment in ALS.

We found no differences between limb-onset and bulbar-onset phenotype in the decoding of emotions; however, a correlation between non-social cognitive deficits and bulbar-onset phenotype has been detected. The bulbar onset phenotype is not only characterized by a greater rate of disease progression but also by a greater impairment of higher cognitive functions, as previously described [48]. The lack of correlation between bulbar-onset and emotion recognition further supports the hypothesis that social cognition and non-social cognition, while clearly sharing some neural networks, must maintain at least part of their own anatomical and functional independence.

Our results showed that the number of recognition mistakes was related to age; this is in line with a previous study that revealed a decline in GERT total score with increasing age [35]. Conversely, it was not related to the duration of disease or to the education level, neither to the MRC muscle scale or to the ALSFRS-R total score, thus indicating that it is not related to the degree of motor deficits and patient's disability.

5. Conclusion

In this study patients with ALS have shown deficits in the dynamic processing of a wider range of emotions than previously detected.

Interestingly, these deficits are not necessarily associated with a decline in higher cognitive functions: this could therefore lead to an underestimation of the phenomenon and a lack of consideration of aspects that should instead be analyzed in the context of ALS. The difficulty in recognizing emotions may justify the unexpected low depression rate and moderately preserved QoL scores reported in ALS patients.

Those difficulties also imply an impairment of social cognition and [49]. The result is a greater difficulty in the doctor-patient relationship and in the relationship with the caregiver, family and friends. Medical and therapeutic choices can also be affected by this progressive cognitive and non-cognitive decline.

The potential clinical implications of social cognition impairment in patients with classic ALS have major importance and should be taken into account when patient care is planned as it may compromise capacity to make decisions about health care or financial circumstances, and the ability to engage competently in end-of-life decisions. Social cognition impairment can also reduce initiative and compliance with interventions such as occupational and physical therapy, or with the awareness of safety issues, such as falls or choking episodes.

These findings should be taken into account when approaching patients both in clinical routine practice, as well as psychological counseling and support, such as the end-of-life decisions.

CRediT authorship contribution statement

Marco Ceccanti: Investigation, Formal analysis, Data curation. **Laura Libonati:** Investigation, Data curation. **Federica Moret:** Methodology, Investigation. **Edoardo D'Andrea:** Investigation, Data curation. **Maria Cristina Gori:** Formal analysis, Conceptualization. **Francesco Saverio Bersani:** Supervision. **Maurizio Inghilleri:** Supervision, Methodology, Conceptualization. **Chiara Cambieri:** Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors report there are no competing interests to declare.

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