Deficits in emotion recognition as markers of frontal behavioral dysfunction in Amyotrophic Lateral Sclerosis

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with prominent motor symptoms. ALS patients may also manifest frontal behavior and cognitive decline, including impairment in facial emotion recognition. We aimed to investigate whether deficits in emotion recognition are associated with frontal behavior symptoms in ALS.

Methods: We enrolled two groups of participants: 1) patients with probable or definite sporadic ALS (n= 21, 11 male/10 female; median age 62 years-old; median disease duration = 3 years) and 2) age and education matched controls (n = 25, 18 male/11 female; median age 61 years-old). The Facial Emotion Recognition Test (FERT) was applied to all participants. Patients underwent the Cambridge Behavior Inventory-Revised (CBI-R) and were classified according to the presence of frontal behavioral symptoms into two groups: ALS with no behavioral symptom (ALSns, n = 9) and ALS with at least one behavioral symptom (ALSbs, n = 12).

Results: Apathy and mood symptoms were the most frequent neuropsychiatric symptoms in ALS. ALS patients performed worse than controls in the recognition of sadness ($p<0.004$). There was no difference between controls and ALSns for all FERT scores, but ALSbs had lower performance than controls in sadness ($p<0.003$).

Conclusion: Emotion recognition deficit may be a marker of frontal behavior in ALS.

Introduction

Besides prominent motor impairment, patients with amyotrophic lateral sclerosis (ALS) manifest cognitive and behavioral symptoms [1, 2]. While executive impairment is the most common cognitive dysfunction in ALS [3], social cognition deficits have also been reported [1, 4], with decline in abilities such as theory of mind and emotional processing [1, 2]. In this latter regard, deficits in recognition of facial emotion expressions are present in ALS [1, 5-10]. ALS patients also exhibit behavioral symptoms, such as apathy, loss of empathy and personality changes [11], even at early stages of the disease and before motor symptoms [12]. Cognitive and behavioral symptoms in ALS show great overlap with the presentation of behavioral variant frontotemporal dementia (bvFTD).

However, it is not clear whether emotion recognition deficits in ALS occur in the absence of behavioral changes, as some of the previous studies in the field did not assess frontal behavioral symptoms with specific tools [6, 9, 13]. It remains open the issue whether emotion recognition deficits can occur independently of frontal behavioral syndrome in ALS. Therefore, the aim of this exploratory study was to investigate the possible association between recognition of facial emotions and frontal behavioral symptoms (e.g., abnormal eating habits, apathy, stereotypical and motor behaviors, and other abnormal behaviors) in ALS. Taking into account that both emotion recognition and behavioral control rely on the integrity of prefrontal cortex, we hypothesized that deficits in the recognition of facial emotional expressions will be associated with frontal symptoms in ALS.

Methods

This study was conducted at the University Hospital of Federal University of Minas Gerais (Belo Horizonte, Brazil). The Local Ethics Committee approved the study, and all participants provided written informed consent.

We included two groups of subjects: 1) a consecutive series of patients diagnosed with probable or definite sporadic ALS (n = 21; 11 male/10 female; median age 62 years-old), according to Awaji's criteria [14] and 2) healthy controls (n = 25; 18 male/11 female; median age 61 years-old), matched with the ALS group for age, sex and education level. The majority of patients (18/21) had spinal presentation. Table 1 presents demographical and clinical data. ALS patients were evaluated with a standardized clinical protocol described elsewhere [15]. We did not include patients using non-invasive ventilation. Patients with severe psychiatric disorder (e.g. past diagnosis of bipolar disorder or schizophrenia) or with neurological disease other than ALS (e.g. past history of stroke, epilepsy) were not included.

Controls were recruited from the community on a voluntary basis. Controls were not included if they presented any of the following criteria: 1) history of neurological or psychiatric disorders; 2) cognitive complaints. We did not include controls who scored below norms on the Mini Mental Status Exam (MMSE) [16].

All participants underwent a brief examination that included the MMSE and the Facial Emotion Recognition Test (FERT) derived from the Social and Emotional Assessment[17], and the Hospital Anxiety and Depression scale (HAD). The HAD provides separate subscales for anxiety and depression. A score above 8 in each subscale is indicative of depression or anxiety [18]. The FERT is composed by a panel of 35 pictures from Ekman's portfolio [17], with seven different emotions (happiness, sadness, fear, disgust, surprise, anger, and neutral) presented five times each, as described elsewhere [17]. Pictures are shown in a screen in a pseudo-randomized order. Importantly, labels of emotions (happiness, sadness, fear, disgust, surprise, anger, and neutral) are presented during the entire task to avoid impaired performance due to memory disorder. Participants pointed or verbally indicated their answers, which were computed by the investigator. ALS patients also underwent Verbal Fluency test (letter S in 1 minute) and the Portuguese version of the Cambridge Behavior Inventory-

Revised (CBI-R) [19]. The CBI-R assesses ten domains including functional abilities and cognitive, behavioral and psychiatric symptoms. Here we considered the four domains that identify bvFTD symptomatology (abnormal eating habits, apathy, stereotypical and motor behaviors, and abnormal challenging behaviors). Any particular behavior is rated on a scale from 0 (no impairment) to 4 (constant occurrence). Patients were then classified in terms of severity of impairment according to CBI-R score on each subscale: 0-25% was considered as mild; 26-50% as moderate; 51-75% as severe and higher than 75% as very severe [20]. We classified ALS patients according to the presence of moderate to very severe bvFTD symptom (Figure 1A). Two subgroups were then established: one subgroup without any bvFTD feature (ALS without behavioral symptoms [ALSns]; n = 9[43%]) and ALS patients with at least one behavioral feature of bvFTD (ALS behavioral symptom [ALSbs], n = 12 [57%]). Of note, two patients (9%) in ALSbs group had impairment in three of these domains, then fulfilling criteria for bvFTD (Figure 1A).

Statistical Analyses

Descriptive statistics were performed to characterize the sample. Normality assumption was investigated with the Kolmogorov-Smirnov test. The statistical assumption of normality was refuted. Accordingly, non-parametric tests were adopted. Group comparisons were performed in two steps. We firstly used Mann-Whitney U test to compare continuous variables between healthy controls and ALS (total group). Secondly, Kruskal-Wallis test was employed for comparing continuous variables among groups (healthy controls, ALSns and ALSbs), and, when pertinent, Mann-Whitney U test was applied to perform two-by-two group comparisons. Chi-Square test was used for comparing categorical variables between groups. After applying Bonferroni correction, the p-value was set at 0.005. Effect size was calculated with Pearson'r. Correlations among variables were performed using Spearman's correlation test with

Bonferroni correction. We used the Statistical Package for Social Sciences (SPSS version 22) for all analyses.

Results

There was no difference among groups (healthy controls, ALSns and ALSbs) regarding sociodemographic variables (age, educational level and sex distribution). ALSns and ALSbs did not differ on disease duration.

Most of ALS exhibited behavioral impairments according to CBI-R. Apathy was the most frequent behavioral disorder (48% of patients), with moderate to very severe intensity in all of them (Figure 1B).

Patients had higher scores than controls on HAD-anxiety and HAD-depression scales (Table 1). Moreover, nine patients (9/21, 43%) scored above cut-off on the anxiety measure, and seven patients (7/21, 33%) scored above cut-off on the depression measure, indicating clinically relevant symptoms. Four ALSbs patients had both depression and apathy and four patients (including one patient with ALS-bvFTD) had both anxiety and apathy. Two ALSbs patients (including one patient with ALS-bvFTD) had depression, anxiety and apathy.

Compared to controls, ALS patients had lower performance on cognitive screening measures, the MMSE ($p<0.02$, $r = 0.35$) (Table 1). Due to motor and/or speech impairment, 11 out 21 patients (52%) of patients did not complete the entire MMSE. Without these patients with incomplete MMSE, there was no difference on the MMSE between the ALS and the control groups.

Patients (total group) did not differ from controls on the total score on the FERT and on all Ekman Faces Test categories, except sadness ($p<0.004$, $r = 0.43$), with patients performing worse than controls (Table 1).

There was no difference between controls and ALSns for all FERT scores, while ALSbs had lower performance than controls in sadness ($p<0.003$, $r = 0.49$). We re-ran comparison

between controls and ALSbs without ALS-bvFTD patients (n =2) and there was a trend ($p<0.02$) for the same difference on the recognition of sadness. There was no difference between ALS subgroups (ALSbs vs ALSns) for all demographical, clinical and cognitive measures, including FERT (Table 1).

No correlation was found between FERT and MMSE in the ALS group. Similarly, there was no correlation between FERT and verbal fluency. There was no statistically significant correlation between FERT (Total Score) and HAD-anxiety and HAD-depression scales.

Discussion

This study investigated the potential association between emotion recognition and behavioral symptoms in ALS. Apathy was the most prominent neuropsychiatric syndromes, which is in line with previous studies [11]. Lack of motivation, changes in eating habits, abnormal behavior, stereotypical and motor behavior are observed in bvFTD and are considered as core diagnostic criteria for this condition [21]. In our sample, 57% of ALS patients had at least one of these domains affected and two patients (9%) had impairment in three of these domains, then fulfilling criteria for bvFTD. This finding is in agreement with previous reports of estimated prevalence of bvFTD in up to 15% ALS patients [2, 4]. These findings support the concept of frontotemporal spectrum disorder in ALS [4].

Depressive symptoms were also frequent as 33% of patients had clinically relevant depressive symptoms according to HAD-depression. Depressive symptoms may be observed in bvFTD [22] and are commonly observed in ALS [23-25]. Here we found that depressive or anxiety symptoms may overlap with apathy and other bvFTD features in ALS. Apathy, challenging behavior and other neuropsychiatric features co-occur in frontotemporal lobar degeneration syndromes [26]. It

is unclear why there is association between depression, anxiety and bvFTD features in ALS. Further research is warranted to clarify this question.

Emotion recognition did correlate neither with MMSE nor with an executive task (verbal fluency). Actually, there was no correlation between FERT and scores on psychiatric scales for anxiety (HAD-A) and depression (HAD-D). Social cognition impairment in ALS was not associated with depressive symptoms in a recent meta-analysis [1]. Moreover, emotion recognition did correlate neither with MMSE nor with an executive task (verbal fluency). These findings suggest that emotion recognition impairment in ALS does not reflect neither mood disorders nor deficits in general cognition/executive functions. This pattern is similar to the one seen in bvFTD, but not in other neurodegenerative diseases such as Alzheimer's disease in which social cognition decline is mediated by executive dysfunction [27].

ALS (total group) performed worse than controls in recognition of sadness. Functional neuroimaging studies in healthy subjects found that the processing of sad faces is related to the activation on amygdala, insula, thalamus and lingual gyrus [28]. Interestingly, these regions are progressively affected during the spread of 43kDa TAR DNA binding protein (TDP-43)-pathology through the clinical stages of ALS [29, 30]. A recent study investigated metabolic correlates of processing emotional faces in ALS patients and reported increased metabolism in the right inferior frontal gyrus and decreased activity in the hippocampi during processing sad faces [5]. In sum, impairment in sadness recognition in ALS suggests pathological involvement of insula, limbic structures and prefrontal regions during the course of the disease, but neuropathological studies are warranted to confirm this hypothesis. Deficits in other emotions such as disgust and surprise have also been reported [1].

Even though it is well established that ALS patients have impairments in emotion recognition [1], some studies in the field did not control for FTD-related behavioral symptoms [6, 9, 13]. Interestingly, after categorizing ALS patients into those with (ALSbs) or without (ALSns)

frontal features, only the subgroup with coexisting behavioral impairment (ALSbs) was impaired in emotion recognition, as previously reported[7]. Taken together, these results suggest that deficits in emotion recognition co-occur with frontal behavioral symptoms in ALS.

The study has some caveats that should be considered. The small sample size may explain some of the lack of associations found and may limit the generalizability of the results. Moreover, we did not perform neuroimaging analyses which would be of value for understanding the neural basis of emotional recognition in ALS. Despite these limits, our results highlight the cognitive and neuropsychiatric heterogeneity of ALS and suggest that emotion recognition deficits may be a marker of frontal behavior in ALS.

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Competing Interests

The authors declare no conflict of interest in the present paper.

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Contributorship Statement

APM collected data, performed statistical analysis and critically reviewed the manuscript for intellectual content. LGRP collected data and critically reviewed the manuscript for intellectual content. PL critically reviewed the manuscript for intellectual content. EM and ALT designed the study and critically reviewed the manuscript for intellectual content. LCS designed the study, performed statistical analysis and drafted the first version of the manuscript.

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Table 1: Demographic, clinical and neuropsychological data for participants

	Controls (n = 25)		ALS (n = 21)				ALS no behavioral symptoms (n = 9)				ALS behavioral (n = 12)			
Characteristic	Median	P25-P75	Median	P25-P75	p value vs controls (M-W test)	r	Median	P25-P75	p value vs controls (M-W test)	r	Median	P25-P75	p value vs controls (M-W test)	r
Age (years)	61	54-65	62	56-66.5	0.740	0.05	64	49-66.5	0.969	0.10	61	(58-66)	0.666	0.07
Schooling (Years of Education)	5	4-11	5	1-3.5	0.787	0.04	6	4-9.5	0.848	0.03	5	(4-10)	0.597	0.09
Sex (Male/Female)	14/11	NA	14/11	NA	0.806 §	NA	5/4	NA	0.982 §	NA	6/6	NA	0.732 §	NA
Disease Duration (years)	NA	NA	3	1-3.5	NA	NA	3	1-3.5	NA	NA	3	(1-4)	NA	NA
HAD Anxiety (HAD-A)	4	2-6	8 *	4-13*	0.002	0.47	6	4-12	0.066	0.32	8 *	5-13*	0.001	0.55
HAD Depression (HAD-D)	2	1-5	6 *	4-10*	0.002	0.46	6	3-11	0.055	0.34	7 *	4-11*	0.003	0.48
MMSE (/30)	26	25-28	24	20-27	0.018	0.35	25	23-27	0.130	0.27	23	18-28	0.030	0.36
Fluency Letter S	NA	NA	7	5-9	NA	NA	7	6-10	NA	NA	6	1-9	NA	NA
FERT - Total score (/35)	23	21-26	21	17-26	0.147	0.21	23	17-28	0.730	0.06	19	17-26	0.066	0.30
FERT - Happiness (/ 5)	5	5-5	5	5-5	0.571	0.08	5	5-5	0.848	0.06	5	5-5	0.761	0.09
FERT - Surprise (/ 5)	4	2-4	3	2-4	0.640	0.07	4	2-5	0.908	0.02	3	2-5	0.597	0.09
FERT - Disgust (/ 5)	3	3-4	4	3-5	0.255	0.17	4	3-5	0.419	0.15	4	3-5	0.378	0.16
FERT - Fear (/ 5)	2	1-3	2	1-3	0.751	0.05	2	1-4	0.565	0.10	2	1-3	1.0	0.01
FERT - Anger (/ 5)	3	3-4	2	1-4	0.037	0.31	3	2-4	0.442	0.14	2	1-3	0.021	0.39
FERT - Sadness (/ 5)	3	3-4	2*	1-3*	0.004	0.43	3	2-4	0.140	0.27	2 *	1-3*	0.003	0.49
FERT - Neutral (/ 5)	4	3-5	3	1-4	0.170	0.20	4	2-5	0.848	0.04	2	1-4	0.077	0.30

Table 1

Legend

ALS = Amyotrophic Lateral Sclerosis; FERT = facial emotion recognition test; HAD = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Exam; M-W: Mann-Whitney; NA = Not applicable; P25 = 25th Percentile; P75 = 75th Percentile.

* $p<0.005$ vs controls (Mann-Whitney test)

§ p value for Chi-square test.

Figure 1

Legend

A. Proportion of patients in the Amyotrophic Lateral Sclerosis (ALS) – Frontotemporal dementia (FTD) spectrum. B. Behavioral symptoms measured by the Cambridge Behavioral Inventory Revised (CBI-R) in patients with ALS.

S&M behavior = Stereotypical and motor abnormal behavior