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ORIGINAL COMMUNICATION

Emotional responding in amyotrophic lateral sclerosis

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Abstract Amyotrophic lateral sclerosis (ALS) is a fatal disease, leaving the patient in a partially or completely deafferented state. In an explorative study, we investigated responses to visual socio-emotional stimuli in ALS patients. Pictures from the International Affective Picture System (IAPS) were verbally judged by 12 moderately affected ALS patients with a spinal onset and a slow progression and 18 age-matched controls, and data were compared with psychophysiological responses. Verbal emotional judgments of patients were more positive than ratings of controls. Regarding arousal, patients neutralized extreme pictures, in that they rated calm pictures as more exciting than controls and exciting pictures as more calm. These changes of emotional processing were unrelated to depression or frontal lobe dysfunction. There were no major differences between patients and controls concerning physiological responses to emotional stimuli. We conclude that emotional responses of ALS patients tend to be altered towards positive valence and towards a more balanced arousal state in early stages of the disease. These findings contradict assumptions of a generally negative impact of the disease on the emotional disposition and may indicate compensatory cognitive or neuroplastic changes.

Key words amyotrophic lateral sclerosis (ALS) · emotions · psychophysiology

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal motoneuron disease which leads to progressive immobility and profound constraints on everyday life. Neurodegeneration in ALS is not restricted to the motoneuronal pathway. Neuropsychological deficits caused by a dysfunction of the frontal network have been shown, including mild cognitive impairment of executive functions such as verbal and nonverbal fluency [1, 20, 21, 38], and reduced working and recognition memory [2, 39, 52] in up to 35 % of non-demented ALS patients [23]. Frontotemporal dementia is found in about 2–5 % of ALS patients [18]. While these neuropsychological deficits have been well described, affection and emotional processing in ALS is poorly understood beyond the general agreement that these patients are specifically positive people. Remarkably, most patients do not develop a depressive disorder despite the severe impact on their lives [25, 43].

Cortical and subcortical degenerative processes in ALS might lead to blunted emotional processing while on the other hand cortical reorganization might compensate for neurodegeneration. Although there have been some studies proposing dysregulation of affective behavior as a result of prefrontal damage in ALS [40–43], there is no conclusive evidence of emotional impairments in ALS. In an earlier study, we demonstrated compensatory activity of visual information processing areas in ALS patients compared with con-

trols in response to emotional words [28]. Unpublished data from our laboratory show altered emotional responses to emotional stimuli of some specific categories (reduced pleasantness and arousal for sportive and erotic visual stimuli) in a group of ALS patients. The present study was conducted to investigate systematically emotional responses in ALS. Verbal judgments and physiological responses were taken as an index of the emotional state [33, 34]. The goal was a better understanding of emotional processing in ALS patients which might also help caregivers in dealing with patients.

Material and methods

Participants

Twelve patients suffering from the sporadic form of ALS participated in the study (10 men and 2 women; mean age 59 years, range 36–69). Only ALS patients with slow progression were included in the study to ensure that first, the patients had had time to adapt to their new life after the diagnosis and second, that the patients were not too advanced in their stage of disease for the exhaustive investigations. Probable (N = 9) or definite ALS (N = 3) was diagnosed according to the revised El Escorial criteria (http://www.wfnals.org/guidelines/1998elescorial/elescorial1998.htm) [14]. None of the patients had a history of other neurological or psychiatric disorders. All patients presented with a spinal onset, and none of the patients exhibited major bulbar symptoms. The mean duration of the disease was 40 ± 26 months (range 12–84), determined by the onset of motor symptoms. Mean clinical severity of ALS measured by the Norris Scale [13] was 75.5 ± 12.6 (range 50–92), and mean manual BMRC muscle score [30] was 90.6 (range 77.5–105.5). All patients were still able to walk; two patients were intermittently ventilated by non-invasive positive pressure ventilation at the time of the study.

Eighteen age-matched healthy volunteers (7 women and 11 men; mean age 54 years, range 35–71) served as controls; none of them had a history of neurological or psychiatric disorder and all were free of CNS affecting medication.

The study was approved by the Ethics Committee of the University of Ulm and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave their written informed consent for the study.

Psychological testing

General psychological testing included Beck's Depression Inventory [6, 24], Mini Mental State Examination [19], and a German version of the Wechsler Memory Scale [36]. Specific neuropsychological testing was focused on frontal lobe functions including verbal fluency (Regensburg Fluency Test) [3], design fluency (5-Point Fluency Test) [50], categorization, planning and concept formation (PC version of the Wisconsin Card Sorting Test) [22, 45], and alertness (Symbol Digit Modalities Test) [37]. Additionally, visual memory (Doors Test) [4] was tested. One patient did not meet inclusion criteria (BDI, two tests of verbal fluency, SDMT; see Table 1) and data of this patient were excluded from further analyses.

Stimuli

In a pilot study, 42 subjects evaluated 90 pictures of persons in social situations selected from the International Affective Picture System (IAPS) [32], with regard to emotional valence, arousal and association of movement (AOM). Pictures were presented for 6 s, and afterwards valence and arousal ratings were obtained for each picture using the Self-Assessment Manikin (SAM) [31]. Motor associations were rated on a visual 9-point scale (1 = no AOM; 9 = high AOM). Based on these data, each picture was assigned to one of three evaluative valence categories (negative, neutral, positive), one of three arousal categories (calm, medium, exciting) and one of two movement association categories (low, high). 104 pictures from the IAPS were used in the main study, including the 90 pictures of the pilot study, and 14 additional pictures that were categorized as described above according to mean standard ratings [32]. Two pseudorandomized (balanced with respect to mean valence, arousal and association of movement) sets of 52 pictures were generated, and either of them was shown to each participant.

Procedure

Each subject participated in two runs, one during which physiological responses were recorded and one during which verbal ratings were obtained. In each run, the pictures were presented via video goggles for 6 s, with an intertrial interval of 14 s. Participants were asked to concentrate on the picture content as a nonactive observer in the displayed situation and to continue visualization during the intertrial interval. Verbal ratings were obtained in the second run of the presentation, following the procedure of the pilot study.

Physiological parameters

Recording procedure of physiological parameters

Startle response [9–11, 16, 33] and heart rate [12, 51] were recorded as an index of valence and galvanic skin response as an index of arousal [12, 34]. All physiological parameters were registered with Beckmann Ag/Ag-Cl electrodes using a Picker EEG-amplifier or, for heart rate, a Siemens® sirecust device (Siemens, Erlangen, Germany). The data were A/D converted, stored on a computer by use of the Neuroscan® software (Neuro Scan Inc., Herndon, VA, USA), and converted into ASCII format. For the startle response and galvanic skin response amplitudes that diverged for more than two standard deviations from the mean of each individual and trials with zero amplitude were discarded.

Startle response

The startle probe was a 50 ms white noise burst of 110 dB with instantaneous rise and was presented via headphones pseudorandomized at 500 ms, 1000 ms or 1500 ms after picture offset. Electromyographic activity (EMG) of the orbicularis oculi muscle as an index for the size of a startle blink reflex was recorded from two electrodes beneath the left eye [8]. The EMG signal was rectified by an external analogous device and bandpass-filtered (16–300 Hz; time constant, 0.01 s). Startle amplitude was determined as the maximum voltage between 30 and 150 ms after probe onset, relative to the average activity of a 200 ms interval before probe onset. Four controls and one patient did not startle and data were excluded.

Galvanic skin response

The galvanic skin response (GSR) was measured with electrodes fixed to the medial thenar and to the dorsum of the hand. The signal was bandpass-filtered from 0.016 to 30 Hz (time constant, 10 s). Galvanic skin response amplitudes were determined as the maximum conductance between 3 and 6 s after picture onset, relative to the average of a 500 ms period before picture onset. Additionally, the latency of the maximum relative to stimulus onset was determined. One ALS patient showed no GSR. The skin responses of another patient and two controls were excluded because of artefacts.

Heart rate (HR)

The heart rate was acquired from electrodes attached to the right arm and the left leg, using a Sirecust® electrocardiogram device (Siemens, Erlangen, Germany). The signal was filtered from 0.26 to 15 Hz (time constant, 0.6 s). Amplitudes were determined relative to the 500 ms period before picture presentation. The 95 % confidence interval for the mean latency of the maximum negative deviation of all subjects was 8 to 11 s after picture onset, and only maxima within this interval were included in the analysis. Data of ten controls and four patients were discarded because of artefacts.

Eye movements

To record eye movements along the horizontal axis, electrodes were placed temporolaterally to each eye. The signal was digitally rectified and bandpass-filtered from 0.016 to 30 Hz (time constant, 10 s). The average eye position during the 1 s period before picture onset was set as baseline. Mean values of the deviation of the position were determined before picture onset (5 s), during picture presentation (6 s) and during the interstimulus interval (9 s).

Statistics

Startle and GSR amplitudes were log-transformed (log [x + 1]), heart rate of each subject was centered to zero. Average pilot study ratings of each picture were used to sort individual verbal judgements and psychophysiological responses. One-way analyses of variance (ANOVAs) assured that there were no significant differences in verbal emotional ratings in healthy controls between the pilot study and the main study.

To estimate the effect of pictorial valence, arousal and AOM on individual verbal and physiological responses, mean responses of each subject and category were subjected to two-way repeated measure ANOVAs with between-subject factor group and within-subject factor valence, arousal or AOM category. Based on previous studies [e. g. 10, 32, 33], startle amplitudes and amplitudes of heart rate responses were tested for valence effects, and amplitudes of galvanic skin response were tested for arousal effects. Response latencies were tested for group effects only.

For differences in neuropsychological scores between patients and controls, one-way ANOVAs were conducted with between subject factor groups. To estimate the relation between frontal lobe dysfunction and verbal judgements in patients, Pearson correlations were calculated between verbal judgements and psychological test scores that differed significantly between patients and controls. A threshold of $p < 0.05$ (two-tailed) was adopted for all statistical inference. Owing to the small number of participants, all tests were conducted in an explorative manner and thresholds were not adjusted for multiple testing.

Results

Psychological testing

A synopsis of the psychological test results in patients and controls including significance levels is given in Table 1. The BDI showed a significantly higher score in the patient group compared with healthy controls

Table 1 Synopsis of psychological test results. Comparison between ALS patients and controls (mean value ± standard deviation; * indicates statistical significance); participants with scores that deviated for more than 2 standard deviations were excluded from further analysis [21]

	ALS patients (N = 12)	controls (N = 18)	F	significance level	exclusion criterion
Age	59.0±9.0	54.4±12.0	F = 1.28	p = 0.267	< 35
school years	12.6±3.4	12.9±2.7	F = 0.11	p = 0.746	
BDI	8.9±4.1	4.9±4.1	F = 6.58	p = 0.016*	> 18
MMSE	28.5±1.1	29.5±0.5	F = 11.70	p = 0.002**	< 23
WST-IQ	103.6±11.8	110.1±9.4	F = 2.66	p = 0.115	< 80
Doors	10.6±2.7	10.6±2.6	F = 0.01	p = 0.937	< 5
verbal fluency					< 5 for more than 2 tests
vf-P	46.7±31.6	54.3±20.4	F = 0.62	p = 0.44	
vf-GR	36.4±35.8	55.6±29.7	F = 2.44	p = 0.13	
vf-an	45.3±31.8	56.4±22.2	F = 1.24	p = 0.275	
vf-sp/fr	51.8±32.3	68.8±16.3	F = 3.56	p = 0.07	
nonverbal fluency					
nvf-c	24.4±6.1	32.4±9.0	F = 5.03	p = 0.026*	< 12
nvf-f	2.1±3.4	1.3±1.6	F = 0.68	p = 0.418	< 9
symbol digit modalities test					
SDMT-c	44.0±10.5	56.2±9.0	F = 11.12	p = 0.002**	< 23
SDMT-f	0.4±0.7	0.27±0.6	F = 10.13	p = 0.717	< 2
Wisconsin card sorting test					
WCST-c	59.5±1.4	59.9±0.2	F = 1.15	p = 0.294	
WCST-f	27.6±16.9	24.0±12.9	F = 0.53	p = 0.474	
WCST-cc	5.9±0.29	5.9±0.24	F = 0.10	p = 0.758	< 5

MMSE Mini Mental State Examination; *BDI* Beck's Depression Inventory; *Doors* Doors test age-scaled score; *WST-IQ* estimated premorbid intelligence; *vf-P* verbal fluency p-words, age-scaled percentile; *vf-G/R* verbal fluency alternating g- and r-words; age-scaled percentile; *vf-an* verbal fluency animals, age-scaled percentile; *vf-sp/fr* verbal fluency alternating semantic categories, age-scaled percentile; *nvf-c/f* non-verbal fluency, correct/errors; *SDMT-c/f* Symbol Digit Modalities Test, correct/errors; *WCST-c/f/cc* Wisconsin Card Sorting Test, correct/errors/completed categories

($F = 6.58$; $p = 0.016$), but only one patient (who was excluded from further analysis) showed signs of moderate depression. The total score of the MMSE was significantly decreased in ALS patients compared with controls ($F = 11.7$; $p = 0.002$), but none of the patients showed signs of dementia according to MMSE criteria. On the verbal fluency task, patients tended to produce fewer words in all subtests, but this effect was not significant. Patients performed significantly worse than controls in non-verbal fluency ($F = 5.60$; $p = 0.026$) and showed significant deficits ($F = 11.1$; $p = 0.002$) in alertness. For visual memory testing, planning and concept formation or premorbid intelligence, no differences were found between patients and controls.

Verbal ratings

A synopsis of the analysis of verbal ratings of the pictures in patients and controls is given in Table 2. In the analysis of verbal ratings, two significant differences between patients and controls became evident. First, there was a main effect of group on verbal valence ratings in all three ANOVAs (factor valence $F = 5.0$ $p = 0.034$; factor arousal $F = 4.6$ $p = 0.041$; factor AOM $F = 4.8$ $p = 0.037$; Fig. 1). Compared with controls, patients rated all stimuli as more positive, regardless of levels of pleasantness, arousal or AOM. Second, there was a significant interaction between group and arousal category in verbal arousal judgements ($F = 3.7$; $p = 0.031$). Calm and neutral stimuli were rated as more arousing by patients, but the more arousing a picture was, the lower was the level of individual arousal of patients compared with controls. The most arousing pictures and particularly those with an erotic component were evaluated as less arousing by patients.

Verbal judgements of AOM did not differ between healthy controls and patients, nor did they show a significant interaction between group and AOM category.

Post-hoc analysis confirmed that the different male/female ratio in the patient and the control groups had no influence on the group effect in emotional evaluation.

Interaction of verbal judgements and neuropsychological dysfunctions

Significantly affected frontal lobe functions in patients were tested for effects on individual mean valence ratings and individual mean within-category arousal judgements (calm, medium, exciting). In the case of arousal judgements, we used within category means because the direction of the difference in arousal judgements of patients and controls depended on the category (patients judged the pictures in the calm category as more exciting and in the exciting categories as more calm than healthy controls).

Neither depression score nor any other psychometric test score (MMSE, SDMT, NVF-C) showed an effect on individual valence or arousal ratings (Pearson correlation, $df = 10$, $r < 0.5$, $p > 0.12$ for all tests).

Physiological parameters

The results of the correlation analysis between verbal ratings and physiological data in patients and controls including significance levels are summarized in Table 3.

Startle

Startle eye blink responses peaked between 30 to 150 ms after the startle probe in both patients and controls, and response amplitudes did not differ between the two groups. There was a significant linear relation between valence category and the startle response amplitude ($F = 6.3$; $p = 0.02$; Fig. 2a) with unpleasant pictures leading to a stronger reflex in patients and controls.

Galvanic skin response

Generally, the galvanic skin response showed two peaks in both groups, one following picture onset and a second after the startle probe. Galvanic skin responses were significantly delayed in patients (latency of the first peak, 5.09 ± 1.34 s) compared with controls (latency, 4.01 ± 1.0 s; $F = 5.2$ $p = 0.031$). The amplitude of the galvanic skin response tended to be higher in patients than

Table 2 Synopsis of category main effects (valence, arousal, association of movement) on individual ratings of main study (valence, arousal) for patients compared to healthy controls (* indicates statistical significance)

	linear main effect		group effect		interaction	
effect of:	F	p	F	p	F	p
valence on valence	276.1	0.001***	5.0	0.034*	0.05	0.95
arousal on valence	241.8	0.001***	4.6	0.041*	0.1	0.872
AOM on valence	256.4	0.001***	4.8	0.037*	0.04	0.84
valence on arousal	23.0	0.001***	0.7	0.413	0.9	0.399
arousal on arousal	29.4	0.001***	0.8	0.367	3.7	0.031*
AOM on arousal	55.6	0.001***	0.8	0.385	1.2	0.274

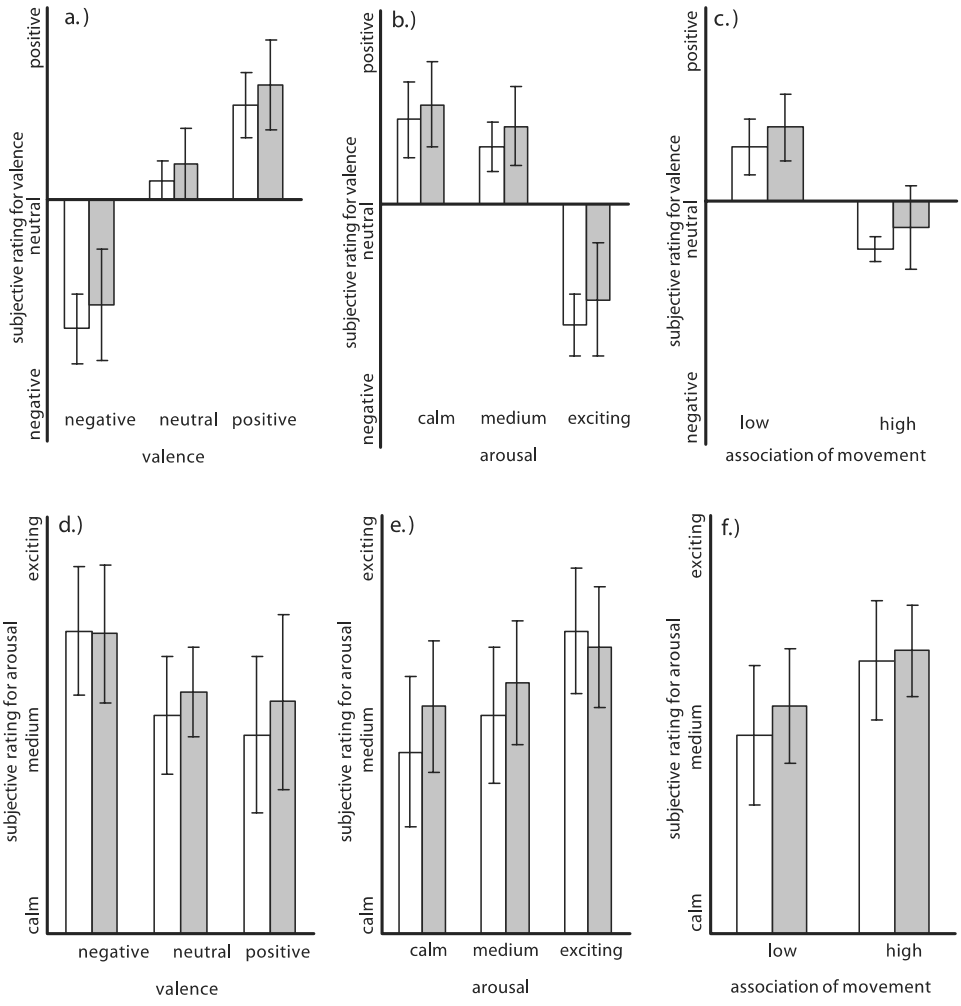

Fig. 1 Subjective ratings of the stimuli for controls (white bars) and patients (grey bars); ratings of valence on the three different emotional dimensions of the slides (**a**) valence, (**b**) arousal and (**c**) associations of movement; arousal ratings for the three different emotional dimensions of the slides (**d**) arousal, (**e**) valence and (**f**) associations of movement; (means and 95% confidential range)

Table 3 Summary of correlations of verbal ratings and physiological results in patients and controls including significance levels

	linear main effect		group effect		interaction	
effect	F	p	F	p	F	p
valence on startle (small initial letter)	6.3	0.02*	0.1	0.756	0.3	0.713
arousal on GSR	4.7	0.041*	0.02	0.892	0.6	0.572
valence on HR change	8.8	0.01*	1.0	0.323	0.7	0.502

in controls, and the level of activity remained higher in patients. Consequently, the second rise in response to the startle probe was less pronounced in patients whereas the two peaks were easily distinguishable in controls. Interestingly, the only patient with late ALS symptoms showed no galvanic skin response (GSR).

For predefined arousal categories, there was neither a linear relation between arousal category and GSR amplitudes nor an interaction between group and arousal category. However, post-hoc analysis revealed that if pictures were assigned to arousal categories based on individual arousal ratings, there was a significant linear relation between arousal category and GSR amplitudes for both patients and controls ($F = 4.7$; $p = 0.040$; Fig. 2b).

Heart rate

Both patients and controls showed a deceleration of 1–2 beats per minute following picture onset. Generally, deceleration was more pronounced and faster in patients (1.3 beats after 9.1 ± 1.5 s) than in controls (0.8 beats after 9.5 ± 1.8 s), but these differences were not statistically

significant. There was a significant linear relation between valence category and peak heart rate deceleration ($F = 8.8$; $p = 0.01$) with a stronger deceleration for unpleasant stimuli than for pleasant ones for both patients and controls (Fig. 2c).

Eye movements

During the presentation of the pictures, all subjects showed more eye movements; the level of activity returned to baseline when the stimulus was turned off. Patients did not differ from controls with respect to their reactions and the level of eye movements was independent of emotional picture content.

Discussion

The present explorative study suggests that, despite their fatal prognosis, ALS patients develop a surprisingly positive and emotionally balanced disposition, at least in the early stage of the disease at least in the patients investigated here. This was indicated by more positive subjective ratings of pleasant, neutral and unpleasant emotional stimuli of ALS patients compared with matched healthy controls. Furthermore, ALS patients seem to be more responsive to calm and neutral pictures and experienced unexciting stimuli as more exciting than controls. Interestingly, exciting pictures were rated as less arousing by patients than by controls but this was not correlated with BDI scores. These findings contradict the general belief that ALS patients are emotionally indifferent or oversensitive, as the circumstances of their life would suggest. It supports the observation of caretakers and medical staff that ALS patients are positive people.

There was no differential effect for the movements associated with the depicted scene of the presented stimuli on individual valence or arousal ratings of patients and controls. This might be explained by the fact that the patients participating in our study were still relatively mobile. We would expect this factor to become more important in patients with a more advanced stage of ALS.

The neuronal networks underlying emotional processing involve various cortical and subcortical regions. The prefrontal lobes play a central role in the integration of responses from these areas [26, 49]. Since dysfunctions of frontal networks have been repeatedly demonstrated in ALS [2, 20, 27, 38, 39], it might be speculated that emotional changes in these patients are associated with frontal dysfunction. However, our data do not support this hypothesis, at least not for the early stages of the disease: The altered rating of emotional stimuli in ALS patients was not correlated with frontal lobe dysfunctions.

Sympathetic and startle activity varied in patients and controls with emotional picture content, as Lang and colleagues have previously shown [35]. There were no statistically significant group differences in physiological reactions, but there were a number of remarkable differential tendencies. The deceleration of the heart rate tended to be faster and more pronounced in patients, and the galvanic skin response was delayed, stronger and more persistent in patients than in controls. The autonomic change may represent an emotional modulation related to coping mechanisms in ALS patients. As a deceleration of the heart rate during pic-

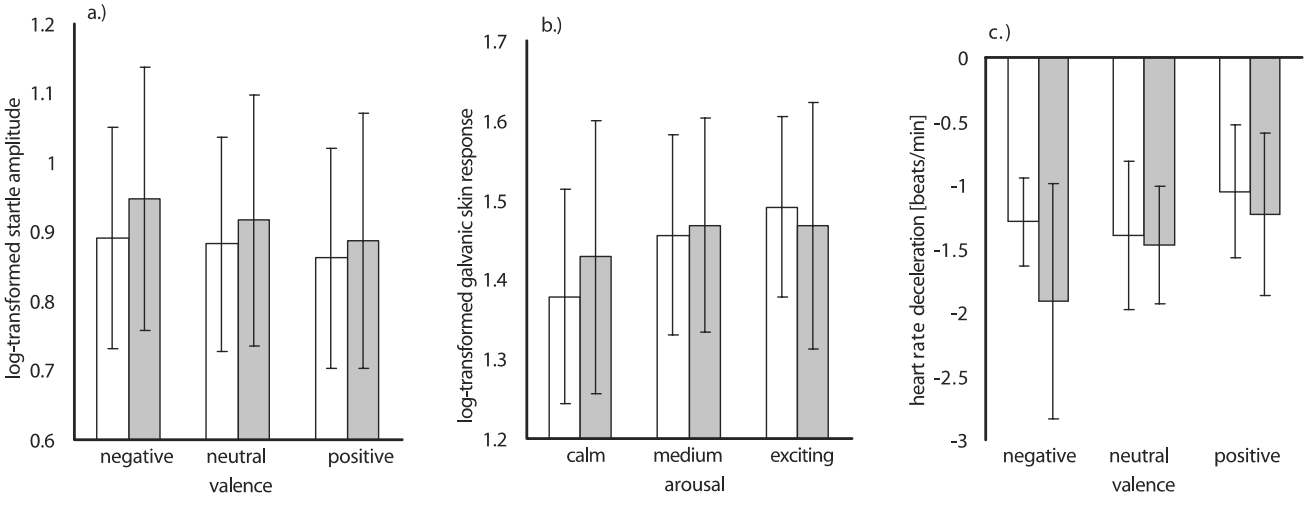

Fig. 2 Physiological responses for controls (white bars) and patients (grey bars); (**a**) valence and the amplitude of startle responses for controls (N = 14) and patients (N = 10); (**b**) arousal and amplitude of galvanic skin response within a period of 3 to 7 s after picture onset for controls (N = 16) and patients (N = 11); (**c**) valence and amplitudes of heart rate deceleration within 7 to 11 s after picture presentation for healthy controls (N = 8) and patients (N = 7). All mean values and 95 % confidential range for each dimension with 500 ms baseline before picture onset and normalized to the mean value of all amplitudes for each individual

ture processing indicates an increase of attention [29], the patients' stronger HR change might represent a more attentive involvement in emotional stimuli. Likewise, the stronger GSR in ALS patients might be the consequence of an overall increased level of emotional involvement. Although, we cannot decide whether these changes actually indicate altered emotional processing or are physiological concomitants of the disease process [5, 7, 15, 17, 44, 46–48], the correlation between GSR and individual but not standard arousal ratings points to an association of physiological and subjective changes in the patients.

In conclusion, emotional responses of ALS patients seem to be altered towards positive valence and decreased excitability for extreme emotional stimuli. Cognitive deficits or depressive symptoms as a probable reason for the changes in emotional processing found in our study were excluded. However, an open question remains whether these changes in emotional processing are a result of persistent neurodegenerative processes sensu stricto or rather a conscious psychological reaction to the changed situation in which the patient finds himself.

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