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Emotional processing, cognition and well-being in ALS: evidence from behavioral and physiological level and professional medical encounter

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Abbreviations

ALS: amyotrophic lateral sclerosis

BA: Brodmann area

BDI: Beck's Depression Inventory

BOLD: blood oxygen level dependency

CERAD plus: Consortium to Establish a Registry for Alzheimer's Disease plus Scale

CNS-LS: Center of Neurologic Study Lability Scale

ECAS: Edinburgh Cognitive and Behavioural ALS Screen

EMG: electromyography

FEEST: Facial Expressions of Emotion Test

fMRI: functional magnetic resonance imaging

FTD: frontotemporal dementia

GSR: galvanic skin response

IADS: International affective digital sounds

IAPS: International affective picture system

IFG: inferior frontal gyrus

IV: invasive ventilation

MMSE: Minimental State Examination

NIV: non-invasive ventilation

PEG: percutaneous endoscopic gastrostomy

PLC: pathological laughing and crying

SAHD: Schedule of Attitudes Toward Hastened Death

1. Introduction

Diagnosis of the fatal disease amyotrophic lateral sclerosis (ALS) brings about devastating changes in the patients' and their caregivers' life. ALS is characterized by progressive loss of upper and lower motor neurons resulting in muscle weakness. Death due to respiratory failure generally occurs 3-5 years after onset (Kiernan et al. 2011). Although the most prominent feature is the progressive functional impairment, ALS patients might also present with cognitive and behavioral manifestations (Goldstein and Abrahams 2013; Beeldman et al. 2016). Similarly, prefrontal cortical dysfunctions, which are common in patients suffering from frontotemporal dementia (FTD) (Hornberger et al. 2011) may also be present in some ALS patients (Kew et al. 1993). In line with this, co-morbidity of ALS and FTD is well known (Boeve et al. 2012), about 5-15% of ALS patients being diagnosed with ALS-FTD (Giordana et al. 2011; Murray et al. 2011). Cognition in ALS is age and education dependent as we have addressed earlier (Loose et al. 2016), and assessment of patients' cognition is important as cognitive and behavioral decline is associated with poorer prognosis (Elamin et al. 2013; Hu et al. 2013), lower quality of life (Hu et al. 2013) and increased caregiver burden (Burke et al. 2015).

In addition to cognitive and behavioral impairments, ALS patients may present with changes in emotional processing. It has been reported that some ALS patients show reduced memory capacity for emotional material (Papps et al. 2005) and regard negative pictures as less arousing and more positive (Lule et al. 2005). The change in emotional processing abilities especially for aversive emotional information might be caused by neurodegeneration of cortical, especially frontal cortical areas (Lule et al. 2010; Braak et al. 2013), and limbic structures such as the amygdala (Kawashima et al. 2001; Pinkhardt et al. 2006) and nucleus accumbens (Bede et al. 2013). Based on the earlier findings on emotional processing in ALS, the doctorate candidate aimed to assess patients' emotion recognition and its neural correlates at cortical level. As it has been suggested that social contacts are a protective factor against cognitive decline (Fankhauser et al. 2015), possible involvement of social activity on emotional processing in cortical level was additionally studied.

Impaired frontal cortex function might also account for pathological laughing and crying (PLC), which is present in up to 50% of ALS patients (Olney et al. 2011). PLC represents a pattern of motor dysinhibition phenomena characterized by involuntary outbursts of laughter and/or crying, which might be provoked by stimuli often causing opposite reaction in healthy subjects

(Parvizi et al. 2009; Olney et al. 2011) or stimuli without any specific emotional quality for healthy subjects (Poeck 1969; Hartje 2005). The doctorate candidate together with the co-authors aimed to address whether PLC in ALS is a response to weak emotional stimuli or an inappropriate response to emotionally incongruent stimuli and whether the phenomenon is associated with a pathological modulation of emotional stimuli or due to reduced inhibition of emotional behavior display.

However, the primary disabling factor in ALS is the progressive loss of voluntary musculature. In the course of the disease ALS patients most likely suffer from respiratory insufficiency and swallowing difficulties caused by the weakening muscle function (Kiernan et al. 2011), but the employment of non-invasive (NIV) or invasive (IV) artificial ventilation and/or nutrition via a feeding tube (percutaneous endoscopic gastrostomy, PEG) may prolong patients' survival and improve their quality of life (McDonald et al. 1996; Connolly et al. 2015). However, while some patients desire employment of these life prolonging measures, others prefer to decline them. Whether patients choose for or against certain measures depends on several factors, such as religiousness (Murphy et al. 2000), feeling of being a burden (Lule et al. 2014) or interaction of family and health care professionals (Martin et al. 2016). Additionally, it has been suggested that cognitive status of the patient might influence their decision making (Martin et al. 2014; Connolly et al. 2015). Owing to the possibly occurring cognitive deficits and signs of FTD, some have also expressed a concern whether ALS patients are able to judge pending medical decisions appropriately and therefore called for surrogate decision-making (Connolly et al. 2015; Khin Khin et al. 2015). To disentangle the multifaceted process of decision making in ALS, the doctorate candidate and co-authors aimed to study whether patients' tendency to decide for or against therapeutic options is dependent on their cognitive status.

Additionally, sufficient capacity to make decisions can be guaranteed only when the patient's ability to communicate is spared. As ALS affects entire voluntary musculature (Kiernan et al. 2011) formal ways of communication will eventually be impaired. Therefore, other means such as communication via eye movements can be an option. The doctorate candidate was also included in studies providing evidence for this (Keller et al. 2015; Keller et al. 2016).

Secondly, the decisions regarding therapeutic options are not solely made by the patient, but in practice, these are influenced by their social environment (Ruffell et al. 2013; Wilson et al. 2013). This comprises first of all neurologists who have medical expertise and are acquainted with life prolonging measures thus being in a crucial role in the patient's decision making process. However, physicians' appraisal of therapeutic options might be framed according to

their own attitudes (Martin et al. 2016) and perception of the patient's psychological well-being (Uhlmann and Pearlman 1991; Sullivan et al. 1996; Junod Perron et al. 2002). This in turn might influence the way the available therapeutic options are introduced to the patient (Sullivan et al. 1996; Greenaway et al. 2015). Therefore, as physician's perception on patient's well-being with certain therapeutic measures might influence the way he/she introduces these to the patients, the doctorate candidate studied neurologists' perception of the impact of certain life prolonging measures on ALS patients' psychological well-being.

2. Perception of emotional facial expressions in amyotrophic lateral sclerosis (ALS) at behavioral and brain metabolic level

2.1 Subjects and Methods

Overall, N=30 patients (16 females; 21 with spinal, 9 with bulbar onset; mean age 60±10 years) diagnosed with probable or definite ALS according to the revised El Escorial criteria (Ludolph et al. 2015), were asked to determine basic facial emotions on a computer screen (behavioral task). Additionally, a subgroup of N=15 patients (5 females, all spinal onset, mean age 54±12 years) viewed the emotional face expressions in a functional magnetic resonance imaging (fMRI) paradigm (fMRI task). Twenty-nine age, gender and education matched healthy volunteers (8 females, mean age 61±8 years) served as controls for the emotion recognition task and fourteen of them (7 females, mean age 61±10 years) for the fMRI task.

All the subjects were assessed with Minimental State Examination (MMSE) (Folstein MF. et al. 1975) and subjects with cognitive deficits (MMSE ≤ 26) were excluded. In addition, all the participants were assessed with the Beck`s Depression Inventory (BDI, range for mild depression 12-19) (Hautzinger et al. 1995). Furthermore, the participants of the fMRI task received more extensive neuropsychological assessment. Social activity was assessed by using an in-house questionnaire determining the number of people seen (at least one minute per person) on average per day and the average time spent with each person.

ALS patients and healthy controls first performed a verbal rating of Ekman faces stimuli (facial expressions of emotion test; FEEST) (Young et al. 2002) showing basic emotions of anger, disgust, fear, sadness, surprise and happiness. For this, participants viewed 60 black-and-white pictures of facial expressions of basic emotions (10 stimuli of each emotion) on a computer screen and were asked to choose the emotion depicted on the face.

In the fMRI task the subjects viewed the same stimuli displaying basic emotions while lying in a 3 Tesla whole body scanner (Symphony, Siemens, Erlangen, Germany). Subjects were asked to look at the displayed emotions without providing any additional response. An event related design, optimised for maximal blood oxygen level dependent (BOLD) signal amplitude was used (Robinson et al. 2006).

2.2 Results

Compared to the healthy controls, ALS patients of the behavioral task presented with increased depression (BDI: p<0.01) and the patients of the fMRI task presented with decreased premorbid intelligence (p<0.01) and increased depression (BDI: p<0.01).

In the behavioral task, ALS patients recognized anger (p=0.04), disgust (p<0.01) and fear (p<0.01) less accurately than healthy controls. Patient subgroup measured in fMRI recognized fear (p<0.01), disgust (p=0.02) and happiness (p=0.03) less than healthy controls. However, when corrected for patients' higher depression score only difference in rating disgust and fear prevailed (for both p<0.05).

During the fMRI task of processing all types of emotional facial expressions, ALS patients presented with a significantly increased activity in right inferior frontal gyrus (BA 44/45). In addition, patients showed increased activity in right angular gyrus, right insula and right precuneus. In comparison, the patients presented with significantly decreased activity in inferior frontal gyrus, orbitofrontal gyrus, precentral gyrus, middle temporal gyrus and calcarine sulcus on the left side and in lingual gyrus, sub-lobar frontal gyrus, and cerebellum on the right side.

When viewing sad faces ALS patients presented with increased activity in the right inferior frontal gyrus (p<0.005) but decreased activity in hippocampus bilaterally (p<0.005) compared to the healthy controls. No significant differences in brain activity between the patients and healthy controls were seen for any of the other emotional expressions.

Regression analysis revealed a statistically significant positive correlation between social activity and activity in right inferior frontal gyrus (BA 44/45; p=0.003) for ALS patients (Fig 1). This correlation was not seen for healthy controls.
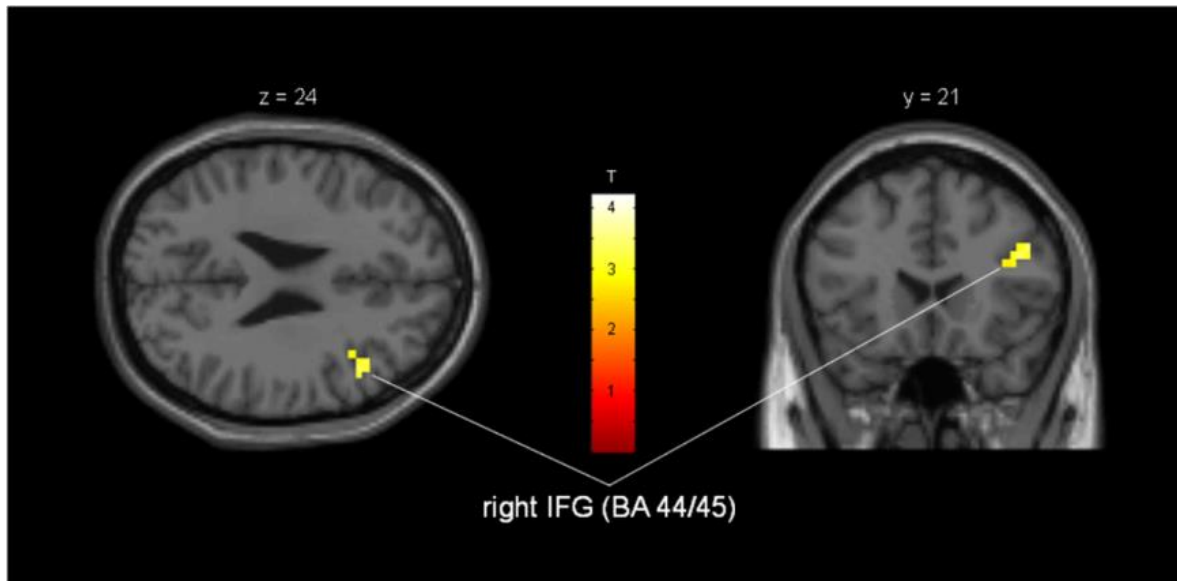
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Fig 1. Regression analysis of brain activity and social activity during processing of emotional facial stimuli in ALS patients. Activation in a subregion of right inferior frontal gyrus/Brodmann Area 44 and 45. MNI-coordinates: x=44mm, y=21mm, z=30mm; cluster-size=12 voxels; T=3.36; p_{uncorr}=0.003. Original source: (Aho-Ozhan et al. 2016) page: 9

2.3 Discussion

The doctorate candidate aimed to study changes in emotional processing in ALS by assessing patients' ability to recognize different facial emotions. Additionally, using fMRI, neural correlates of facial emotional processing were studied and correlated with the patients' social activity.

Our results confirm earlier findings (Lule et al. 2005; Papps et al. 2005) that emotional processing is impaired in ALS. Patients showed reduced performance in facial emotion recognition for disgust and fear. During the fMRI task of processing facial expressions, patients showed decreased activity in areas related to processing of negative emotions such as disgust and fear (Sprengelmeyer et al. 1998; Fusar-Poli et al. 2009). When processing sad faces, patients showed increased brain activity in right inferior frontal gyrus (BA 44/45), an area associated with imitating emotional responses, also referred to as "mirror neuron area" (Rizzolatti and Craighero 2004), and decreased activity in hippocampus bilaterally.

These changes in brain activation might result from alterations in excitability of cortical areas suggested earlier. Several studies have reported involvement of cortical hyper excitability (Vucic and Kiernan 2006; Vucic et al. 2008; Menon et al. 2015) and reduced corticocortical inhibition (Ziemann et al. 1997) in ALS. It has also been suggested that not just hyper excitability but imbalance between cortical excitation and inhibition might account for the

changes in ALS (Khedr et al. 2011). Most likely these pathological changes also increase in the course of the disease being more prominent in advanced ALS, which might partly explain brain activity differences between patients and healthy controls in this study.

However, some have also suggested cortical reorganisation in different cerebral networks in ALS (Schoenfeld et al. 2005). Functional cortical connectivity may be reduced (Mohammadi et al. 2009) or alternatively increased (Agosta et al. 2013) in some brain areas of ALS patients. Similarly, in our study when viewing emotional expressions, especially sadness, patients presented with increased activity in the right inferior frontal gyrus and decreased activity in hippocampus bilaterally. Thus, to counteract reduced hippocampal activity, patients might increase the activation in the right inferior frontal gyrus, which is also known to be important for facial expression recognition (Enticott et al. 2008). This might be considered as functional compensation.

Furthermore, interestingly the possibly compensating activity in the right inferior frontal gyrus increased as the patient's social activity increased. Therefore, our results also provide intriguing evidence for the importance of including ALS patients in social life to counteract possible negative effects of pathological changes on social-emotional information processing.

3. Pathological laughing and crying in amyotrophic lateral sclerosis is related to frontal cortex function

3.1 Subjects and Methods

Overall, N=10 ALS patients with PLC (6 males, mean age 64.0±12.2 years) and N=10 healthy gender-, age- and education- matched controls (6 males, mean age 65.8±10.8 years) were included. All patients and controls completed the Center of Neurologic Study Lability Scale for quantification of PLC (CNS-LS) (Smith et al. 2004) regarding occurrence of emotional lability. It was split into positive and negative scores to differentiate between pathological laughing and pathological crying. Screening for cognitive deficits was performed with the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) (Abrahams et al. 2014; Lule et al. 2015) in N=7 patients and all controls and with the Consortium to Establish a Registry for Alzheimer' s Disease plus Scale (CERAD plus) (Morris et al. 1988) in N=3 patients.

Subjects were shown pictures with three different emotional qualities (happy, sad, neutral). The pictures were chosen from the International affective picture system (IAPS) (Lang et al. 2008). Subjects were asked to rate the pictures according to their emotional quality for valence on a non-numeric scale. While watching the pictures, subjects were listening to classical instrumental music sequences presented via headphones. As were the pictures, also the auditory stimuli were chosen from a standardized set of objectively validated happy and sad musical extracts that induce different mood states in normal subjects (International Affective Digital Sounds, IADS, http://csea.phhp.ufl.edu/media/iadsmessage.html). Subjects were exposed to emotionally congruent and incongruent picture-music combinations.

Additionally, for an index of valence the heart rate was acquired from electrodes attached to the right and left arm or leg, using an in-house amplifier. Galvanic skin response (GSR) was measured with electrodes fixed to the medial thenar and palm of the hand and used as an index of arousal. Additionally, facial electromyography (EMG) of the corrugator supercilii muscle, the orbicularis oris muscle and orbicularis oculi muscle were recorded to assess the activity of mimic muscles to detect facial expressions of certain emotions.

3.2 Results

All patients and controls had a normal cognitive status. ALS patients scored significantly higher in the "overall" CNS-LS compared to healthy controls (p<0.01). When looking at the sub-scores, patients had a significantly higher CNS-LS-negative score compared to CNS-LS-positive (p=0.01), while controls did not show a difference between the two sub-scores. When

comparing both groups, patients had also a significantly higher CNS-LS-negative score compared to CNS-LS-negative in controls (p<0.01).

Both patients and controls rated pictures with different emotional contents significantly differently when listening to sad music compared to the condition with happy music (p<0.01). Compared to controls, patients rated neutral pictures accompanied by sad music more negatively (p=0.03). Regarding CNS-LS, we observed that patients with a high positive CNS-LS score rated happy pictures more positively (r=0.53, p<0.01) and sad pictures more negatively (r=-0.34, p=0.05), while patients with a high negative CNS-LS score tended to rate happy pictures more negatively, indicated by non-significant correlation (r=-0.31, p=0.07).

Patients and healthy subjects did not differ in their changes in electrophysiological responses during the tasks. ECAS performance assessing frontal cortex function explained the differences between the two musical conditions: EMG activity of the orbicularis oris muscle (p<0.01) and the orbicularis oculi muscle (p=0.036) and a non-significant trend for heart rate (p=0.096) and GSR (p=0.109).

3.3 Discussion

The doctorate candidate and co-authors aimed to clarify the underlying causes of bursts of involuntary pathological laughing and crying in ALS patients with PLC by exposing patients to emotionally laden (negative and positive) and neutral visual and auditory stimuli.

Similarly to our study on emotional processing in ALS, also the results of this study on ALS patients with PLC suggested changes in processing of negative emotional material. Emotion regulation in PLC was altered at behavioral, physiological and subjective level. ALS patients were more susceptible to mood-incongruent (but not weak mood-congruent) stimuli and rated pictures with a neutral content more negatively when listening to sad music. Additionally, patients' altered facial expressions recorded by EMG were explained by frontal cortex function. Patients also scored significantly higher on the negative (CNS-LS-negative) scale compared to their positive (CNS-LS-positive) scale and compared to the negative scale of the controls. This all suggests that patients with PLC are in general more sensitive to the negative component of emotion regulation.

Our findings are in line with a previous study reporting reduced ability of PLC patients on regulating their facial expression voluntarily (Olney et al. 2011). ALS patients might exhibit reduced inhibitory mechanisms as they show an increased suggestibility and were influenced in their behavior when exposed to stimuli of opposing emotional content. Additionally, our

findings show that PLC is associated with enhanced emotional lability and is not only an involuntary motor activation of facial expression.

It has been suggested that frontal cortex is crucial in pathophysiology of PLC (McCullagh et al. 1999; Olney et al. 2011). Our results also show that EMG changes of mimic muscles elicited by different emotional stimuli are closely related to cognitive performance and frontal function in PLC patients, suggesting that altered facial expression in PLC is related to frontal cortex function/dysfunction.

4. Medical decisions are independent of cognitive impairment in amyotrophic lateral sclerosis (ALS)

4.1 Subjects and Methods

In total, N=169 ALS patients responded to standardized questionnaires regarding their decisions about NIV, IV and PEG and the hypothetical ideation to turn off these treatments in case of physical decline. Additionally, patients filled out the schedule of attitudes toward hastened death (SAHD) (Rosenfeld et al. 2000). All patients were screened for cognition by using the ECAS and N=140 of patients' caregivers gave information about patients' behavioral changes. Regression analyses were used to analyze association between cognition and behavior, and decision making.

4.2 Results

Deficits in at least one cognitive domain were present in N=93 ALS patients (55%). Caregivers reported behavioral changes for N=21 (15%) patients (mostly apathy), including N=15 (11%) patients with additional cognitive impairment. Logistic regression analyses showed that neither cognitive impairment nor behavioral changes were associated with ALS patients´ decisions regarding use or decline of PEG, NIV and IV, hypothetical ideation to turn off treatments in case of physical decline or patients' wish for hastened death (all p>0.05).

4.3 Discussion

The doctorate candidate together with the co-authors addressed the claim that patient's cognitive status would influence his/her tendency to accept or decline certain life prolonging measures (Martin et al. 2014; Connolly et al. 2015).

Our results on a large cohort of ALS patients showed that mild to moderate cognitive and behavioral impairments do not have an influence on patients' decision making for or against certain therapeutic measures. Therefore, decision making by proxies should not be rushed.

5. Experience matters: neurologists' perspectives on ALS patients' well-being

5.1 Subjects and Methods

In total, N=105 neurologists were included in the study. Neurologists received a questionnaire addressing experience of the physician with ALS, estimation of the level of quality of life and depressiveness of the ALS patients with NIV, IV and PEG and demographics. Experience of the neurologist was defined as the average number of ALS patients seen per month multiplied with the average number of years of experience with ALS. According to this, physicians were divided into groups of low (average number of ALS patients seen in total < median), moderate (average number of ALS patients seen in total = median) and high (average number of ALS patients seen in total > median) experienced neurologists. Additionally, physicians were asked whether they had completed palliative care training.

Neurologists were requested to estimate the psychological well-being (depressiveness and quality of life) of ALS patients with NIV, IV and PEG in general. Depressiveness was assessed on a Likert scale ranging from 0 to 10 and quality of life on a Likert scale ranging from -5 to 5. Additionally, data of N=52 ALS patients with NIV, IV and/or PEG who had been interviewed in a previous study (Lule et al. 2014) on their subjective well-being were included in the study. Patients' reports were compared with the neurologists' reports on the quality of life and depressiveness of ALS patients with fore mentioned life prolonging measures.

5.2 Results

Neurologists with high experience estimated quality of life close to patients' subjective estimation for all measures as no statistically significant difference was seen between them (NIV: p>0.01; IV: p>0.01; PEG: p>0.01). High experienced neurologists also estimated depressiveness of patients with PEG in the range of reports of the patients (p>0.01) but significantly higher for patients with NIV (p=0.001) and IV (p=0.002). In contrast to this, neurologists with low experience estimated depressiveness higher than what was reported by patients with all measures (NIV: p<0.001; IV: p<0.001; PEG: p=0.001). Less experienced neurologists also estimated quality of life lower for patients with IV (p=0.001) but not for patients with NIV (p>0.01) and PEG (p>0.01). (Fig 2).

Negative correlation was seen between experience of neurologist (patients seen in total) and his/her estimation of depressiveness of patients with NIV (r=-0.217, p=0.028) and with IV (r=-0.241, p=0.017) but not with PEG (r=-0.088, p>0.05) and positive correlation between

experience of neurologists and estimation of quality of life of patients with IV (r=0.263, p=0.009) but not with NIV (r=0.167, p>0.05) or PEG (r=0.185, p>0.05).
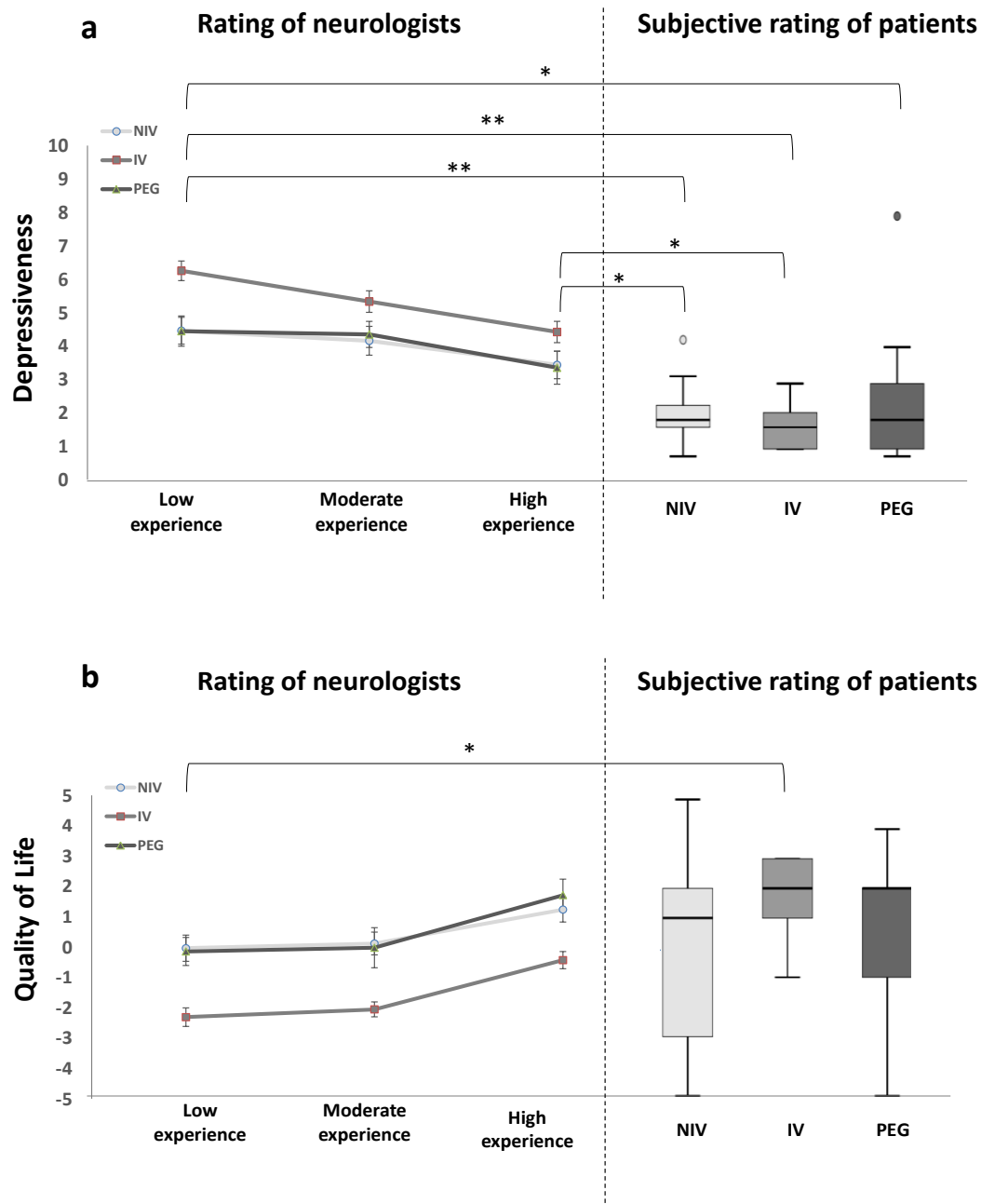

Fig 2. Rating of depressiveness (a) and quality of life (b) of ALS-patients by neurologists' with varying degree of experience compared with patients' own reports. Depressiveness estimated on a Likert scale ranging from 0 to 10 and the quality of life on a Likert scale ranging from -5 to 5. The line charts (left figure in a and b) show change in neurologists' estimation of patients' well-being in relation to his/her experience. Box plots (right figure of a and b) show patients' subjective rating on their depressiveness and quality of life. Medians, first and third quartiles, range and the outliers are shown. * indicates statistical significance with p<0.01 and ** with p<0.001 between the patients' and neurologists' (with either low or high experience) in Mann-Whitney U test. Low experience: average number of ALS patients seen by the neurologist <

median; moderate experience: average number of ALS patients seen by neurologist = median, high experience: average number of ALS patients seen by neurologists > median. NIV = non-invasive ventilation, IV=invasive ventilation, PEG=percutaneous endoscopic gastrostomy. Original source: (Aho-Özhan et al. 2017) page: 5

Neurologists with completed palliative care training estimated higher quality of life for patients with NIV ($p=0.006$) and PEG ($p=0.005$) but not with IV ($p>0.01$) than the neurologists without palliative care training. Neurologists with and without palliative care training did not significantly differ in their estimation of depressiveness (NIV: $p>0.01$; IV: $p>0.01$; PEG: $p>0.01$). When comparing patients' and the neurologists with palliative care training, no statistically significant difference was seen in rating of depressiveness (NIV: $p>0.01$; IV: $p>0.01$; PEG: $p>0.01$) or quality of life (NIV: $p>0.01$; IV: $p>0.01$; PEG: $p>0.01$). However, regarding quality of life neurologists without palliative care training differed in estimation for patients with IV ($p=0.001$) but not with NIV ($p>0.01$) or PEG ($p>0.01$) and in estimation of depressiveness with patients with all measures (NIV: $p<0.001$; IV: $p<0.001$; PEG: $p<0.001$). (Fig 3).
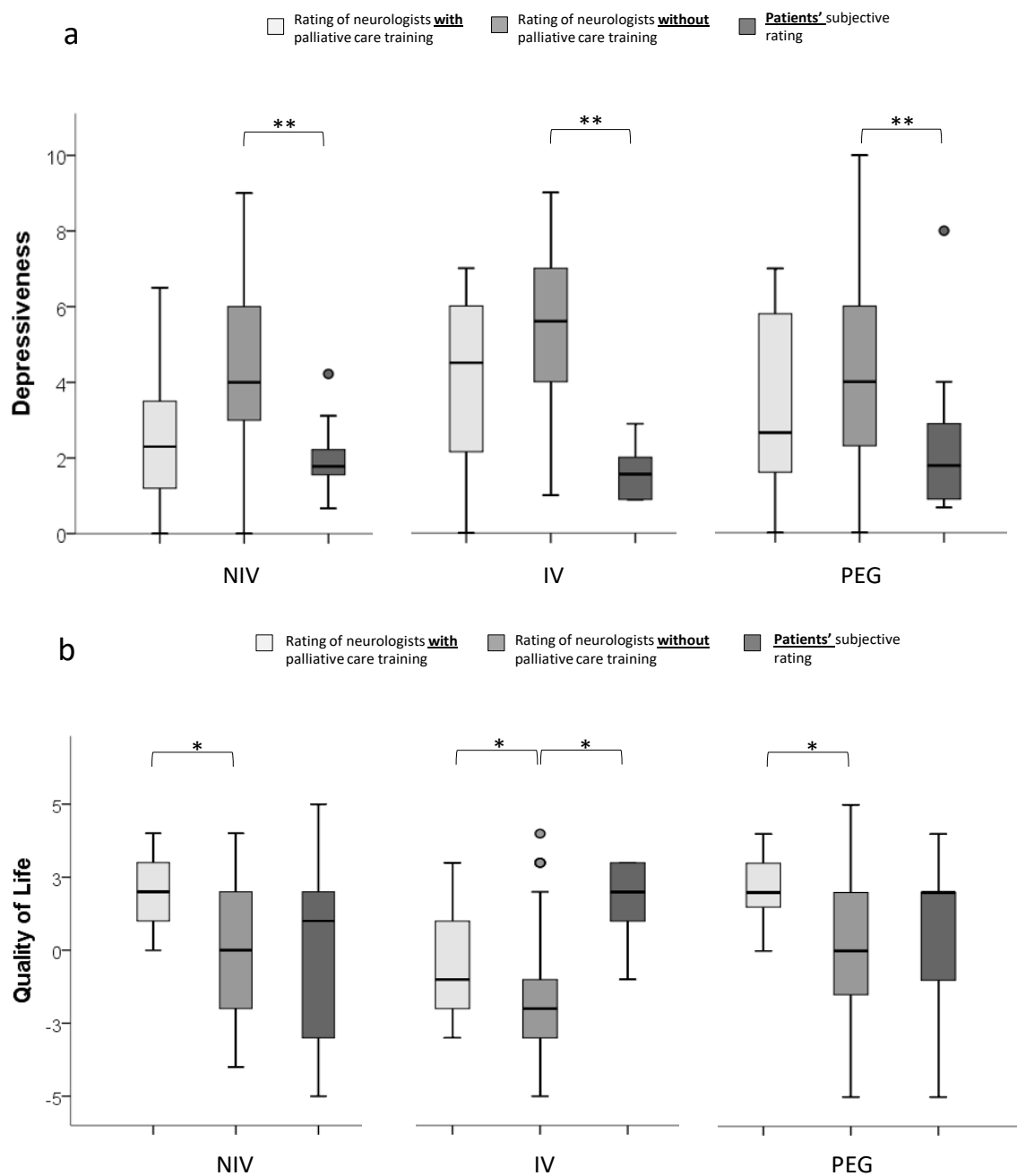
Fig 3. Estimation of patients' depressiveness (a) and quality of life (b) by neurologists with and without completed palliative care training compared to patients' subjective rating. Depressiveness estimated on a Likert scale ranging from 0 to 10 and quality of life on a Likert scale ranging from -5 to 5. Box plots show comparison of the neurologists' (with completed palliative care training: n=12; without completed palliative care training: n=93) estimation on patients' well-being as well as patients' own reports. Medians, first and third quartiles, range and the outliers are shown. * Indicates statistical significance with p<0.01 and ** with p<0.001 in Mann-Whitney U test. NIV=non-invasive ventilation, IV=invasive ventilation, PEG=percutaneous endoscopic gastrostomy. Original source: (Aho-Özhan et al. 2017) page: 6

5.3 Discussion

Based on earlier suggestions of physician's own appraisal influencing the way he/she introduces therapeutic options to the patients (Uhlmann and Pearlman 1991; Sullivan et al. 1996; Junod Perron et al. 2002; Martin et al. 2016), the doctorate candidate aimed to assess how neurologist reflect the well-being of ALS patients with life prolonging measures.

Results showed that especially neurologists with significant experience in ALS, are able to estimate patient's well-being in similar range with the patient's subjective experience. Similarly, neurologists with completed palliative care training estimated well-being close to patients' subjective reports. This is in line with earlier studies indicating benefits of palliative care training for physicians in treating patients with fatal illness (Fischer et al. 2003; Anderson et al. 2008; Pelayo et al. 2011; Long et al. 2016). Therefore, besides experience, our results support also the importance of knowledge on palliative care when treating patients with ALS.

On the other hand, neurologists with low experience on ALS showed more difference in their estimation of patients well-being compared to patients' subjective ratings. Therefore, non-professionals' often biased perception of well-being of patients with serious illness (Hoppe 2013), might be also present in professionals with insufficient experience. Overall, physicians with significant experience are able to correctly recognize patients' affective state and sympathize with their life with certain therapeutic measures.

6. <u>Conclusion</u>

ALS is a multisystem disorder involving dysfunctions of several brain regions (Braak et al. 2013) leading besides physical impairment to various extra-motor manifestations (Kiernan et al. 2011; Martinez et al. 2014; McCombe et al. 2017). For instance, frontal cortex dysfunctions in ALS might cause changes in emotional processing or cognition, but also pathological laughing and crying. Together with reducing physical function, possibly extra-motor symptoms have an influence on patients' contentment in life and affective state. The current work highlights these changes at behavioral and physiological level.

However, some extra-motor impairments might be counteracted by positive social contacts and they are not necessarily associated with patients' psychosocial adaptation and decision making regarding life prolonging measures. Additionally, psychological well-being of ALS patients with life prolonging measures might often be underestimated by social environment with insufficient knowledge on the disease. On the other hand, patients' good psychosocial adaptation is probably well understood among neurologists with significant experience in ALS. Therefore, patients with a rare disease such as ALS would be ideally treated by experienced neurologists, when they might receive both more advanced medical expertise and better understanding for their condition with regard to psychological well-being.

All in all, the findings of the current work can be considered important for the understanding of the pathological processes in ALS and for the therapeutic relationship in the clinical setting encouraging clinicians to emphasize the importance of social factors in counselling. Correct interpretation of symptoms of PLC and ability to reflect the psychological well-being of ALS patients with life prolonging interventions are also valuable aspects in the professional relationship between the physician and the patient. This is especially important in ALS where options for symptom management are limited and their timely employment often crucial for patient's survival and satisfactory life with the disease. The results also present intriguing information which will promote researchers in providing pathological models of ALS taking the extra-motor changes such as emotional processing or pathological laughing and crying into account.

7. <u>Summary</u>

In addition to physical impairment, patients with amyotrophic lateral sclerosis (ALS) may present with some extra-motor symptoms such as changes in emotional processing, behavior and cognition. So far it has not been fully understood how these symptoms interfere with patients' well-being and how they influence medical encounter with professionals. Therefore, the aim was to study extra-motor manifestations including emotional processing, signs of pathological laughing and crying and cognition. Additionally, impact of these on patients' decision status for or against therapeutic interventions and professionals' perspective on the influence of these interventions on patients' well-being were studied.

Emotional processing in ALS was studied by asking patients (N=30) and healthy controls (N=29) to rate basic facial emotions on a computer screen and view the facial expressions in a functional magnetic resonance image scanner (subset of N=15 patients and N=14 healthy controls) while their cortical activity was recorded. Furthermore, patients (N=10) and healthy controls (N=10) were asked to rate emotionally laden and neutral pictures while listening to happy or sad music extracts. This was correlated with their emotional lability score. Influence of patients' cognition on their therapy preferences was studied by including N=169 patients who filled out a questionnaire on their decision making regarding life prolonging measures. This was correlated with patients' cognitive status. Finally, physicians perspectives were studied by asking N=105 neurologists to estimate depressiveness and quality of life of ALS patients with life prolonging measures and by comparing these with patients' subjective ratings.

Emotional processing, especially of negative material, was impaired: ALS patients recognized disgust and fear less than healthy controls and showed decreased activity in cortical areas related to these emotions. Especially when viewing sad faces patients presented with decreased activity in hippocampus bilaterally together with increased activity in the right inferior frontal gyrus, which was positively correlated with the patient's social activity. This suggests a compensatory cortical function that might be enhanced by positive influence of social activity in life.

ALS patients with pathological laughing and/or crying tended to rate neutral pictures accompanied by sad music more negatively. Patients with a high positive emotional lability score rated happy pictures more positively and sad pictures more negatively, while patients with a high negative lability score rated happy pictures more negatively. Therefore, our results suggest that ALS patients with pathological laughing and/or crying might exhibit reduced

inhibitory mechanisms and are in general more sensitive to the negative component of emotion regulation.

Patients' decisions regarding life prolonging measures, hypothetical ideation to turn off these measures or patients' wish for hastened death were not associated with their cognitive status or behavioral changes. Therefore, decision making by proxies should not necessarily be rushed. Furthermore, with regards to patients' psychological well-being with life prolonging measures, highly experienced neurologists estimated quality of life and depressiveness closer to patients' subjective estimation than neurologists with low experience on ALS. Thus, neurologists with significant experience are able to correctly recognize patients' affective state and sympathize with their life with certain therapeutic measures. Similarly, in contrast to those without palliative care training, neurologists with palliative care training estimated depressiveness and quality of life of patients similarly with patients' subjective ratings.

Some in ALS occurring extra-motor symptoms might be counteracted by positive social contacts and they are not necessarily associated with patients' psychosocial adaptation and decision making regarding life prolonging measures. Patients' well-being might often be underestimated by social environment with insufficient knowledge on the disease. On the other hand, patients' good psychosocial adaptation is probably well understood among highly experienced neurologists. Therefore, patients with a rare disease such as ALS would be ideally treated by experienced neurologists, when they might receive both more advanced medical expertise and better understanding for their condition with regard to psychological well-being.

8. References

Abrahams S, Newton J, Niven E, Foley J, Bak TH. 2014. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 15:9–14.

Agosta F, Canu E, Valsasina P, Riva N, Prelle A, Comi G, Filippi M. 2013. Divergent brain network connectivity in amyotrophic lateral sclerosis. Neurobiol Aging. 34:419–427.

Aho-Ozhan HEA, Keller J, Heimrath J, Uttner I, Kassubek J, Birbaumer N, Ludolph AC, Lule D. 2016. Perception of Emotional Facial Expressions in Amyotrophic Lateral Sclerosis (ALS) at Behavioural and Brain Metabolic Level. PLoS One. 11:e0164655.

Aho-Özhan HEA, Böhm S, Keller J, Dorst J, Uttner I, Ludolph AC, Lulé D. 2017. Experience matters: Neurologists' perspectives on ALS patients' well-being. J Neurol.

Anderson WG, Williams JE, Bost JE, Barnard D. 2008. Exposure to death is associated with positive attitudes and higher knowledge about end-of-life care in graduating medical students. J Palliat Med. 11:1227–1233.

Bede P, Elamin M, Byrne S, McLaughlin RL, Kenna K, Vajda A, Pender N, Bradley DG, Hardiman O. 2013. Basal ganglia involvement in amyotrophic lateral sclerosis. Neurology. 81:2107–2115.

Beeldman E, Raaphorst J, Klein Twennaar M, Visser M de, Schmand BA, Haan RJ de. 2016. The cognitive profile of ALS: a systematic review and meta-analysis update. J Neurol Neurosurg Psychiatry. 87:611–619.

Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, Dickson DW, Josephs KA, Rush BK, Machulda MM, Fields JA, Ferman TJ, Baker M, Rutherford NJ,

Adamson J, Wszolek ZK, Adeli A, Savica R, Boot B, Kuntz KM, Gavrilova R, Reeves A, Whitwell J, Kantarci K, Jack CR JR, Parisi JE, Lucas JA, Petersen RC, Rademakers R. 2012. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 135:765–783.

Braak H, Brettschneider J, Ludolph AC, Lee VM, Trojanowski JQ, Del Tredici K. 2013. Amyotrophic lateral sclerosis--a model of corticofugal axonal spread. Nat Rev Neurol. 9:708–714.

Burke T, Elamin M, Galvin M, Hardiman O, Pender N. 2015. Caregiver burden in amyotrophic lateral sclerosis: a cross-sectional investigation of predictors. J Neurol. 262:1526–1532.

Connolly S, Galvin M, Hardiman O. 2015. End-of-life management in patients with amyotrophic lateral sclerosis. The Lancet Neurology. 14:435–442.

Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B, O'Brien C, Phukan J, Lynch C, Pender N, Hardiman O. 2013. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology. 80:1590–1597.

Enticott PG, Johnston PJ, Herring SE, Hoy KE, Fitzgerald PB. 2008. Mirror neuron activation is associated with facial emotion processing. Neuropsychologia. 46:2851–2854.

Fankhauser S, Forstmeier S, Maercker A, Luppa M, Luck T, Riedel-Heller SG. 2015. Risk of dementia in older adults with low versus high occupation-based motivational processes: differential impact of frequency and proximity of social network. J Geriatr Psychiatry Neurol. 28:126–135.

Fischer SM, Gozansky WS, Kutner JS, Chomiak A, Kramer A. 2003. Palliative care education: an intervention to improve medical residents' knowledge and attitudes. J Palliat Med. 6:391–399.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method
for grading the cognitive state of patients for the clinician. J Psychiatr Res.
12:189–198.

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F,
Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P. 2009.
Functional atlas of emotional faces processing: a voxel-based meta-analysis of
105 functional magnetic resonance imaging studies. J Psychiatry Neurosci.
34:418–432.

Giordana MT, Ferrero P, Grifoni S, Pellerino A, Naldi A, Montuschi A. 2011.
Dementia and cognitive impairment in amyotrophic lateral sclerosis: a review.
Neurol Sci. 32:9–16.

Goldstein LH, Abrahams S. 2013. Changes in cognition and behaviour in
amyotrophic lateral sclerosis: Nature of impairment and implications for
assessment. The Lancet Neurology. 12:368–380.

Greenaway LP, Martin NH, Lawrence V, Janssen A, Al-Chalabi A, Leigh PN,
Goldstein LH. 2015. Accepting or declining non-invasive ventilation or gastrostomy
in amyotrophic lateral sclerosis: patients' perspectives. J Neurol. 262:1002–1013.

Hartje W, editor. 2005. Kognitive Neurologie: Störungen des emotionalen Verhaltens.
Stuttgart: Thieme.

Hautzinger M, Bailer M, Worall H, Keller F. 1995. Beck-Depressions-Inventar, BDI –
Testhandbuch. 2nd. Bern: Verlang Hans Huber.

Hoppe S. 2013. Chronic Illness as a Source of Happiness: Paradox or perfectly
normal? hcs. 5:265–278.

Hornberger M, Geng J, Hodges JR. 2011. Convergent grey and white matter
evidence of orbitofrontal cortex changes related to disinhibition in behavioural
variant frontotemporal dementia. Brain. 134:2502–2512.

http://csea.phhp.ufl.edu/media/iadsmessage.html (14.02.2017)

Hu WT, Shelnutt M, Wilson A, Yarab N, Kelly C, Grossman M, Libon DJ, Khan J, Lah JJ, Levey AI, Glass J. 2013. Behavior matters--cognitive predictors of survival in amyotrophic lateral sclerosis. PLoS One. 8:e57584.

Junod Perron N, Morabia A, Torrente A de. 2002. Quality of life of Do-Not-Resuscitate (DNR) patients: how good are physicians in assessing DNR patients' quality of life? Swiss Med Wkly. 132:562–565.

Kawashima T, Doh-ura K, Kikuchi H, Iwaki T. 2001. Cognitive dysfunction in patients with amyotrophic lateral sclerosis is associated with spherical or crescent-shaped ubiquitinated intraneuronal inclusions in the parahippocampal gyrus and amygdala, but not in the neostriatum. Acta Neuropathol. 102:467–472.

Keller J, Gorges M, Aho-Ozhan HEA, Uttner I, Schneider E, Kassubek J, Pinkhardt EH, Ludolph AC, Lule D. 2016. Eye-Tracking Control to Assess Cognitive Functions in Patients with Amyotrophic Lateral Sclerosis. J Vis Exp.

Keller J, Gorges M, Horn HT, Aho-Ozhan HEA, Pinkhardt EH, Uttner I, Kassubek J, Ludolph AC, Lule D. 2015. Eye-tracking controlled cognitive function tests in patients with amyotrophic lateral sclerosis: a controlled proof-of-principle study. J Neurol. 262:1918–1926.

Kew JJ, Goldstein LH, Leigh PN, Abrahams S, Cosgrave N, Passingham RE, Frackowiak RS, Brooks DJ. 1993. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis. A neuropsychological and positron emission tomography study. Brain. 116 (Pt 6):1399–1423.

Khedr EM, Ahmed MA, Hamdy A, Shawky OA. 2011. Cortical excitability of amyotrophic lateral sclerosis: transcranial magnetic stimulation study. Neurophysiol Clin. 41:73–79.

Khin Khin E, Minor D, Holloway A, Pelleg A. 2015. Decisional Capacity in

Amyotrophic Lateral Sclerosis. J Am Acad Psychiatry Law. 43:210–217.

Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing

MC. 2011. Amyotrophic lateral sclerosis. The Lancet. 377:942–955.

Lang PJ, Bradley MM, Cuthbert BN. 2008. International affective picture system

(IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8.

Gainesville, FL: University of Florida.

Long AC, Downey L, Engelberg RA, Ford DW, Back AL, Curtis JR. 2016. Physicians'

and Nurse Practitioners' Level of Pessimism About End-of-Life Care During

Training: Does It Change Over Time? J Pain Symptom Manage. 51:890-897.e1.

Loose M, Burkhardt C, Aho-Ozhan H, Keller J, Abdulla S, Bohm S, Kollewe K, Uttner

I, Abrahams S, Petri S, Weber M, Ludolph AC, Lule D. 2016. Age and education-

matched cut-off scores for the revised German/Swiss-German version of ECAS.

Amyotroph Lateral Scler Frontotemporal Degener. 17:374–376.

Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, Shefner J.

2015. A revision of the El Escorial criteria - 2015. Amyotroph Lateral Scler

Frontotemporal Degener. 16:291–292.

Lule D, Burkhardt C, Abdulla S, Bohm S, Kollewe K, Uttner I, Abrahams S, Bak TH,

Petri S, Weber M, Ludolph AC. 2015. The Edinburgh Cognitive and Behavioural

Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of

established screening tools in a German-Swiss population. Amyotroph Lateral

Scler Frontotemporal Degener. 16:16–23.

Lule D, Diekmann V, Muller H, Kassubek J, Ludolph AC, Birbaumer N. 2010.

Neuroimaging of multimodal sensory stimulation in amyotrophic lateral sclerosis. J

Neurol Neurosurg Psychiatry. 81:899–906.

Lule D, Kurt A, Jurgens R, Kassubek J, Diekmann V, Kraft E, Neumann N, Ludolph AC, Birbaumer N, Anders S. 2005. Emotional responding in amyotrophic lateral sclerosis. J Neurol. 252:1517–1524.

Lule D, Nonnenmacher S, Sorg S, Heimrath J, Hautzinger M, Meyer T, Kubler A, Birbaumer N, Ludolph AC. 2014. Live and let die: existential decision processes in a fatal disease. J Neurol. 261:518–525.

Martin NH, Landau S, Janssen A, Lyall R, Higginson I, Burman R, McCrone P, Sakel M, Ellis CM, Shaw CE, Al-Chalabi A, Leigh PN, Goldstein LH. 2014. Psychological as well as illness factors influence acceptance of non-invasive ventilation (NIV) and gastrostomy in amyotrophic lateral sclerosis (ALS): a prospective population study. Amyotroph Lateral Scler Frontotemporal Degener. 15:376–387.

Martin NH, Lawrence V, Murray J, Janssen A, Higginson I, Lyall R, Burman R, Leigh PN, Al-Chalabi A, Goldstein LH. 2016. Decision Making About Gastrostomy and Noninvasive Ventilation in Amyotrophic Lateral Sclerosis. Qual Health Res. 26:1366–1381.

Martinez H, Moreno-Cuevas J, Gonzalez-Garza M, Tenorio AR, Ocañas CE, Marioni SS, Martínez U. 2014. Extra-Motor Symptoms in Amyotrophic Lateral Sclerosis. Analysis of 112 Patients (P7.034). Neurology. 82:P7.034.

McCombe PA, Wray NR, Henderson RD. 2017. Extra-motor abnormalities in amyotrophic lateral sclerosis: another layer of heterogeneity. Expert Rev Neurother:1–17.

McCullagh S, Moore M, Gawel M, Feinstein A. 1999. Pathological laughing and crying in amyotrophic lateral sclerosis: an association with prefrontal cognitive dysfunction. J Neurol Sci. 169:43–48.

McDonald ER, Hillel A, Wiedenfeld SA. 1996. Evaluation of the psychological status of ventilatory-supported patients with ALS/MND. Palliat Med. 10:35–41.

Menon P, Kiernan MC, Vucic S. 2015. Cortical hyperexcitability precedes lower motor

neuron dysfunction in ALS. Clin Neurophysiol. 126:803–809.

Mohammadi B, Kollewe K, Samii A, Krampfl K, Dengler R, Munte TF. 2009. Changes

of resting state brain networks in amyotrophic lateral sclerosis. Exp Neurol.

217:147–153.

Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. 1988. Consortium to

establish a registry for Alzheimer's disease (CERAD) clinical and

neuropsychological assessment of Alzheimer's disease. Psychopharmacol Bull.

24:641–652.

Murphy PL, Albert SM, Weber CM, Del Bene ML, Rowland LP. 2000. Impact of

spirituality and religiousness on outcomes in patients with ALS. Neurology.

55:1581–1584.

Murray ME, DeJesus-Hernandez M, Rutherford NJ, Baker M, Duara R, Graff-Radford

NR, Wszolek ZK, Ferman TJ, Josephs KA, Boylan KB, Rademakers R, Dickson

DW. 2011. Clinical and neuropathologic heterogeneity of c9FTD/ALS associated

with hexanucleotide repeat expansion in C9ORF72. Acta Neuropathol. 122:673–

690.

Olney NT, Goodkind MS, Lomen-Hoerth C, Whalen PK, Williamson CA, Holley DE,

Verstaen A, Brown LM, Miller BL, Kornak J, Levenson RW, Rosen HJ. 2011.

Behaviour, physiology and experience of pathological laughing and crying in

amyotrophic lateral sclerosis. Brain. 134:3458–3469.

Papps B, Abrahams S, Wicks P, Leigh PN, Goldstein LH. 2005. Changes in memory

for emotional material in amyotrophic lateral sclerosis (ALS). Neuropsychologia.

43:1107–1114.

Parvizi J, Coburn KL, Shillcutt SD, Coffey CE, Lauterbach EC, Mendez MF. 2009.

Neuroanatomy of pathological laughing and crying: a report of the American

Neuropsychiatric Association Committee on Research. J Neuropsychiatry Clin Neurosci. 21:75–87.

Pelayo M, Cebrian D, Areosa A, Agra Y, Izquierdo JV, Buendia F. 2011. Effects of online palliative care training on knowledge, attitude and satisfaction of primary care physicians. BMC Fam Pract. 12:37.

Pinkhardt EH, van Elst LT, Ludolph AC, Kassubek J. 2006. Amygdala size in amyotrophic lateral sclerosis without dementia: an in vivo study using MRI volumetry. BMC Neurol. 6:48.

Poeck K. 1969. Pathological laughing and weeping in patients with progressive balbar palsy. Ger Med Mon. 14:394–397.

Rizzolatti G, Craighero L. 2004. The mirror-neuron system. Annu Rev Neurosci. 27:169–192.

Robinson PA, Drysdale PM, van der Merwe H, Kyriakou E, Rigozzi MK, Germanoska B, Rennie CJ. 2006. BOLD responses to stimuli: dependence on frequency, stimulus form, amplitude, and repetition rate. Neuroimage. 31:585–599.

Rosenfeld B, Breitbart W, Galietta M, Kaim M, Funesti-Esch J, Pessin H, Nelson CJ, Brescia R. 2000. The schedule of attitudes toward hastened death: Measuring desire for death in terminally ill cancer patients. Cancer. 88:2868–2875.

Ruffell TO, Martin NH, Janssen A, Wijesekera L, Knights C, Burman R, Oliver DJ, Al-Chalabi A, Goldstein LH. 2013. Healthcare professionals' views on the provision of gastrostomy and noninvasive ventilation to amyotrophic lateral sclerosis patients in England, Wales, and Northern Ireland. J Palliat Care. 29:225–231.

Schoenfeld MA, Tempelmann C, Gaul C, Kuhnel GR, Duzel E, Hopf J, Feistner H, Zierz S, Heinze H, Vielhaber S. 2005. Functional motor compensation in amyotrophic lateral sclerosis. J Neurol. 252:944–952.

Smith RA, Berg JE, Pope LE, Thisted RA. 2004. Measuring pseudobulbar affect in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 5 Suppl 1:99–102.

Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. 1998. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci. 265:1927–1931.

Sullivan KE, Hebert PC, Logan J, O'Connor AM, McNeely PD. 1996. What do physicians tell patients with end-stage COPD about intubation and mechanical ventilation? Chest. 109:258–264.

Uhlmann RF, Pearlman RA. 1991. Perceived quality of life and preferences for life-sustaining treatment in older adults. Arch Intern Med. 151:495–497.

Vucic S, Kiernan MC. 2006. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. Brain. 129:2436–2446.

Vucic S, Nicholson GA, Kiernan MC. 2008. Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. Brain. 131:1540–1550.

Wilson F, Gott M, Ingleton C. 2013. Perceived risks around choice and decision making at end-of-life: a literature review. Palliat Med. 27:38–53.

Young A, Perrett D, Calder A, Sprengelmeyer R, Ekman P. 2002. Facial Expressions of Emotion: Stimuli and Tests (FEEST), Version for PC. Thurston, UK: Thames Valley Test Company.

Ziemann U, Winter M, Reimers CD, Reimers K, Tergau F, Paulus W. 1997. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis. Evidence from paired transcranial magnetic stimulation. Neurology. 49:1292–1298.

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Perception of Emotional Facial Expressions in Amyotrophic Lateral Sclerosis (ALS) at Behavioural and Brain Metabolic Level

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Abstract

Introduction

Amyotrophic lateral sclerosis (ALS) primarily impairs motor abilities but also affects cognition and emotional processing. We hypothesise that subjective ratings of emotional stimuli depicting social interactions and facial expressions is changed in ALS. It was found that recognition of negative emotions and ability to mentalize other's intentions is reduced.

Methods

Processing of emotions in faces was investigated. A behavioural test of Ekman faces expressing six basic emotions was presented to 30 ALS patients and 29 age-, gender and education matched healthy controls. Additionally, a subgroup of 15 ALS patients that were able to lie supine in the scanner and 14 matched healthy controls viewed the Ekman faces during functional magnetic resonance imaging (fMRI). Affective state and a number of daily social contacts were measured.

Results

ALS patients recognized disgust and fear less accurately than healthy controls. In fMRI, reduced brain activity was seen in areas involved in processing of negative emotions replicating our previous results. During processing of sad faces, increased brain activity was seen in areas associated with social emotions in right inferior frontal gyrus and reduced activity in hippocampus bilaterally. No differences in brain activity were seen for any of the other emotional expressions. Inferior frontal gyrus activity for sad faces was associated with increased amount of social contacts of ALS patients.

Conclusion

ALS patients showed decreased brain and behavioural responses in processing of disgust and fear and an altered brain response pattern for sadness. The negative consequences of

neurodegenerative processes in the course of ALS might be counteracted by positive emotional activity and positive social interactions.

Introduction

Amyotrophic lateral sclerosis (ALS) is a multi-system disorder with the most prominent feature of progressive pyramidal tract pathology but also involving extra-motor cortical areas and other spinal systems [1]. Prefrontal cortical dysfunctions may occur in 30–40% of ALS patients [2]. Furthermore, ALS patients may present with reduced memory capacity for i.e. emotional material [3]. Other domains of emotional processing are similarly affected such as evaluation of emotional stimuli of social situations. ALS patients regard negative pictures as less arousing and more positive [4]. Neurodegeneration of cortical [1,5] and limbic structures such as the amygdala [6] and nucleus accumbens [7] might affect emotional processing abilities especially for aversive emotional information [8] but environmental factors may also contribute to these changes [9]. Furthermore, reduced afferent peripheral inflow (i.e. "somatic markers") [10] to subcortical and cortical networks such as the limbic system may explain variance in emotional processing and "dampening" of negative feelings.

As ALS patients often face an increasing dependency on others, changes in emotional perception might become especially burdensome for the caretakers and clinical staff [11]. Evidence from previous studies suggests cortical compensatory functional reorganization especially in the early course of ALS [12]. Whether these reorganisation processes have a compensatory effect at behavioural level is not clear.

In the current study, emotional processing of facial cues was measured in ALS patients compared to healthy participants. Using functional magnetic resonance imaging (fMRI), we explored brain processing of emotional facial expressions in a subgroup of ALS patients and healthy participants.

Furthermore, degree of brain activity was correlated with degree of depression and number of social contacts in everyday life across all the subjects, as we have hypothesized that positive contact with caregivers and family reduces negative emotional perception and improves positive emotional response in ALS [9].

Methods

Participants

Thirty patients (16 females; 21 with spinal, 9 with bulbar onset; mean age 60±10 years) diagnosed with probable or definite ALS according to the revised El Escorial criteria [13] by a board certified neurologist, participated in the emotion recognition task and a subgroup of fifteen patients (5 females, all sporadic cases, all spinal onset, mean age 54±12 years) in the fMRI paradigm. ALS patients were consecutively recruited from the outpatient clinic of the Department of Neurology at the University of Ulm. All the patients had at least six months between the diagnosis and testing.

Patients' disease status was assessed with ALS functional rating scale revised (ALS-FRS-R) [14]. Patients who met the criteria of frontotemporal dementia (FTD) were excluded. N = 12 patients were intermittently treated by non-invasive ventilation and had shortness of breath when lying supine in the scanner and N = 4 patients used a wheelchair. They were all excluded from the fMRI study.

Twenty-nine age, gender and education matched healthy volunteers (8 females, mean age 61±8 years) served as controls for the emotion recognition task and fourteen of them (7 females, mean age 61±10 years) for the fMRI paradigm. Healthy controls were contacted via email by the organizing committee for senior education at the University of Ulm. All the patients and healthy controls were also included in another study reported previously [15].

The participants were all right-handed [16] with normal vision. None of the patients and healthy controls had a history of neurological or psychiatric disorder. N = 24 patients received Riluzole, including all the patients participating in the fMRI paradigm. The participants received no other medication affecting central nervous system.

The study was approved by the Ethics Committees of the Universities of Ulm and Tübingen (174/2008) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All healthy controls and patients gave written informed consent prior to inclusion in the study.

Neuropsychological assessment

To make sure the participants were able to understand instructions they all were screened for major cognitive deficits by assessing Mini Mental State Examination (MMSE) [17]. Patients with cognitive deficits (cut-off ≤ 26) were excluded. In addition, all the participants were assessed with the Beck`s Depression Inventory (BDI, range for mild depression 12–19) [18].

Furthermore, the participants of the fMRI paradigm received more extensive neuropsychological assessment. They were screened for cognitive deficits by assessing the MMSE and a Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) measuring premorbid crystallized verbal intelligence [19]. Additionally, specific neuropsychological testing was focused on frontal lobe functions including verbal fluency (Regensburg Fluency Test) [20], design fluency (5-Point Fluency Test) [21] and attention (Symbol Digit Modalities Test) [22]. Social contacts were assessed by using an in-house questionnaire determining social activity as the number of people seen (at least one minute per person) on average per day and the average time spent with each person.

Experimental design

Facial emotion processing at behavioural level.   ALS patients and healthy controls first performed a verbal rating of Ekman faces stimuli (facial expressions of emotion test; FEEST) [23]. For the verbal rating task participants viewed 60 black-and-white pictures of facial expressions of basic emotions (10 stimuli of each emotion: anger, disgust, fear, sadness, surprise and happiness) on a computer screen. Participants were asked to choose either of six displayed emotions according to what he/she most likely saw expressed on the face. Faces were displayed for 6s but participants had unlimited time to tick the box of any of the six displayed emotions.

Facial emotion processing at functional cortical level (fMRI).   In the fMRI paradigm an event related design, optimised for maximal blood oxygen level dependent (BOLD) signal amplitude was used [24]. Basic emotions of anger, disgust, fear, sadness, surprise and happiness were presented. In total 24 stimuli of each of the six emotions (including emotion intensities of 50%, 75% and 100%, 8 stimuli of each), 45 neutral faces and 45 "meaningless" stimuli with random scattered patterns were presented in a randomized order. The stimuli were presented in three trials consisting of 26 stimulation sequences. Each stimulation sequence was 14s of duration consisting stimulus of epochs of 5s (a block of three stimuli of about 1s interleaved by rest epochs of about 1s) and followed by a rest period of 9s, similar to the methods described earlier [5] (Fig 1). Stimuli were presented via video goggles in pseudo-randomised order balanced with respect to the categories of basic emotions.
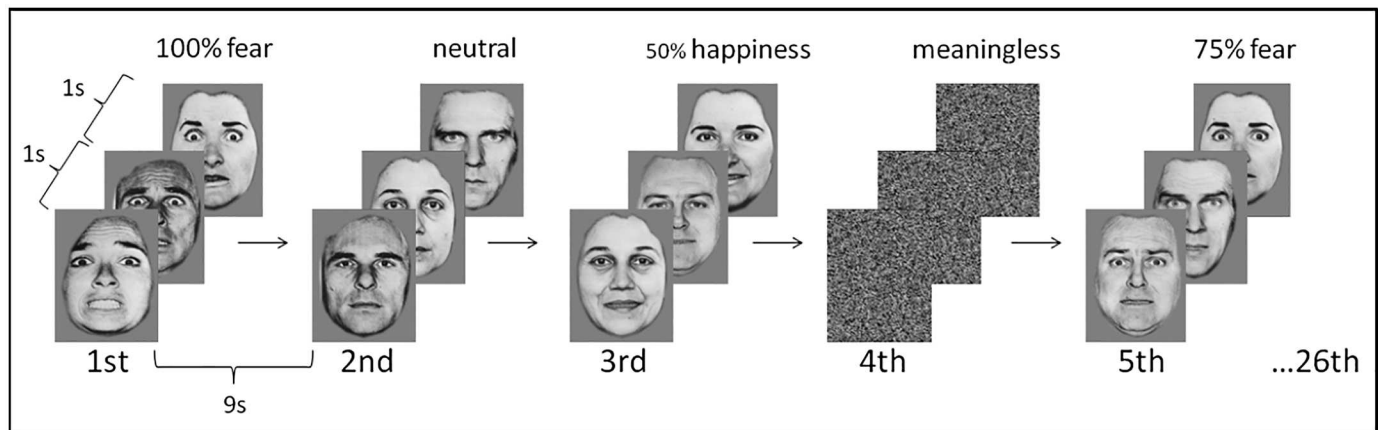
Fig 1. Example sequence of the event related fMRI paradigm of different intensities of emotions and meaningless and neutral stimuli. In total three trials, each including 26 stimulation sequences was presented. A stimulation sequence consisted of a block of three stimuli of one second interleaved by rest epochs of one second. Each block was followed by a rest period of nine seconds. Stimulus blocks of different emotions (anger, disgust, fear, sadness, surprise and happiness; here only fear and happiness are displayed as examples) with different intensities and neutral and meaningless stimuli were presented in a randomized order. Reprinted from FEEST [23] under a CC BY license, with permission from Paul Ekman Group, LLC, original copyright 2002.

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fMRI Data Acquisition and analysis. Images were acquired using a 3 Tesla whole body scanner (Symphony, Siemens, Erlangen, Germany). T1-weighted anatomical images and functional images were collected as described earlier [5]. To optimize data acquisition, imaging slice orientation was tilted by 30° [25].

Image processing was performed using SPM8 (Statistical parametric mapping, Wellcome Department of Imaging Neuroscience, London, UK) [26] as described previously [5]. The parameter estimates were modelled with six regressors for the basic emotions anger, disgust, fear, sadness, surprise and happiness. Each regressor was parametrically described according to intensity of emotional expression ranging from neutral to 50%, 75% and 100% (Fig 1). Regressors were convolved with a theoretical hemodynamic response function (hrf; sum of two gamma functions) [27]. The voxel time series were high pass filtered (time constant 141s) and the noise component in the model was described by a first order autoregressive model.

Statistical analysis

All statistical analyses were performed with Statistical package for Social Sciences (SPSS version 21.0 IBM). Mean values ± standard deviations are given in the tables. One-way ANOVAs with between factor group (ALS patients, healthy controls) and within factors demographics, psychological adjustment (depression), and neuropsychological test performance were conducted. For behavioral performance of face recognition ability, ANCOVA with between factor group (ALS patients, healthy controls) and within subject factor facial emotion (percentage of correctly identified emotions) corrected for depressiveness was used. A threshold of $p < 0.05$ was adopted for statistical significance.

For fMRI data, individual weighting factors of the emotion regressors for each participant and trial were computed. Individual parametric maps were subjected to a second level group (ALS patients vs. healthy controls) analysis using a two way ANOVA with emotional facial expressions for between-group differences.

The association between BOLD response and level of degree of social contacts was tested using a second level analysis of simple regression. Only areas with a significance of uncorrected

Table 1. Participants of the behavioral emotion recognition task.

	ALS-patients N = 30	Healthy controls N = 29		
	mean±SD	mean±SD	F	p
Age [years]	60±10	61±8	0.39	0.54
Gender	16 females	8 females	4.2	0.05
Education [years]	9.7±1.5	10.0±1.7	0.83	0.37
Symptom onset	21 spinal	N/A		
ALS-FRS-R	27.9±11.4	N/A		
Disease duration [months]	41±18	N/A		
Progression rate	0.9 ± 0.7	N/A		
Depression				
BDI	12.9±4.9	6.2±4.0	32.24	<0.01*
Dementia				
MMSE	29.5±0.8	29.7±0.7	0.90	0.35

ALS-FRS-R: ALS functional rating scale revised [14]; BDI: Beck´s Depression Inventory; MMSE: Mini Mental State Examination.

* indicates statistical significance with $p < 0.05$ in a two-sample t-test.

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$p < 0.005$ at voxel level and with an extended cluster threshold ≥ 12 voxels were considered significant.

Results

Demographic, clinical, social and neuropsychological variables

ALS patients and healthy controls were matched with respect to demographics (Tables 1 and 2). ALS patients of the behavioural task presented with increased depression (BDI: $p < 0.01$) compared to healthy controls (Table 1). The patients of the fMRI paradigm presented with decreased premorbid intelligence ($p < 0.01$) and increased depression (BDI: $p < 0.01$), compared to the healthy controls. No statistically significant difference was seen between patients and healthy controls in other neuropsychological variables or in degree of social contacts (Table 2).

Facial emotion processing at behavioural level

ALS patients (n = 30) recognized anger (p = 0.04), disgust ($p < 0.01$) and fear ($p < 0.01$) less accurately than healthy controls (Fig 2, Table 3). Patient subgroup (n = 15) measured in fMRI recognized fear ($p < 0.01$), disgust (p = 0.02) and happiness (p = 0.03) less than healthy controls (Table 3). However, analysis of covariance revealed that variance between the patients and the control groups in rating angry faces and happy faces were explained by the higher depression of the patients compared to healthy controls ($p > 0.05$, when corrected for depression). Higher depression score of the patients did not explain the variance in rating of disgust and fear (both $p < 0.05$ when corrected for depression).

BOLD-Response to emotional facial expressions: ALS patients versus controls

During the fMRI task of processing all types of emotional facial expressions, ALS patients presented with a significantly increased activity in right inferior frontal gyrus (BA 44/45). In addition, patients showed increased activity in right angular gyrus, right insula and right precuneus (Fig 3; Table 4). In comparison, the patients presented with significantly decreased activity in inferior frontal gyrus, orbitofrontal gyrus, precentral gyrus, middle temporal gyrus and

Table 2. Participants of the fMRI paradigm.

	ALS-patients N = 15	Healthy controls N = 14		
	mean±SD	mean±SD	F	p
Age [years]	54±12	61±10	2.9	0.10
Gender	5 females	7 females	0.79	0.38
Education [years]	10.1±1.6	10.8±1.6	0.83	0.37
Symptom onset	15 spinal	N/A		
ALS-FRS-R	28.7±9.6	N/A		
Disease duration [months]	33 ± 18	N/A		
Progression rate	1.0 ± 0.7	N/A		
Handedness	All right handed	All right handed		
Depression				
BDI	14.3±5.3	4.5±3.9	16.8	<0.01*
Social contacts				
Number	16±15	25±34	0.7	0.40
Hours	12.5±8.4	8.4±7.4	1.9	0.20
Dementia				
MMSE	29.6±0.7	29.1±0.9	2.3	0.14
Premorbid crystallized verbal intelligence				
MWT-B	98.0±12.6	117.4± 0.0	16.1	<0.01*
Phonematic verbal fluency				
single initial letter ("p")	10.2±5.5	21.0±2.8	6.4	0.05
alternating initial letters ("g" and "r")	15.2±4.9	17.0±4.2	0.2	0.67
Semantic verbal fluency				
animals	27.0±8.3	35.5±0.7	1.9	0.23
Design fluency				
5-point fluency	25.0±7.2	38.5±10.6	3.6	0.13
Attention				
SDMT	39.2±7.2	54.5±9.2	5.7	0.06

ALS-FRS-R: ALS functional rating scale revised version; BDI: Beck´s Depression Inventory; Number: people seen (at least for a one minute per person) on average per day; Hours: hours spent with people on average per day; MMSE: Mini Mental State Examination; MWT-B: Mehrfachwahl-Wortschatz-Intelligenztest-B, premorbid crystallized verbal intelligence test; Phonematic verbal fluency single initial letter ("p"): listing words with initial letter "p", age-scaled percentile; verbal fluency alternating initial letters ("g" and "r"): listing alternating words with initial letters "g" and "r", age-scaled percentile; Semantic verbal fluency animals: listing animals, age-scaled percentile; 5-Point fluency: non-verbal design fluency; SDMT: Symbol Digit Modalities Test—correct items.

* indicates statistical significance with p<0.05 in a two-sample t-test.

calcarine sulcus on the left side and in lingual gyrus, sub-lobar frontal gyrus, and cerebellum on the right side (Table 5).

Response to different types of emotional facial expressions: ALS patients versus controls. Significant differences between the ALS patients and healthy controls were seen only for sad faces. Compared to the healthy controls ALS patients presented with increased activity in the right inferior frontal gyrus (p<0.005) but decreased activity in hippocampus bilaterally (p<0.005), when processing images of sad faces. No significant differences in brain activity between the patients and healthy controls were seen for any of the other emotional expressions.

Brain responses to emotional facial expressions: association with cognition and social contacts. Premorbid intelligence was the only assessed neuropsychological domain where the patients presented with significantly lower scores than the controls. However, a post-hoc
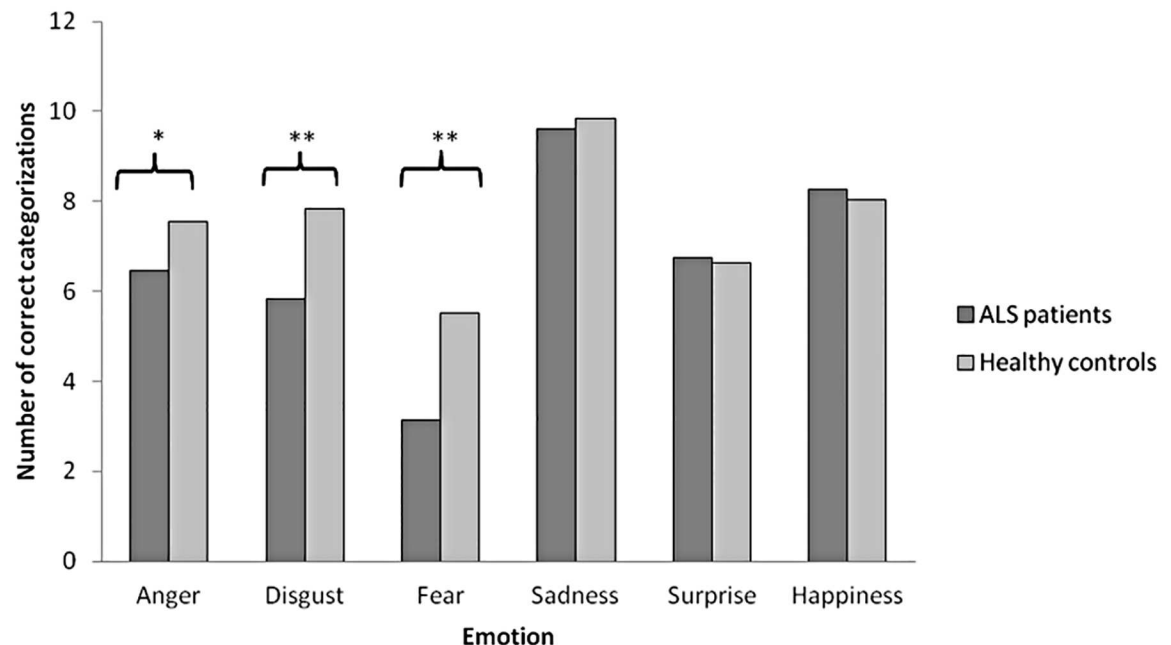
Fig 2. Number of correct categorizations of facial emotion expressions. * indicates statistical significance with p<0.05 and ** indicates statistical significance with p<0.01 between patients (n = 30) and healthy controls (n = 29) in a two-sample t-test.

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regression analysis of fMRI responses and premorbid intelligence provided no association of premorbid intelligence and the number of activated voxels in the patients' brain areas with decreased or increased activation.

Regression analysis revealed a statistically significant positive correlation between number of social contacts and activity in right inferior frontal gyrus (BA 44/45; p = 0.003) for ALS patients (Fig 4). This correlation was not seen for healthy controls.

Discussion

In the current study, faces of the six basic emotions were presented to medium and advanced affected ALS patients and healthy controls. Data of correct emotion categorization and cortical BOLD responses in fMRI were recorded.

Table 3. Means and standard deviations of correct categorization of facial stimuli in ALS patients and healthy controls of the emotion recognition task at behavioral level of all patients and patients that participated in fMRI.

Emotion	ALS patients N = 30 mean ± SD	ALS patients (fMRI) N = 15 mean ± SD	Healthy controls N = 29 mean ± SD	ALS patients (n = 30) vs. healthy controls F	p	ALS patients (n = 15) vs. healthy controls F	p
Anger	6.53 ± 2.68	6.80 ± 2.54	7.55 ± 2.13	4.6	0.04*	1.1	0.31
Disgust	6.27 ± 2.55	5.73 ± 3.03	7.83 ± 2.33	9.8	<0.01**	3.2	0.02*
Fear	3.23 ± 1.87	3.47 ± 2.07	5.52 ± 2.21	34.2	<0.01**	0.1	<0.01**
Happiness	9.63 ±0.67	9.40 ± 0.83	9.83 ± 0.47	2.5	0.11	6.9	0.03*
Sadness	6.70 ± 2.00	6.53 ± 2.23	6.62 ± 2.09	0.3	0.60	0.3	0.90
Surprise	8.23 ± 1.52	7.53 ± 1.73	8.03 ± 1.48	0.7	0.39	0.3	0.32

* indicates statistical significance with p<0.05
** with p<0.01 in a two-sample t-test.

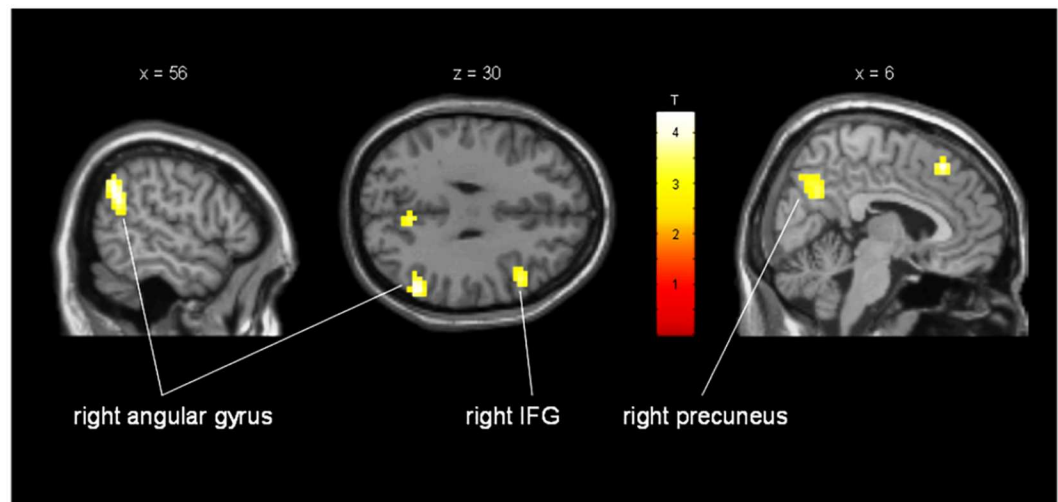doi:10.1371/journal.pone.0164655.t003

Fig 3. Increased activation of ALS patients compared to healthy controls when processing different emotional facial expressions. Activation in a sub region of the right inferior frontal gyrus (MNI coordinates: x = 49mm y = 18mm z = 30mm; cluster size = 37 voxels; T = 3.53; p_{uncorr} = 0.001), right angular gyrus (MNI coordinates: x = 56mm y = -58mm z = 34mm; cluster size = 102 voxels; T = 4.40; p_{uncorr}<0.001) and right precuneus (MNI coordinates: x = 6mm y = -62mm z = 34mm; cluster size = 31 voxels; T = 3.42; p_{uncorr} = 0.001). Activations show areas with significant increase of activity in patients in average for all emotions.

Patients showed reduced performance in facial emotion recognition for disgust and fear. Patients presented with increased activity in the right inferior frontal gyrus and decreased activity in hippocampus bilaterally during processing of emotions in faces, especially for sadness. Activity in the right inferior frontal gyrus was positively correlated with number of daily social contacts.

ALS patients reduced recognition of disgust and fear might be interpreted as a change in the network of facial emotion processing. Lower cognitive abilities of ALS patients suggested earlier [28] most likely do not account for the changes in emotion recognition, as most of the tests assessing cognition did not reveal significant difference between the patients and the controls.

During the fMRI task of processing facial expressions, patients showed decreased activity in areas related to the emotions they also recognized less. Reduced brain activity was seen i.e. in left middle temporal and left precentral gyrus that might be involved in processing of negative facial expressions like disgust [29]. Furthermore, patients showed reduced activity in left inferior frontal gyrus (BA 44/45), an area known to be involved in processing of facial expressions of anger and fear [30].

When analyzing brain activities for each emotion separately, differences between the patients and controls were found only for sad faces. When processing sad faces patients showed

Table 4. Regions of increased activation in processing emotional facial stimuli in ALS patients compared to healthy controls (all emotions averaged).

Area	Left/Right	MNI Coordinates	Cluster Size	T	p_{uncorr}
Angular Gyrus	R	56 –58 34	102	4.40	<0.001
Insula	R	38 28 5	16	3.77	<0.001
IFG	R	49 18 30	37	3.53	0.001
Precuneus	R	6 –62 34	31	3.42	0.001

Displayed are clusters >15 voxels with uncorrected threshold of p<0.001; IFG = Inferior Frontal Gyrus

Table 5. Regions of decreased activation in processing emotional facial stimuli in ALS patients compared to healthy controls (all emotions averaged).

Area	Left/Right	MNI Coordinates	Cluster Size	T	p_uncorr
OFG	L	-26 39–16	98	7.47	<0.001
MTG	L	-55–54 0	283	6.25	<0.001
		-59–40 9	28	4.92	<0.001
Precentral Gyrus	L	-44 7 51	42	5.48	<0.001
Lingual Gyrus	R	13–87–8	44	5.17	<0.001
IFG	L	-44 36 26	70	5.07	<0.001
sub-lobar Frontal Gyrus	R	17 32–8	20	4.94	<0.001
Calcarine Sulcus	L	-26–58–9	43	4.61	<0.001
Cerebellum	R	31–54–42	25	4.56	<0.001

Displayed are clusters >15 voxels with uncorrected threshold of $p<0.001$; IFG = Inferior Frontal Gyrus; OFG = Orbitofrontal Gyrus; MTG = Middle Temporal Gyrus

increased brain activity in right inferior frontal gyrus (BA 44/45), an area associated with imitating emotional responses, also often called "mirror neuron area" [31] and decreased activity in hippocampus bilaterally.

Hippocampus is a main target for storage and retrieval of information and memory [32] and it might be affected in the course of ALS [1] thus being associated with memory impairment in ALS [33]. Healthy controls might use hippocampus for memory retrieval to correctly categorize emotional expressions [34], whereas patients may have impaired access to this retrieval loop. Alternatively, the patients might increase the activation in the right inferior frontal gyrus, which is also known to be important for facial expression recognition [35].

However, this all remains highly speculative as hippocampus is considered to be mainly involved in retrieval of recent memories [36] which is not the case in facial emotion recognition.
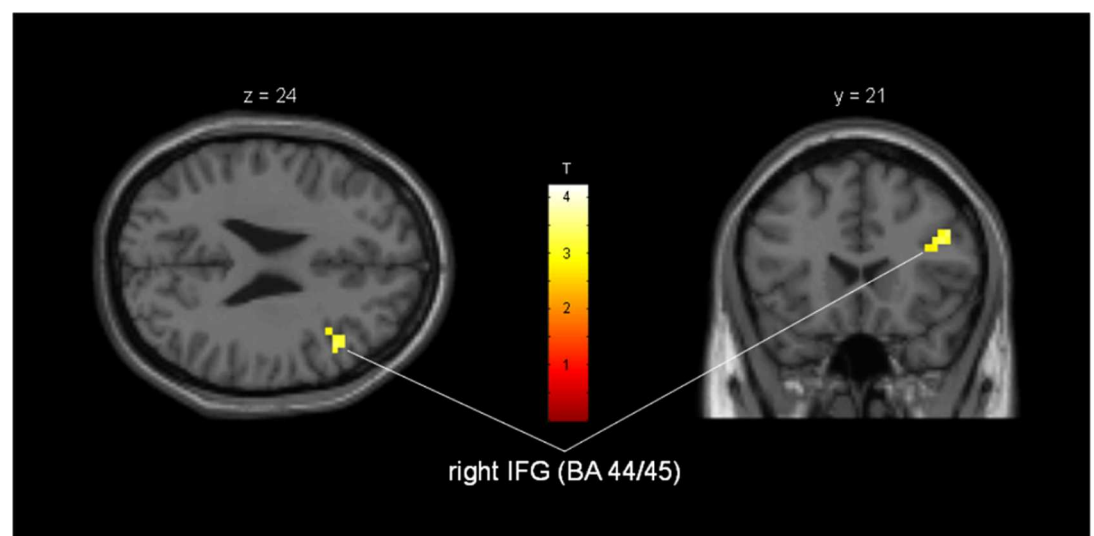

Fig 4. Regression analysis of brain activity and social contacts during processing of emotional facial stimuli in ALS patients. Activation in a subregion of right inferior frontal gyrus/Brodmann Area 44 and 45. MNI-coordinates: x = 44mm, y = 21mm, z = 30mm; cluster-size = 12 voxels; T = 3.36; p_{uncorr} = 0.003.

Also the patients of the current study did not show any memory deficits. Alternatively, other aspects might account for the change in cortical activity. Several studies have reported involvement of cortical hyper excitability [37,38,39] and reduced corticocortical inhibition [40] in ALS. It has also been suggested that not just hyper excitability but imbalance between cortical excitation and inhibition might take place in ALS [41]. Most likely these pathological changes also increase in the course of the disease being more prominent in advanced ALS, which might partly explain brain activity differences between patients and healthy controls in the current study.

Some have suggested cortical reorganisation in different cerebral networks in ALS [1,12]. Functional cortical connectivity may be reduced [42] or alternatively increased [43] in some brain areas of ALS patients. Until now, there has been no evidence for a functional relevance of these reorganisation processes. Therefore, this is to our knowledge the first study on emotional processing in ALS suggesting that in the course of ALS increased activity (in right inferior frontal areas) might be considered as functional compensation and reorganization in the best sense.

Furthermore, the increased activity in inferior frontal gyrus was associated with increased number of daily social contacts of ALS patients. This suggests that positive impact of social contacts on affective state might be reflected in the inferior frontal gyrus network activity. It has been suggested that social contacts are a protective factor against cognitive decline [44]. Thus, neurodegenerative processes in the course of ALS might be counteracted by positive emotional activity in social life, possibly via the indirect pathway of reducing depression in patients at later stages of the disease.

The ALS sample investigated here showed increased depression compared to the healthy sample. Depressive mood increases after the diagnosis but even already one year before the diagnosis patients may show increased depression [45]. However, often in the course of the disease acceptance of artificial respiration, quality of life and depression draw closer to the level of the healthy population [15,46,47]. In the later phases of the disease patient's attention is focused on caretaking family members [15] and many caretakers show a positive attitude and positive emotional responsiveness to the patient thus increasing the force of the positive emotional-social buffer [48].

These data replicate our earlier results with a comparable group of ALS patients using the IAPS. We found increased positive affective responding to positive slides and decreased negative affective responding to negative emotional slides in ALS compared to the matched controls [4]. In another study of ours, ALS patients demonstrated positive subjective responding and increased activity in the supramarginal gyrus in the course of the disease [9]. The supramarginal gyrus just as the right inferior frontal gyrus can be considered as part of the brain network related to positive emotional-social perception [9]. Overall, the current study provides intriguing evidence for the importance of including ALS patients in social life to counteract possible negative effects of pathological changes on social-emotional information processing.

Limitations

A shortcoming of our study is the limited number of patients. However, the criterion of a homogenous group and the time consuming investigations were limiting factors for participation. Furthermore, patients showed reduced scores in premorbid crystallized verbal intelligence, which however was unlikely affecting the performance of the patients as we found no correlation of premorbid intelligence and the number of activated voxels in the areas described. Patients were also able to perform the task properly and presented with increased activity in prefrontal areas rather than reduced activity as it might be expected in case of cognitive deficits or FTD.

Additionally, patient cohort presented with increased depression compared to controls. It has been shown that depressed individuals are more reactive to sad faces [49] and might direct more attention to images expressing sadness [50] which could explain increased cortical activation when viewing sad faces. Furthermore, depression is associated with impaired memory [51] and reduced hippocampal volume [52] which might lead to reduced hippocampal activation as seen in the patients of the current study. Additionally, depressed individuals might have difficulties with selective attention [50], which may reduce performance in the emotion recognition task. However, in the current sample there was no evidence for globally impaired attention performance, neither in neuropsychological assessment nor in the facial recognition task.

Furthermore, unlike mostly in the studies on depression none of our patients presented with clinically relevant depression according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [53]. Despite the significant difference between the patients and healthy controls in depression score, the patient cohort presented only with mild depression, some having no depressive symptoms at all. Therefore, it is unlikely that patients' increased negative mood heavily influenced their emotion processing at behavioural or cortical level.

Supporting Information

S1 File. Copyright permission for Fig 1.
(PDF)

S2 File. Questionnaire on social contacts in English.
(DOCX)

S3 File. Questionnaire on social contacts in German.
(DOCX)

Acknowledgments

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Formal analysis: DL HAO J. Keller.

Funding acquisition: DL ACL NB.

Investigation: DL JH.

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Validation: JH DL J. Kassubek.

Visualization: HAO J. Keller.

Writing – original draft: HAO DL J. Keller.

Writing – review & editing: IU J. Kassubek NB.

References

1. Braak H, Brettschneider J, Ludolph AC, Lee VM, Trojanowski JQ, Del Tredici K. Amyotrophic lateral sclerosis—a model of corticofugal axonal spread. Nat Rev Neurol 2013; 9:708–714. doi: 10.1038/nrneurol.2013.221 PMID: 24217521

2. Kew JJM, Goldstein LH, Leigh PN, Abrahams S, Cosgrave N, Passingham RE. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis. Brain 1993; 116:1399–1423. PMID: 8293278

3. Papps B, Abrahams S, Wicks P, Leigh PN, Goldstein LH. Changes in memory for emotional material in amyotrophic lateral sclerosis (ALS). Neuropsychologia 2005; 43:1107–1114. doi: 10.1016/j.neuropsychologia.2004.11.027 PMID: 15817168

4. Lulé D, Kurt A, Jürgens R, Kassubek J, Diekmann V, Kraft E, et al. Emotional responding in amyotrophic lateral sclerosis. J Neurol 2005; 252:1517–1524. doi: 10.1007/s00415-005-0907-8 PMID: 15977000

5. Lulé D, Diekmann V, Müller HP, Kassubek J, Ludolph AC, Birbaumer N. Neuroimaging of multimodal sensory stimulation in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2010; 81:899–906. doi: 10.1136/jnnp.2009.192260 PMID: 20543183

6. Kawashima T, Doh-ura K, Kikuchi H, Iwaki T. Cognitive dysfunction in patients with amyotrophic lateral sclerosis is associated with spherical or crescent-shaped ubiquitinated intraneuronal inclusions in the parahippocampal gyrus and amygdala, but not in the neostriatum. Acta Neuropathol 2001; 102:467–472. PMID: 11699560

7. Bede P, Elamin M, Byrne S, Mclaughlin RL, Kenna K, Vajda A, et al. Basal ganglia involvement in amyotrophic lateral sclerosis. Neurology 2013; 81:2107–2115 doi: 10.1212/01.wnl.0000437313.80913.2c PMID: 24212388

8. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002; 16:331–348. doi: 10.1006/nimg.2002.1087 PMID: 12030820

9. Lulé D, Diekmann V, Anders S, Kassubek J, Kübler A, Ludolph A, et al. Brain responses to emotional stimuli in patients with amyotrophic lateral sclerosis (ALS). J Neurol 2007; 254:519–527. doi: 10.1007/s00415-006-0409-3 PMID: 17401515

10. Damasio AR, Tranel D, Damasio H. Somatic markers and the guidance of behaviour: theory and preliminary testing. In: Levin HS, Eisenberg HM, Benton AL, eds. Frontal Lobe Function and Dysfunction. New York, NY: Oxford University Press; 1991:217–229.

11. Lillo P, Mioshi E, Hodges JR. Caregiver burden in amyotrophic lateral sclerosis is more dependent on patients' behavioral changes than physical disability: a comparative study. BMC Neurol 2012; 12:156. doi: 10.1186/1471-2377-12-156 PMID: 23216745

12. Schoenfeld MA, Tempelmann C, Gaul C, Kühnel GR, Düzel E, Hopf JM, et al. Functional motor compensation in amyotrophic lateral sclerosis. J Neurol 2005; 252:944–952. doi: 10.1007/s00415-005-0787-y PMID: 15750701

13. Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, et al. A revision of the El Escorial criteria-2015. Amyotroph Lat Scl Fr 2015; 16:291–292.

14. Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999; 169:13–21. PMID: 10540002

15. Lulé D, Pauli S, Altintas E, Singer U, Merk T, Uttner, et al. Emotional adjustment in amyotrophic lateral sclerosis (ALS). J Neurol 2012; 259:334–341. doi: 10.1007/s00415-011-6191-x PMID: 21808983

16. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 1971; 9:97–113. PMID: 5146491

17. Folstein MF, Folstein SE, McHugh PR. Mini-Mental-State: A practical method for grading the cognitive state of patients for the clinician. J Psych Res 1975; 12:189–198.

18. Hautzinger M, Bailer M, Worall H, Keller F. Beck-Depressions-Inventar, BDI—Testhandbuch. 2nd ed. Bern: Verlag Hans Huber; 1995.

19. Lehrl S. Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. Manual, 2nd ed. Erlangen: Perimed Fachbuch-Verlagsgesellschaft; 1989.

20. Aschenbrenner S, Tucha O, Lange K. Regensburger Wortflüssigkeits-Test. Erlangen: Hogrefe-Verlag; 2000.

21. Regard M, Strauss E, Knapp P. Childrens'production on verbal and non-verbal fluency tasks. Percept Mot Skills 1982; 55:839–844. doi: 10.2466/pms.1982.55.3.839 PMID: 7162920

22. Lewandowski LJ. The symbol digits modalities test: A screening for brain-damaged children. Percept Mot Skills 1984; 59:615–618. doi: 10.2466/pms.1984.59.2.615 PMID: 6083544

23. Young A, Perrett D, Calder A, Sprengelmeyer R, Ekman P. Facial Expressions of Emotion: Stimuli and Tests (FEEST), Version for PC. Thurston, UK: Thames Valley Test Company; 2002.

24. Robinson PA, Drysdale PM, Van der Merwe H, Kyriakou E, Rigozzi MK, Germanoska B, et al. BOLD responses to stimuli: Dependence on frequency, stimulus form, amplitude, and repetition rate. Neuroimage 2006; 31:585–599. doi: 10.1016/j.neuroimage.2005.12.026 PMID: 16466935

25. Deichmann R, Turner R. Improvement of local BOLD sensitivities in the presence of susceptibility gradients by using tilted slices. Proc Intl Soc Mag Reson Med 2002; 10:1414.

26. Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Map 1995; 2:189–210.

27. Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. Neuroimage 1998; 7:30–40. doi: 10.1006/nimg.1997.0306 PMID: 9500830

28. Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol 2013; 12:368–330. doi: 10.1016/S1474-4422(13)70026-7 PMID: 23518330

29. Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 2009; 34:418–432. PMID: 19949718

30. Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 1998; 265:1927–1931. doi: 10.1098/rspb.1998.0522 PMID: 9821359

31. Rizzolatti G, Craighero L. The mirror-neuron system. Annu. Rev. Neurosci. 2004; 27:169–192. doi: 10.1146/annurev.neuro.27.070203.144230 PMID: 15217330

32. Thomas SA. Neuromodulatory signaling in hippocampus-dependent memory retrieval. Hippocampus 2015; 25:415–431. doi: 10.1002/hipo.22394 PMID: 25475876

33. Machts J, Loewe K, Kaufmann J, Jakubiczka S, Abdulla S, Petri S, et al. Basal ganglia pathology in ALS is associated with neuropsychological deficits. Neurology 2015; 85:1301–1309. doi: 10.1212/WNL.0000000000002017 PMID: 26385880

34. Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, et al. An fMRI Study of Facial Emotion Processing in Patients With Schizophrenia. Am J Psychiatry 2002; 159:1992–1999. doi: 10.1176/appi.ajp.159.12.1992 PMID: 12450947

35. Enticott PG, Johnston PJ, Herring SE, Hoy KE, Fitzgerald PB. Mirror neuron activation is associated with facial emotion processing. Neuropsychologia 2008; 46:2851–2854. doi: 10.1016/j.neuropsychologia.2008.04.022 PMID: 18554670

36. McClelland J, McNaughton B, O'Reilly R. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist model of learning and memory. Psychological Review 1995; 102:419–457. PMID: 7624455

37. Menon P, Kiernan MC, Vucic S. Cortical hyperexcitability precedes lower motor neuron dysfunction in ALS. Clin Neurophysiol 2015; 126:803–809. doi: 10.1016/j.clinph.2014.04.023 PMID: 25227219

38. Vucic S, Nicholson GA, Kiernan MC. Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. Brain 2008; 131:1540–1550. doi: 10.1093/brain/awn071 PMID: 18469020

39. Vucic S, Kiernan MC. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. Brain 2006; 129:2436–2446. doi: 10.1093/brain/awl172 PMID: 16835248

40. Ziemann U, Winter M, Reimers CD, Reimers K, Terqau F, Paulus W. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis. Evidence from paired transcranial magnetic stimulation. Neurology 1997; 49:1292–8. PMID: 9371911

41. Khedr EM, Ahmed MA, Hamdy A, Shawky OA. Cortical excitability of amyotrophic lateral sclerosis: Transcranial magnetic stimulation study. NEUROPHYSIOL CLIN 2011; 41:73–79. doi: 10.1016/j. neucli.2011.03.001 PMID: 21624709

42. Mohammadi B, Kollewe K, Samii A, Krampfl K, Dengler R, Münte TF. Changes of resting state brain networks in amyotrophic lateral sclerosis. Exp Neurol 2009; 217:147–153. doi: 10.1016/j.expneurol. 2009.01.025 PMID: 19416664

43. Agosta F, Canu E, Valsasina P, Riva N, Prelle A, Comi G, et al. Divergent brain network connectivity in amyotrophic lateral sclerosis. Neurobiol Aging 2013; 34:419–427. doi: 10.1016/j.neurobiolaging.2012. 04.015 PMID: 22608240

44. Fankhauser S, Forstmeier S, Maercker A, Luppa M, Luck T, Riedel-Heller SG. Risk of Dementia in Older Adults With Low Versus High Occupation-Based Motivational Processes: Differential Impact of Frequency and Proximity of Social Network. J Geriatr Psychiatry Neurol 2014;

45. Pisa FE, Logroscino G, Casetta A, Cecotti L, Verriello L, Bratina A, et al. The Use of Antidepressant Medication before and after the Diagnosis of Amyotrophic Lateral Sclerosis: A Population-Based Cohort Study. Neuroepidemiology; 2015; 44:91–98. doi: 10.1159/000374119 PMID: 25765191

46. Lulé D, Nonnenmacher S, Sorg S, Heimrath J, Hautzinger M, Meyer T, et al. Live and let die: existential decision processes in a fatal disease. J Neurol 2014;doi: 10.1007/s00415-013-7229-z PMID: 24413639

47. Lulé D, Ehlich B, Lang D, Sorg S, Heimrath J, Kübler A, et al. Quality of life in fatal disease: the flawed judgment of the social environment. J Neurol 2013; 260:2836–2843. doi: 10.1007/s00415-013-7068-y PMID: 23989341

48. Hecht MJ, Graesel E, Tigges S, Hillemacher T, Winterholler M, Hilz M-J, et al. Burden of care in amyotrophic lateral sclerosis. Palliative Medicine 2003; 17:327–333. PMID: 12822849

49. Bistricky SL, Ingram RE, Atchley RA. Facial affect processing abd depression susceptibility: Cognitive biases and cognitive neuroscience. Psychol Bull 2011;doi: 10.1037/a0025348 PMID: 21895353

50. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. Annu Rev Clin Psychol 2005; 1:167–95. doi: 10.1146/annurev.clinpsy.1.102803.143916 PMID: 17716086

51. Hickie I, Naismith S, Ward PB, Turner K, Scott E, Mitchell P, et al. Reduced hippocampla volumes and memory loss in patients with early- and late-onset depression. Br J Psychiatry 2005; 186:197–202. doi: 10.1192/bjp.186.3.197 PMID: 15738499

52. Campbell S, Marriott M, Claude N, MacQueen GM. Lower Hippocampal Volume in Patients Suffering From Depression: A Meta-Analysis. Am J Psychiatry 2004; 161:598–607. doi: 10.1176/appi.ajp.161.4. 598 PMID: 15056502

53. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

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ORIGINAL COMMUNICATION

Pathological laughing and crying in amyotrophic lateral sclerosis is related to frontal cortex function

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Abstract The syndrome of pathological laughing and crying (PLC) is characterized by episodes of involuntary outbursts of emotional expression. Although this phenomenon has been referred to for over a century, a clear-cut clinical definition is still lacking, and underlying pathophysiological mechanisms are not well understood. In particular, it remains ill-defined which kind of stimuli—contextually appropriate or inappropriate—elicit episodes of PLC, and if the phenomenon is a result of a lack of inhibition from the frontal cortex ("top-down-theory") or due to an altered processing of sensory inputs at the brainstem level ("bottom-up-theory"). To address these questions, we studied ten amyotrophic lateral sclerosis (ALS) patients with PLC and ten controls matched for age, sex and education. Subjects were simultaneously exposed to either emotionally congruent or incongruent visual and auditory stimuli and were asked to rate pictures according to their emotional quality. Changes in physiological parameters (heart rate, galvanic skin response, activity of facial muscles) were recorded, and a standardized self-assessment lability score (CNS-LS) was determined. Patients were influenced in their rating behaviour in a negative direction by mood-incongruent music. Compared to controls, they were influenced by negative stimuli, i.e. they rated neutral pictures more negatively when listening to sad music. Patients rated significantly higher on the CNS-LS. In patients, changes of electromyographic activity of mimic muscles during different emotion-eliciting conditions were explained by frontal cortex dysfunction. We conclude that PLC is associated with altered emotional suggestibility and that it is preferentially elicited by mood-incongruent stimuli. In addition, physiological reactions as well as behavioural changes suggest that this phenomenon is primarily an expression of reduced inhibitory activity of the frontal cortex, since frontal dysfunction could explain changes in physiological parameters in the patient group. We consider these findings being important for the clinical interpretation of emotional reactions of ALS patients.

Keywords Pathological laughing and crying ·
Pseudobulbar affect · Amyotrophic lateral sclerosis ·
Frontal cortex · Emotion induction

Introduction

Pathological laughing and crying (PLC) or pseudobulbar affect (PBA) describes episodes of involuntary, often irresistible attacks of laughing and/or crying and is part of a large variety of neurological conditions, but most common in patients with amyotrophic lateral sclerosis (ALS) [5, 7, 9, 26]: some estimate that up to 50 % of this patient group, in particular those with bulbar deficits, are affected by this condition [15]. Although the first description of this phenomenon by Oppenheim and Siemerling dates back to the end of the nineteenth century [20], a clear-cut clinical definition is still lacking. PLC is commonly described as being preferentially provoked by inappropriate or incongruent stimuli [19, 22], while others claim that even unspecific stimuli, i.e. stimuli without any specific emotional quality for healthy subjects, account for PLC in

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patients [23]. Hartje [8] asserts that PLC represents a pattern of motor dysinhibition phenomena being provoked by unspecific stimuli or emerging spontaneously without being associated with any emotional changes.

As diverse as the definitions are the proposed theories about possible underlying pathomechanisms. Two main hypotheses are being discussed: The first one, also called "top-down" theory, has been proposed by Wilson [29] who hypothesized that phenomena of exaggerated or involuntary emotional expression were caused by lesions of the motor cortex. These lesions are supposed to result in a loss of voluntary control of functional brain stem regions controlling emotional expression. For almost a century, this theory was regarded as the best to explain the phenomena caused by PLC and PBA. The second, more recent theory claims that the brainstem response itself is impaired in patients with PLC, which in turn generates a pathological and exaggerated reaction to certain sensory stimuli [21]. This theory was proposed based on observations of different lesions such as stroke [5, 23], abscess [22], or tumours [24] in the pons, cerebellum, and brainstem. Additionally, one recent single photon emission computed tomography study showed decreased serotonin transporter density in the midbrain/pons of stroke patients with PLC [18]. Of note, this study only focussed on pons, midbrain, thalamus and hypothalamus, thus no conclusions can be drawn regarding possible alterations in other brain regions.

Surprisingly, although PLC is a common feature in ALS, only few studies exist targeting the phenomenon in this specific patient group in a systematic approach. One recent diffusion tensor imaging (DTI) study in ALS patients exhibiting PLC showed disruption of fiber tracts descending from the fronto-temporal cortex towards the pons [6]. In a neuropsychological study, McCullagh et al. [14] found that ALS patients with PLC show significant impairment in performing tasks related to frontal cortex function. In a more recent study, Olney et al. [19] report on ALS patients with PLC showing difficulties regulating their facial expression and their emotion voluntarily, which was interpreted as a result of impaired frontal cortex inhibitory activity.

In this psychophysiological study, we address the pathogenesis of PLC by exposing ALS patients to simultaneously presented visual and auditory stimuli, which were either emotionally congruent or incongruent. We designed this setting to systematically address the following questions:

(a) Is PLC in ALS an exaggerated response to comparatively weak emotional stimuli or an inappropriate response to emotionally incongruent stimuli?
(b) Is the phenomenon associated with a pathological modulation of emotional stimuli in a "bottom-up"-

loop or is it due to reduced inhibition of emotional behaviour display due to frontal cortex dysfunction ("top-down"-loop)?

Materials and methods

Subjects

Ten patients with ALS and PLC/PBA (six males, mean age 64.0 ± 12.2 years, mean education years 14.0 ± 2.7) and ten healthy sex-, age- and education-matched controls (six males, mean age 65.8 ± 10.8 years, mean education years 13.2 ± 3.6; $p = 0.73$ for mean age; $p = 0.84$ for education years) were studied. Patients were recruited from the Department of Neurology of the University Hospital of Ulm, Germany. The patients had been diagnosed with ALS according to the revised El Escorial Criteria [4]. Initial symptoms (bulbar or spinal), site of onset (upper or lower extremity, proximal or distal, bulbar, trunk), ALS functional rating scale (ALS-FRS), and the age of the patient at disease onset were recorded as reported by the patients and their relatives and patients were clinically examined. The patients and controls included in this study had no history of other neurological or psychiatric disorders. All patients and controls had given written informed consent. All experiments were conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Ethics Committee of the University Hospital of Ulm (No. 157/13).

Mean age at disease onset was 63.6 ± 10.5 years, mean ALS-FRS at the time of the study was 30.7 ± 10.2. Seven out of ten PLC patients showed a bulbar disease onset. Two patients (both with a bulbar onset) had died at the end of this study, with a total disease duration from symptom onset to death of 21 and 19 months, respectively. Table 1 gives an overview over the clinical data and psychological measures of the ALS patients and controls.

Neuropsychological testing

All patients and controls completed the Center of Neurologic Study Lability Scale for quantification of PLC (CNS-LS) [28] to quantify the occurrence of emotional lability. A score of 13 points was set as the cut-off for emotional lability, as suggested by Smith et al. [28]. To differentiate between pathological laughing and pathological crying, we split the CNS-LS into questions scanning for sadness (questions 1,3,6; maximum score 15; CNS-LS-neg-raw) and for laughing (questions 2,4,5,6; maximum score 20; CNS-LS-pos-raw) and determined the individual CNS-LS-pos and CNS-LS-neg percentage score (CNS-LS-pos/neg-raw divided by maximum score in this subscale times 100).

Table 1 Clinical, demographical and neuropsychological data of ALS patients and controls

Patients

No.	Age	Sex	CNS-LS	CNS-LS-neg-raw	CNS-LS-pos-raw	Induction	ECAS	Education years	ALS-FRS	Age at onset
1	40	F	13	8	5	No	Not done	16	36	48
2	75	M	27	13	14	Incongruent	Not done	13	25	75
3	78	M	14	9	4	Congruent	Not done	16	43	77
4	62	M	24	13	11	No	112	13	24	59
5	57	F	18	13	5	Incongruent	117	14	10	57
6	71	F	19	15	4	Congruent	80	9	28	70
7	49	M	17	5	12	Congruent	111	11	25	48
8	72	M	16	6	10	No	88	16.5	35	70
9	71	F	17	13	4	No	110	13	42	70
10	65	M	16	10	6	No	117	18	39	62

Controls

No.	Age	Sex	CNS-LS	CNS-LS-neg-raw	CNS-LS-pos-raw	Induction	ECAS	Education years
11	54	F	17	8	9	Incongruent	121	8
12	70	F	7	3	4	No	118	11
13	64	M	15	7	8	Congruent	109	16
14	71	M	9	4	5	No	104	11.5
15	46	M	11	3	8	No	120	19.5
16	54	F	10	5	5	No	115	12
17	73	M	14	6	8	No	105	11.5
18	78	M	12	6	6	No	113	18.5
19	73	F	7	3	4	No	120	13
20	75	M	10	4	6	Incongruent	80	11

Screening for cognitive deficits mirroring frontal cortex function was performed by a board certified psychologist using the German version of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [1, 12] in seven patients and all controls and with the Consortium to Establish a Registry for Alzheimer's Disease plus Scale (CERAD plus [17]) in three patients.

Experimental design

Subjects were seated in a darkened room 30 cm in front of a computer screen. They were shown pictures with three different emotional qualities (happy, sad, neutral). The pictures were chosen from the International Affective Picture System (IAPS), a standardized collection of emotional pictures [11]. The pictures depicted either human faces or objects and were balanced with respect to arousal while they varied on the valence scale. They appeared in a semi-randomized order, in which a neutral (N) picture was always separating a happy (H) from a sad (S) picture.

Each picture was presented for six seconds. In total, we presented a set of 40 pictures (10 happy, 10 sad, 20 neutral).

Mood induction and picture rating

Subjects were asked to rate the pictures according to their emotional quality for valence on a non-numeric scale while watching. The scale differentiated between the emotional qualities "unpleasant"/"inducing sadness" and "neutral-pleasant"/"inducing happiness". For rating, subjects used a slide bar with a cursor on the rating scale. All subjects were capable of operating the bar.

While watching the pictures, subjects were listening to classical instrumental music sequences presented via headphones. As were the pictures, also the auditory stimuli were chosen from a standardized set of objectively validated happy and sad musical extracts with a duration of 30 s, respectively [16]. The musical pieces had been shown to robustly induce different mood states in normal subjects [16]. We chose ten pieces with either a happy or a sad character (five happy, five sad) and arranged them in two sets, one with the happy pieces and the other with the sad pieces. In the sets, the musical pieces appeared in randomized order.

In each subject, we performed two runs with 12 min duration, respectively, separated by at least 2 h and maximal 24 h. In the first run, subjects were evaluating the

pictures while listening to the unpleasant musical pieces inducing sadness, in the second run, they were listening to the pleasant music inducing happiness (see "Appendix 1" for the list of musical excerpts).

Electrophysiological parameters

During mood induction, electrophysiological parameters were recorded with surface electrodes (for details see [13]). Heart rate (HR) was used as an index of valence [25] and Galvanic Skin Response (GSR) as an index of arousal [2, 10]. In addition, we recorded surface electromyogram (EMG) activity of mimic muscles to detect facial expression of emotion [27].

Heart rate

HR was acquired from electrodes attached to the right and left arm or leg, using the aforementioned amplifier. The signal was filtered from 0.5 to 15 Hz (time constant, 0.3 s). Data were expressed as the mean period duration in seconds between two heart beats during one picture episode (interstimulus interval from picture onset to onset of next picture, ISI).

Galvanic skin response

GSR was measured with electrodes fixed to the medial thenar and palm of the hand. The signal was bandpass-filtered from 0.016 to 10 Hz (time constant, 10 s). Galvanic skin response amplitudes were determined as the maximum conductance between 1 and 6 s after picture onset, relative to the EMG baseline at picture onset. For GSR, amplitudes of more than two standard deviations from the mean of each individual and trials with zero amplitude were discarded.

Facial EMG

We recorded surface EMG of the corrugator supercilii muscle, the orbicularis oris and the orbicularis oculi muscle. The electrodes were placed over the bellies of these muscles of either the left or the right side except for the corrugator supercilii muscle, where electrodes were placed between the eyebrows (Fig. 1). The EMG signal was externally rectified and bandpass-filtered (16–300 Hz; time constant, 0.01 s). The signal was given as the root mean square of the EMG signal in Volt (V) during ISI.

Statistical analysis

The statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) IBM, version 19.0. In the text, mean and standard deviation (SD) are given. A

priori, data were analyzed for normal distribution using the Kolmogorov–Smirnov test, electrophysiological data were z transformed. Accordingly, analysis of variance was performed with in-between subject factor group and within subject factor demographics, induction behaviour (yes/no), neuropsychological and electrophysiological data, where the latter were corrected for emotional lability (CNS-LS, CNS-LS-pos, CNS-LS-neg) and cognitive performance (ECAS total). To determine differences between groups in rating behaviour according to affective quality of pictures, Scheffé post hoc analysis was performed.

Kendall–Tau correlation analyses were conducted to determine association of mood-induction and emotional lability (PLC) and the association of PLC sub-scores and picture rating behaviour of patients. A threshold of $p < 0.05$ (two-tailed) was used for statistical interference.

Results

Neuropsychological data

ALS patients scored significantly higher in the "overall" CNS-LS compared to healthy controls (18.1 ± 4.5 vs. $11.2. \pm 3.3$ points, $F = 15.96$, $p < 0.01$). Patients had a significantly higher CNS-LS-neg score compared to CNS-LS-pos (70.0 % vs. 37.5 %, $F = 3.09$, $p = 0.01$) and a significantly higher CNS-LS-neg compared to controls ($F = 21.16$, $p < 0.01$), while controls did not show a difference between the two scores (32.7 vs. 31.5 %).

The ECAS scores of seven patients and ten controls where above threshold for cognitive impairment [12], and all subjects were able to understand and perform the task accordingly.

Picture rating

No clinically overt episodes of PLC were triggered during the experiment. For rating behaviour, both ALS patients and controls presented with a highly significant difference in the rating of pictures of different emotional content in both the happy and sad musical condition ($F = 64.44$, $p < 0.01$). In addition, PLC patients tended to rate neutral pictures accompanied by sad music more negatively, i.e. the difference between the rating of neutral and sad pictures in this group was less pronounced (post hoc Scheffé $p = 0.03$) than in controls. Regarding CNS-LS, we observed a significant correlation between CNS-LS score and mood induction for patients ($r = 0.39$, $p = 0.04$). For CNS-LS-pos, we found a correlation between the rating of positive pictures ($r = 0.53$, $p < 0.01$) and negative pictures ($r = -0.34$, $p = 0.05$), while for CNS-LS-neg, we observed a non-significant correlation with positive picture rating ($r = -0.31$, $p = 0.07$),

Fig. 1 Experimental setup. Subjects rated affective quality (valence) of pictures presented on a computer screen using a slide bar while listening to classical music presented via headphones. During the experiment, we measured heart rate, galvanic skin response and facial muscular activity

but not with negative and neutral pictures. In other words, patients with a high positive score rated happy pictures more positively and negative pictures more negatively, while patients with a high negative score tended to rate positive pictures more negatively (Fig. 2). No significant effect could be observed for CNS-LS-pos and neutral pictures ($r = -0.29, p = 0.097$), nor for CNS-LS-neg and neutral ($r = -0.14, p = 0.44$) or sad pictures ($r = 0.14, p = 0.42$).

Electrophysiological parameters

There was no significant difference between the two groups in the change of electrophysiological responses according to affective picture content. Group-differences in electrophysiological data were explained by frontal cortex function as expressed by the ECAS score (ANOVA corrected for ECAS score): EMG activity of the orbicularis oris muscle ($F = 9.01, p < 0.01$) and the orbicularis oculi muscle ($F = 5.48, p = 0.036$) and a non-significant trend for heart rate ($F = 3.18, p = 0.096$) and GSR ($F = 2.95, p = 0.109$) between the two musical conditions, while no difference could be observed for the corrugator supercilii muscle ($F = 0.09, p = 0.77$).

Discussion

Here, we systematically studied ALS patients suffering from PLC to find out whether episodes are elicited by contextually appropriate or inappropriate emotional stimuli, as there are controversial concepts on this issue [19, 22]. To address this question, an experimental set-up was designed with subjects confronted with visual and auditory stimuli of diverging emotional content simultaneously. We found that patients with PLC were more susceptible to mood-incongruent stimuli than controls. In particular, PLC patients rated pictures with a neutral content more negatively when listening to sad music. This mood induction in a negative direction was a consistent finding in PLC patients, but not in controls. We conclude that PLC is, thus, not induced by weak mood-congruent, but by mood-incongruent or contextually inappropriate stimuli. Also, our findings suggest that PLC is associated with enhanced emotional lability and is not only an involuntary motor activation of facial expression. We consider these findings being important for the clinical interpretation of emotional reactions of ALS patients.

It is another controversial question whether PLC is due to frontal cortex dysfunction with decreased inhibitory mechanisms or to altered processing of sensory stimuli, both of which would result in an exaggerated behavioural response. The PLC patients in our study did not exhibit an altered rating behaviour compared to controls when exposed to two emotionally equal stimuli. Thus, one may hypothesize that their reaction to sensory stimuli remained unaltered when there was no need for the emotion regulation system to suppress the answer to one stimulus to appropriately react to another. In contrast, patients were influenced in their behaviour when exposed to two stimuli of a diverging emotional content. This in turn may point to reduced inhibitory mechanisms, resulting in an exaggerated response to one stimulus and thus influencing the reaction to another simultaneously presented stimulus. Impaired voluntary suppression of emotional responses has been described before in ALS patients with PLC and has been interpreted as resulting from impairment of dorsal frontal brain structures [19]. When patients exhibit a clinically overt episode of PLC, this reduced inhibition might result in an exaggerated and contextually inappropriate emotional expression. We observed that PLC patients show an increased suggestibility when exposed to certain emotional stimuli, which in turn has an impact on their voluntary response. It may be hypothesized that this specific reaction is due to a lack of frontal inhibitory mechanisms in
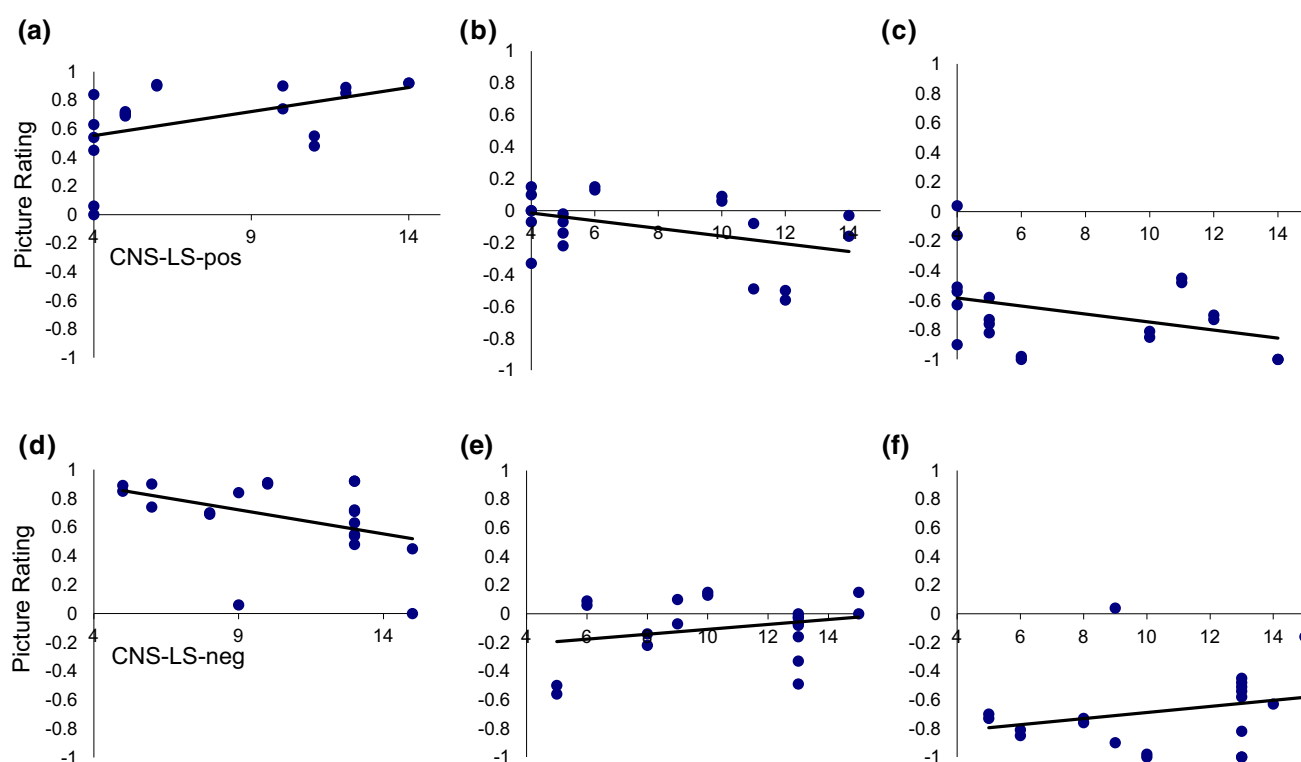
Fig. 2 Mean values of picture ratings of ALS patients plotted against happy (*upper row*) and sad (*lower row*) CNS-LS sub-scores; *x* axis: CNS-LS score, *y* axis: picture rating; **a** happy pictures vs. CNS-LS-pos ($r = 0.53$, $p < 0.01$), **b** neutral pictures vs. CNS-LS-pos ($p = 0.097$, $r = -0.29$), **c** sad pictures vs. CNS-LS-pos ($p = 0.05$, $r = -0.34$), **d** happy pictures vs. CNS-LS-neg ($p = 0.07$, $r = -0.31$), **e** neutral pictures vs. CNS-LS-neg ($r = -0.14$, $p = 0.44$), **f** sad pictures vs. CNS-LS-neg ($r = 0.14$, $p = 0.42$)

patients, resulting in specific behavioural alterations. In support of this, physiological changes in ALS patients, namely alterations of the surface EMG of facial muscles, were explained by frontal cortex function. Our findings are in line with a previous study reporting reduced ability of PLC patients on regulating their facial expression voluntarily [19]. We showed that altered facial expression in PLC is in fact related to frontal cortex function/dysfunction, by demonstrating that EMG changes of mimic muscles elicited by different emotional stimuli are closely related to cognitive performance and frontal function in PLC patients. This further supports the notion that the frontal cortex plays an important role in the pathophysiology of PLC. Recently, it could be convincingly shown in studies by Brettschneider et al. [3] that frontal changes, in particular of association fibres, exist neuropathologically in the majority of ALS patients.

We demonstrated that emotion regulation in PLC is altered at the behavioural as well as at the physiological level. To analyse changes in PLC at a third level of the emotion regulation system, i.e. the subjective level, patients and controls completed a standardized self-assessment questionnaire, the CNS-LS, to quantify the occurrence of emotional lability. We found that patients scored significantly higher on this scale compared to controls. In addition, we observed a significant correlation between CNS-LS and mood-induction. To differentiate between pathological laughing and pathological crying, we split the CNS-LS into questions scanning for sadness and happiness and found that these sub-scores did not only correlate with overall liability, but could in fact predict the direction of mood-induction in PLC patients. Remarkably, patients scored significantly higher on the CNS-LS-neg scale. Together with the fact that patients were influenced in their rating behaviour by sad musical pieces, this may suggest that patients with PLC are in general more sensitive to the negative component of emotion regulation. We conclude that the CNS-LS is a reliable instrument to detect emotional lability and PLC in patients with ALS. Yet, it does not sufficiently differentiate between pathological laughing and crying. We, therefore, suggest that the scale should be further sub-divided and possibly complemented by more specific questions.

One of the limitations of our study is the relatively small number of patients, which reduces the statistical power of our results and forbids general conclusions to a certain degree. Second, our findings are solely based on psychological and electrophysiological methods. While we could demonstrate specific alterations on different emotion regulating levels in our experimental setting, we could not

show changes of functional connectivity between different brain regions.

To further support the hypotheses of involvement of frontal areas in the generation of PLC, additional methods, especially comprising fMRI protocols, should be applied. Standardized fMRI and resting-state protocols in patients with PLC might be able to verify alterations in specific frontal brain regions of these patients. Also, possible changes in connectivity of different functional areas of the brain, which we could not show using this protocol, might be revealed with fMRI and DTI techniques. In particular, it would be interesting to correlate psychophysiological and electrophysiological findings with MRI data. This in turn could help to further clarify the aforementioned concepts of the "top-down" and "bottom-up" theories in the pathogenesis of PLC and to support our hypothesis.

In summary, our study provides evidence that PLC/PBA in patients with ALS is an expression of altered emotional suggestibility. Patients with PLC are more prone to mood induction. In particular, they are easily influenced in their emotional response by mood-incongruent emotional stimuli. We showed that PLC involves alterations at the physiological, behavioural and subjective level of emotion regulation. Concerning underlying pathomechanisms, we hypothesize that PBA is related to frontal cortex dysfunction, in particular to reduced frontal inhibition, resulting in altered behavioural responses and physiological activity in PLC patients. Further studies combining imaging and psychophysiological techniques in larger cohorts will be needed to address the structural and pathophysiological mechanisms underlying PBA in different patient groups.

Compliance with ethical standards

Conflicts of interest The authors declare that they do not have any actual or potential conflicts of interest.

Appendix 1: List of musical excerpts

	Composer	Title
Sad	Albinoni	Adagio in sol minor
	Bruch	Kol Nidrei
	Grieg	Solveig's song—Peer Gynt
	Rodrigo	Concerto de Aranjuez
	Sinding	Suite for violin & orchestra A minor
Happy	Bizet	Chanson du toreador—Carmen
	Mozart	Allegro—A little night music
	Mozart	Rondo Allegro—A little night music
	Strauß	Blue Danube
	Strauß	Radetzky march

References

1. Abrahams S, Newton J, Niven E, Foley J, Bak TH (2014) Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener 15(1–2):9–14. doi:10.3109/21678421.2013.805784
2. Bradley MM, Greenwald MK, Hamm AO (1993) Affective picture processing. In: Birbaumer N, Öhman A (eds) The structure of emotion. Hogrefe and Huber (publ.)
3. Brettschneider J, Del Tredici K, Toledo JB, Robinson JL, Irwin DJ, Grossman M, Trojanowski JQ (2013) Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. Ann Neurol 74(1):20–38. doi:10.1002/ana.23937
4. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron, Diseases (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1(5):293–299
5. Dark FL, McGrath JJ, Ron MA (1996) Pathological laughing and crying. Aust N Z J Psychiatry 30(4):472–479
6. Floeter MK, Katipally R, Kim MP, Schanz O, Stephen M, Danielian L, Meoded A (2014) Impaired corticopontocerebellar tracts underlie pseudobulbar affect in motor neuron disorders. Neurology 83(7):620–627. doi:10.1212/WNL.0000000000000693
7. Gallagher JP (1989) Pathologic laughter and crying in ALS: a search for their origin. Acta Neurol Scand 80(2):114–117
8. Hartje W (2005) Störungen des emotionalen Verhaltens. In: Karnath HO, Hartje W, Ziegler W (eds) Kognitive Neurologie. Thieme, Stuttgart
9. Ironside R (1956) Disorders of laughter due to brain lesions. Brain 79(4):589–609
10. Lang PJ, Greenwald MK, Bradley MM, Hamm AO (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30(3):261–273
11. Lang PJ, Bradley MM, Cuthbert BN (2008) International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville
12. Lule D, Burkhardt C, Abdulla S, Bohm S, Kollewe K, Uttner I, Ludolph AC (2014) The Edinburgh cognitive and behavioural amyotrophic lateral sclerosis screen: a cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Frontotemporal Degener. doi:10.3109/21678421.2014.959451
13. Lule D, Kurt A, Jurgens R, Kassubek J, Diekmann V, Kraft E, Anders S (2005) Emotional responding in amyotrophic lateral sclerosis. J Neurol 252(12):1517–1524. doi:10.1007/s00415-005-0907-8
14. McCullagh S, Moore M, Gawel M, Feinstein A (1999) Pathological laughing and crying in amyotrophic lateral sclerosis: an association with prefrontal cognitive dysfunction. J Neurol Sci 169(1–2):43–48
15. Miller A, Pratt H, Schiffer RB (2011) Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. Expert Rev Neurother 11(7):1077–1088. doi:10.1586/ern.11.68
16. Mitterschiffthaler MT, Fu CH, Dalton JA, Andrew CM, Williams SC (2007) A functional MRI study of happy and sad affective states induced by classical music. Hum Brain Mapp 28(11):1150–1162. doi:10.1002/hbm.20337
17. Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A (1988) Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. Psychopharmacol Bull 24(4):641–652

18. Murai T, Barthel H, Berrouschot J, Sorger D, von Cramon DY, Muller U (2003) Neuroimaging of serotonin transporters in post-stroke pathological crying. Psychiatry Res 123(3):207–211

19. Olney NT, Goodkind MS, Lomen-Hoerth C, Whalen PK, Williamson CA, Holley DE, Rosen HJ (2011) Behaviour, physiology and experience of pathological laughing and crying in amyotrophic lateral sclerosis. Brain 134(Pt 12):3458–3469. doi:10.1093/brain/awr297

20. Oppenheim H, Siemerling E (1886) Mitteilungen uber Pseudobulbarparalyse und akute Bulbarparalyse. Berl kli Woch, 46

21. Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR (2001) Pathological laughter and crying: a link to the cerebellum. Brain 124(Pt 9):1708–1719

22. Parvizi J, Coburn KL, Shillcutt SD, Coffey CE, Lauterbach EC, Mendez MF (2009) Neuroanatomy of pathological laughing and crying: a report of the American Neuropsychiatric Association Committee on Research. J Neuropsychiatry Clin Neurosci 21(1):75–87. doi:10.1176/appi.neuropsych.21.1.75

23. Poeck K (1969) Pathological laughing and weeping in patients with progressive balbar palsy. Ger Med Mon 14(8):394–397

24. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C (1995) Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery 37(5):885–893

25. Schandry R (1981) Psychophysiology: Körperliche Indikatoren menschlichen Verhaltens. US Psychologie, Urban und Schwarzenberg, Munchen Wien Baltimore

26. Schiffer R, Pope LE (2005) Review of pseudobulbar affect including a novel and potential therapy. J Neuropsychiatry Clin Neurosci 17(4):447–454. doi:10.1176/appi.neuropsych.17.4.447

27. Schwartz GE, Fair PL, Salt P, Mandel MR, Klerman GL (1976) Facial muscle patterning to affective imagery in depressed and nondepressed subjects. Science 192(4238):489–491

28. Smith RA, Berg JE, Pope LE, Thisted RA (2004) Measuring pseudobulbar affect in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord 5(Suppl 1):99–102. doi:10.1080/17434470410020058

29. Wilson SAK (1924) Some problems in neurology. II: pathological laughing and crying. J Neurol Psychopathol 4:299–333

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MEDICAL DECISIONS ARE INDEPENDENT OF COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS

Cognitive impairment has been reported in up to 40% of patients with amyotrophic lateral sclerosis (ALS). Alterations in social behavior, such as apathy or reduced empathy, are present in up to 30% of patients.[1,2] Therefore, there is concern whether patients with ALS are able to judge pending medical decisions appropriately and some colleagues have even called for surrogate decision-making.[3,4] However, systematic studies addressing the question of possible association between cognitive and behavioral impairment and decision-making in ALS are rare. Here, we provide prospective data obtained in a large cohort of patients with ALS to address this issue with relevance for patients' crucial decisions in everyday life and clinical context.

Methods. In total, 169 patients with ALS (table) of a German specialized outpatient clinic responded to standardized questionnaires regarding their decisions about percutaneous endoscopic gastrostomy (PEG), noninvasive ventilation (NIV) and invasive ventilation, the hypothetical ideation to turn off these treatments in case of physical decline, and the schedule of attitudes toward hastened death.[5] All patients were screened for cognition by using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[1,6] as this is the first ALS-specific, verbal and motor-free test for cognition with high specificity and sensitivity compared to extended neuropsychological tests.[6] ECAS measures ALS-specific cognitive domains of executive function, verbal fluency, and language and ALS-nonspecific functions of memory and visuospatial function. Moreover, 140 of the patients' caregivers gave information about behavioral changes. Patients fulfilling clinical criteria of behavioral frontotemporal dementia or any other neurologic condition apart from ALS were excluded. After testing the requirements for logistic regression analyses (e.g., multicollinearity), regression analyses were used for statistics adopting a threshold of $p < 0.05$ for significance.

Results. Deficits in at least one cognitive domain were present in 93 (55%) patients with ALS. Caregivers reported behavioral changes for 21 (15%) patients (mostly apathy), including 15 (11%) patients with additional cognitive impairment. Behavioral symptoms were mostly independent of cognitive deficits, except for language impairments, which were associated with presence of behavioral changes ($R^2 = 0.061$, $\beta = 1.141$, $p = 0.022$).

Logistic regression analyses showed that neither cognitive impairment nor behavioral changes were associated with patients' decisions regarding use or decline of PEG, NIV, and invasive ventilation, hypothetical ideation to turn off treatments in case of physical decline, or patients' wish for hastened death (all $p > 0.05$).

Discussion. This study on a large cohort of patients with ALS provides evidence for a lack of influence of moderate cognitive and behavioral impairment on patients' medical decisions.

The findings apply to most patients with ALS with moderate cognitive and behavioral impairment only

Table	Demographic and disease characteristics of 169 patients with ALS		
	Mean or no.	SD	Range
Demographics			
Age, y	59.21	12.91	19–84
Female	65		
Male	104		
Years of education	13.57	3.15	7–24
Type of ALS			
Sporadic	163		
Familial	6		
Spinal onset	118		
Bulbar onset	51		
Duration			
Months since symptom onset	32.80	41.36	2–396
Months since diagnosis	12.44	18.11	1–72
Therapeutic treatments			
Use of PEG	15		
Use of NIV	54		
Physical functioning			
ALSFRS-R	35.49	7.25	10–48

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale Revised Form[7]; NIV = noninvasive ventilation; PEG = percutaneous endoscopic gastrostomy.

but probably not for the subset of patients with ALS/frontotemporal dementia. In addition, we present data on only a single aspect of the multifactorial process of decision-making in the course of ALS. Certainly, decision-making in ALS is primarily determined by physical condition and medical needs. However, decision-making in ALS is also a dynamic process, where patients', caregivers', and physicians' personal perspectives may interfere, and further studies are needed to address this possible interaction.

Our results have considerable implications for patients, caregivers, and families in daily routine and physicians in medical counseling dealing with the question of possible bias in patients' preferences and necessity of surrogate involvement in decision-making. They indicate that patients with ALS, despite moderate cognitive or behavioral impairment, are still competent for making their self-determined decisions. A request for surrogate decision-making in patients with ALS with mild cognitive impairment might not be justified.[4]

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1. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener 2014; 15:9–14.
2. Bock M, Duong YN, Kim A, Murphy J, Lomen-Hoerth C. Cognitive-behavioral changes in amyotrophic lateral sclerosis: screening prevalence, progression, and impact on patients and caregivers. Amyotroph Lateral Scler Frontotemporal Degener 2015;84:1–222.
3. Khin EK, Minor D, Holloway A, Pelleg A. Decisional capacity in amyotrophic lateral sclerosis. J Am Acad Psychiatry Law 2015;43:210–217.
4. Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurol 2015;14:435–442.
5. Rosenfeld B, Breitbart W, Galietta M, et al. The schedule of attitudes toward hastened death. Cancer 2000;88:2868–2875.
6. Lulé D, Burkhardt C, Abdulla S, et al. The Edinburgh cognitive and behavioural amyotrophic lateral sclerosis screen: a cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Frontotemporal Degener 2015;16:16–23.
7. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functioning rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169:13–21.

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ULTRA-EARLY ONSET OF OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT WITH CONGENITAL RICKETS

Ossification of the posterior longitudinal ligament (OPLL) is a condition caused by progressive and abnormal calcification of the posterior longitudinal ligament in the cervical and thoracic spine, leading to gradual compression of the spinal cord. The exact pathogenesis of OPLL is unclear; however, the interaction of genetic and environmental factors such as mechanical stress of the ligaments is speculated to result in the pathogenesis of OPLL.[1] OPLL has an incidence of 1.9% to 4.3% in Japan and 0.01% to 1.7% in Europe; males are twice as likely to have OPLL as females, and the average age at onset is older than 50 years.[1] OPLL is known to have a strong genetic predisposition, and a prevalence of 29% in siblings has been demonstrated.[2] The majority of cases are idiopathic and typically present in the fifth or sixth decades. However, in rare occasions, OPLL can be associated with endocrine abnormalities and may present at a much younger age.[2] We report a case of a 26-year-old woman with congenital X-linked hypophosphatemic rickets (XLHR) who was diagnosed with severe OPLL.

Case report. A 26-year-old Samoan woman with familial XLHR presented with acute incomplete quadriplegia from a hyperextension neck injury after a bicycle accident. Other than taking calcitriol for a short period before her injury, the patient's rickets had been untreated since birth. Her family history is notable for rickets in her mother, maternal aunts, and maternal cousins. Many of them became nonambulatory and bedridden in their mid-30s to early 40s. Physical examination demonstrated partial strength of the bilateral biceps and triceps and absent strength of the distal upper extremities or lower extremities. A CT and MRI of the cervical spine

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ORIGINAL COMMUNICATION

Experience matters: neurologists' perspectives on ALS patients' well-being

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Abstract Despite the fatal outcome and progressive loss of physical functioning in amyotrophic lateral sclerosis (ALS), many patients maintain contentment in life. It has been shown that non-professionals tend to underestimate the well-being of patients with ALS, but professionals' perspective is yet to be studied. In total, 105 neurologists with varying degrees of experience with ALS were included in an anonymous survey. They were asked to estimate the quality of life and depressiveness of ALS patients with artificial ventilation and nutrition. Physicians' estimations were compared with previously reported subjective ratings of ALS patients with life-prolonging measures. Neurologists with significant experience on ALS and palliative care were able to accurately estimate depressiveness and quality of life of ALS patients with life-prolonging measures. Less experienced neurologists' estimation differed more from patients' reports. Of all life-prolonging measures neurologists regarded invasive ventilation as the measure associated with lowest quality of life and highest depressiveness of the patients. Experienced neurologists as well as neurologists with experience in palliative care are able to better empathize with patients with a fatal illness such as ALS and support important decision processes.

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Introduction

In amyotrophic lateral sclerosis (ALS), the employment of non-invasive (NIV) or invasive (IV) artificial ventilation and/or nutrition via a feeding tube (percutaneous endoscopic gastrostomy, PEG) may prolong patients' survival and improve their quality of life [1–3]. In practice, decisions regarding therapeutic options are not solely made by the patient, but are influenced by the social environment [4, 5]. Whether the influence acts pro or con for certain measures strongly depends on the person's image of well-being of patients living with such measures [6].

Neurologists who have medical expertise and are acquainted with life-prolonging measures have a crucial role in the patient's decision-making process [7]. However, similar to non-professionals, the physician's appraisal of therapeutic options might be framed according to his/her own attitudes [8] and perception of the patient's psychological well-being [6, 9, 10]. This, in turn, may influence the way physicians discuss the available therapeutic options with the patient [6, 11].

Despite the fatal outcome and progressive loss of physical functioning in ALS [12], many patients maintain contentment in life [13]. It has been shown that non-professionals have a negatively biased image of the well-being of patients with ALS [14, 15]. Even close relatives tend to underestimate ALS patients' quality of life and overestimate their depressiveness [16, 17]. It is not yet clear how medical professionals reflect the well-being of the patients with ALS.

Health professionals are important sources to drive improvement in ALS care [18], but there is a need for quantitative measures to further support this. Therefore, our aim was to study neurologists' perception of the impact of therapeutic interventions on ALS patients' psychological well-being in relation to their professional expertise and to compare it with patients' own reports.

Subjects and methods

Overall, $n = 813$ German neurologists were considered. $N = 449$ neurologists received a paper version of the questionnaire by mail and $n = 364$ a link by e-mail the online version of the questionnaire, generated with the Survey Monkey online survey tool (http://www.survey monkey.com). Responses were collected between July 2014 and May 2016 from the neurologists of all specialized ALS clinics in Germany and registered neurologists in Southern Germany (states of Saarland, Rhineland-Palatinate, Baden-Wuerttemberg and Bavaria).

In total, $n = 114$ physicians returned the questionnaire (response rate 18% for the paper questionnaires and 11% for the online survey), including $n = 9$ who returned it without answers, claiming to have no experience with ALS. Thus, $n = 105$ neurologists' responses were included in the final analysis (Fig. 1; Table 1).

Out of $n = 813$ neurologists considered, $n = 100$ ($n = 51$ by mail, $n = 49$ by e-mail) were not reached. Out of $n = 114$ who returned the questionnaires, $n = 78$

Table 1 Demographics of the neurologists ($n = 105$) included in the study

Variable		Percentage
Age (mean ± SD)	50.3 ± 12.0	
Gender	68 male	65
	31 female	30
	6 no information	5
Experience with ALS (years)	<1	13
	1–3	61
	4–10	14
	>10	12
ALS patients seen per month	<1	6
	1–5	15
	5–10	14
	>10	65
Completed palliative care training	12 with	11
	93 without	89

SD standard deviation

received it by mail and $n = 36$ online. $N = 9$ returned the questionnaire unanswered due to lack of experience with ALS patients. Reports of $n = 105$ ($n = 30$ online, $n = 75$ regular) neurologists were included in the study.

The 29-item questionnaire was to be filled out anonymously which took about 10 min time. Questions included in the final analysis encompassed items addressing the experience of the physician with ALS and estimation of the level of quality of life and depressiveness of ALS patients with NIV, IV and PEG (additional data are given in Online Resource 1). Because of the need to maintain anonymity, no reminder was possible. The study was approved by the Ethical Committee of the University of Ulm (19/12) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. To maintain anonymity, no written consent was requested. All participating physicians were provided with an informative briefing.

Clinical experience

The experience of the neurologist was defined as the average number of ALS patients seen per month (with four choices from less than one to more than ten patients) multiplied by the average number of years of experience with ALS patients (with four choices from less than 1 year to more than 10 years). Experience was classified as either low (average number of ALS patients seen in total < median, $n = 32$), moderate (average number of ALS patients seen in total = median, $n = 51$) and high experience on ALS (average number of ALS patients seen in
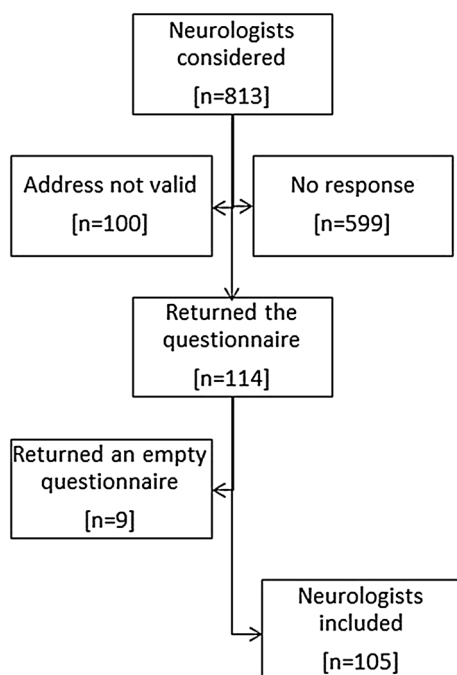

Fig. 1 Neurologists being selected in the study

total > median, $n = 22$). Additionally, physicians were asked whether they had completed specific palliative care training according to the German Medical Association (Bundesärztekammer).

Well-being

Neurologists were requested to estimate the psychological well-being (depressiveness and quality of life) of ALS patients with NIV, IV and PEG. Depressiveness was assessed on a Likert scale ranging from 0 to 10 and quality of life was assessed according to an adapted version of the anamnestic comparative self-assessment (ACSA) [19] on a Likert scale ranging from −5 to 5.

Additionally, the data of $N = 52$ patients diagnosed with probable or definite ALS according to the revised El Escorial criteria [20] were included in the study (Table 2). These patients having NIV, IV and/or PEG had been interviewed in a previous study on their subjective well-being [21]. Neurologists' reports on the quality of life and depressiveness of ALS patients with the aforementioned life-prolonging measures were compared with the reports of ALS patients' own reports published earlier [21]. Patients' depression was measured with the "Allgemeine Depressionsskala" (ADSK) [22], the German version of the Center for Epidemiologic Studies Depression Scale, CES-D, (range: 0–60; threshold >16). To compare the depressiveness scores estimated by the neurologists with patients' reports, neurologists' estimation of patients' depressiveness on a scale of 0–10 was adjusted to the range of the ADSK (0–60) that was used for the patients' subjective rating for depression. Patients' quality of life was assessed with the anamnestic comparative self-assessment (ACSA [19], ranging from −5 for as bad as possible to +5 for as good as possible).

Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, IBM, version 21.0). Mean and standard deviations or alternatively medians are given. The normality of the data was tested with the Kolmogorov–Smirnov test and either parametric or non-parametric statistical tests were applied accordingly. For between group comparisons (patients vs. neurologists; neurologists with palliative care training vs. neurologists without palliative care training vs. patients; neurologists with high experience vs. patients; neurologists with low experience vs. patients) non-parametric Mann–Whitney U tests were conducted. Pearson correlation was conducted for the association of estimation of patients' well-being (the depressiveness and quality of life) and total number of ALS patients seen on average and Spearman correlation for the association of estimation of patients' well-being and years of experience or engagement in ALS research. Linear regression analysis was applied for association between the average number of patients seen per month and estimation of the patients' depressiveness and quality of life. For the analysis of neurologists' reports, a threshold of $p < 0.05$ was adopted for statistical significance. To minimize possible false interpretations owing to small patient groups, a conservative threshold of $p < 0.01$ was chosen for statistical significance for comparisons between neurologists' reports and patients' subjective ratings.

Results

Overall, neurologists (with varying degrees of experience) estimated higher depressiveness scores for patients with any life-prolonging measure (with NIV: $U = 488.5$,

Table 2 Demographics of the ALS patients from Lulé et al. [21]

Variable	Patients with NIV ($n = 29$) mean ± SD	Patients with IV ($n = 6$) mean ± SD	Patients with PEG ($n = 17$) mean ± SD
Age	58.07 ± 12.09	51.50 ± 7.50	53.53 ± 13.43
Gender	8 female	3 female	7 female
	21 male	3 male	10 male
ALS-FRS-R	24.59 ± 10.09	10.50 ± 9.81	15.06 ± 11.48
Time since onset [months]	49 ± 41	104 ± 67	66 ± 53
Progression [loss of ALS-FRS scores per month]	0.9 ± 0.9	0.5 ± 0.3	0.7 ± 0.4
Site of onset	21 spinal	4 spinal	9 spinal
	7 bulbar	2 bulbar	8 bulbar
	1 n/a		

ALS-FRS-R ALS functional rating scale revised form [23]. *NIV* non-invasive ventilation, *IV* invasive ventilation, *PEG* percutaneous endoscopic gastrostomy, *SD* standard deviation

$p < 0.001$; with IV: $U = 39$, $p < 0.001$; with PEG: $U = 380.5$, $p < 0.001$) and lower quality of life scores for patients with IV ($U = 69$, $p = 0.002$), but not with NIV ($U = 1372$, $p > 0.01$) or PEG ($U = 713$, $p > 0.01$) than what the patients had reported previously [21].

However, neurologists with high experience estimated quality of life close to patients' subjective estimation for all measures as no statistically significant difference was seen between them (NIV: $U = 236$, $p > 0.01$; IV: $U = 39$, $p > 0.01$; PEG: $U = 149.5$, $p > 0.01$). Similarly, they estimated depression with PEG ($U = 109$, $p > 0.01$) close to the patients' subjective estimation. High experienced neurologists estimated depressiveness significantly higher for the patients with NIV ($U = 152$, $p = 0.001$) and IV ($U = 10$, $p = 0.002$). In contrast to this, less experienced neurologists' estimation on depressiveness was higher than the reports of the patients with all measures (NIV: $U = 106.5$, $p < 0.001$; IV: $U = 7$, $p < 0.001$; PEG: $U = 99.5$, $p = 0.001$). Neurologists with low experience also estimated quality of life lower for the patients with IV ($U = 12.5$, $p = 0.001$), but not for the patients with NIV ($U = 421.5$, $p > 0.01$) and PEG ($U = 189.5$, $p > 0.01$) (Fig. 2).

Of all life-prolonging measures, neurologists regarded IV as the measure associated with higher depression and lower quality of life than NIV and PEG. Neurologists estimated depressiveness higher (NIV vs. IV: $U = 3350.5$, $p < 0.001$; PEG vs. IV: $U = 3527.5$, $p < 0.001$) and quality of life lower (NIV vs. IV: $U = 2508.5$, $p < 0.001$; PEG vs. IV: $U = 2531.5$, $p < 0.001$) for patients with IV than for patients with NIV and PEG. Quality of life ($U = 5027$, $p > 0.05$) and depressiveness ($U = 5093.5$, $p > 0.05$) of patients with NIV and PEG were estimated in a similar range.

Negative Pearson correlation was seen between the experience of the neurologist (patients seen in total) and his/her estimation of depressiveness of patients with NIV ($r = -0.217$, $p = 0.028$) and with IV ($r = -0.241$, $p = 0.017$) but not with PEG ($r = -0.088$, $p > 0.05$), and positive correlation between experience of neurologists (patients seen in total) and estimation of quality of life of patients with IV ($r = 0.263$, $p = 0.009$) but not with NIV ($r = 0.167$, $p > 0.05$) or PEG ($r = 0.185$, $p > 0.05$).

Linear regression analysis revealed that the more ALS patients were seen by a neurologist monthly, the lower did the neurologist estimate the depressiveness of patients (with NIV: $R^2 = 0.051$, $\beta = -0.226$, $p = 0.022$; with IV: $R^2 = 0.109$, $\beta = -0.33$, $p = 0.001$; with PEG: $R^2 = 0.051$, $\beta = -0.225$, $p = 0.023$) and the higher did he/she estimate the quality of life of the patients (with NIV: $R^2 = 0.053$, $\beta = 0.229$, $p = 0.021$; with IV: $R^2 = 0.057$, $\beta = 0.239$, $p = 0.018$; with PEG: $R^2 = 0.113$, $\beta = 0.337$, $p = 0.001$) with any life-prolonging measure.

Neurologists with completed palliative care training estimated higher quality of life for patients with NIV ($U = 244.5$, $p = 0.006$) and PEG ($U = 243$, $p = 0.005$) but not with IV ($U = 259.5$, $p > 0.01$) than the neurologists without palliative care training. Neurologists with and without palliative care training did not significantly differ in their estimation of depressiveness (NIV: $U = 310.5$, $p > 0.01$; IV: $U = 301.5$, $p > 0.01$; PEG: $U = 434$, $p > 0.01$). When comparing patients [21] and the neurologists with palliative care training, no statistically significant difference was seen in rating of depressiveness (NIV: $U = 138.5$, $p > 0.01$; IV: $U = 16$, $p > 0.01$; PEG: $U = 69$, $p > 0.01$) or quality of life (NIV: $U = 100.5$, $p > 0.01$; IV: $U = 10.5$, $p > 0.01$; PEG: $U = 73$, $p > 0.01$). However, neurologists without palliative care training differed in the estimation of quality of life with patients with IV ($U = 58.5$, $p = 0.001$) but not with NIV ($U = 1271.5$, $p > 0.01$) or PEG ($U = 350$, $p > 0.01$) and in the estimation of depressiveness with patients with all measures (NIV: $U = 350$, $p < 0.001$; IV: $U = 23$, $p < 0.001$; PEG: $U = 311.5$, $p < 0.001$) (Fig. 3).

Additionally, Spearman correlation revealed that the more actively neurologists participated in ALS research, the lower did they estimate patients' depressiveness with all measures (NIV: $r = -0.271$, $p = 0.006$; IV: $r = -0.253$, $p = 0.012$; PEG: $r = -0.330$, $p = 0.001$) and the higher the quality of life for the patients with PEG ($r = 0.237$, $p = 0.017$). Neurologists' engagement in ALS research was not correlated with their estimation of quality of life of the patients with NIV ($r = 0.085$, $p > 0.05$) or IV ($r = 0.061$, $p > 0.05$).

Discussion

In the current study, experienced neurologists accurately estimated psychological well-being in ALS. In terms of rating depressiveness and quality of life of patients with NIV, IV or PEG, neurologists with high experience (high number of ALS patients seen in total) mostly did not differ from the subjective rating of ALS patients with life-prolonging measures. Similarly, the more neurologists were engaged in ALS research, the closer they estimated patients' well-being. Therefore, our results suggest that with increasing patient contacts besides increased general medical expertise, physicians also refine the ability to better recognize patients' affective state and empathize with their life with certain therapeutic measures.

It has been suggested that palliative care training may improve the knowledge, communication, confidence and symptom management of the physician [24] and that earlier exposure to death [25] and experience on palliative care may decrease physician's anxiety [26] and negative

Fig. 2 Rating of depressiveness (**a**) and the quality of life (**b**) of ALS patients by neurologists with varying degrees of experience compared with patients' own reports Depressiveness was estimated on a Likert scale ranging from 0 to 10 and the quality of life on a Likert scale ranging from −5 to 5. The line charts (left figure in a and b) show change in neurologists' estimations of patients' well-being in relation to their experience. Box plots (right figure of a and b) show patients' [21] subjective rating on their depressiveness and quality of life. Medians, first and third quartiles, range and the outliers are shown. * indicates statistical significance with $p < 0.01$ and ** with $p < 0.001$ between patients and neurologists (with either low or high experience) in Mann–Whitney U test. Low experience: average number of ALS patients seen by the neurologist < median; moderate experience: average number of ALS patients seen by neurologists = median; high experience: average number of ALS patients seen by neurologists > median. NIV = non-invasive ventilation, IV = invasive ventilation, PEG = percutaneous endoscopic gastrostomy
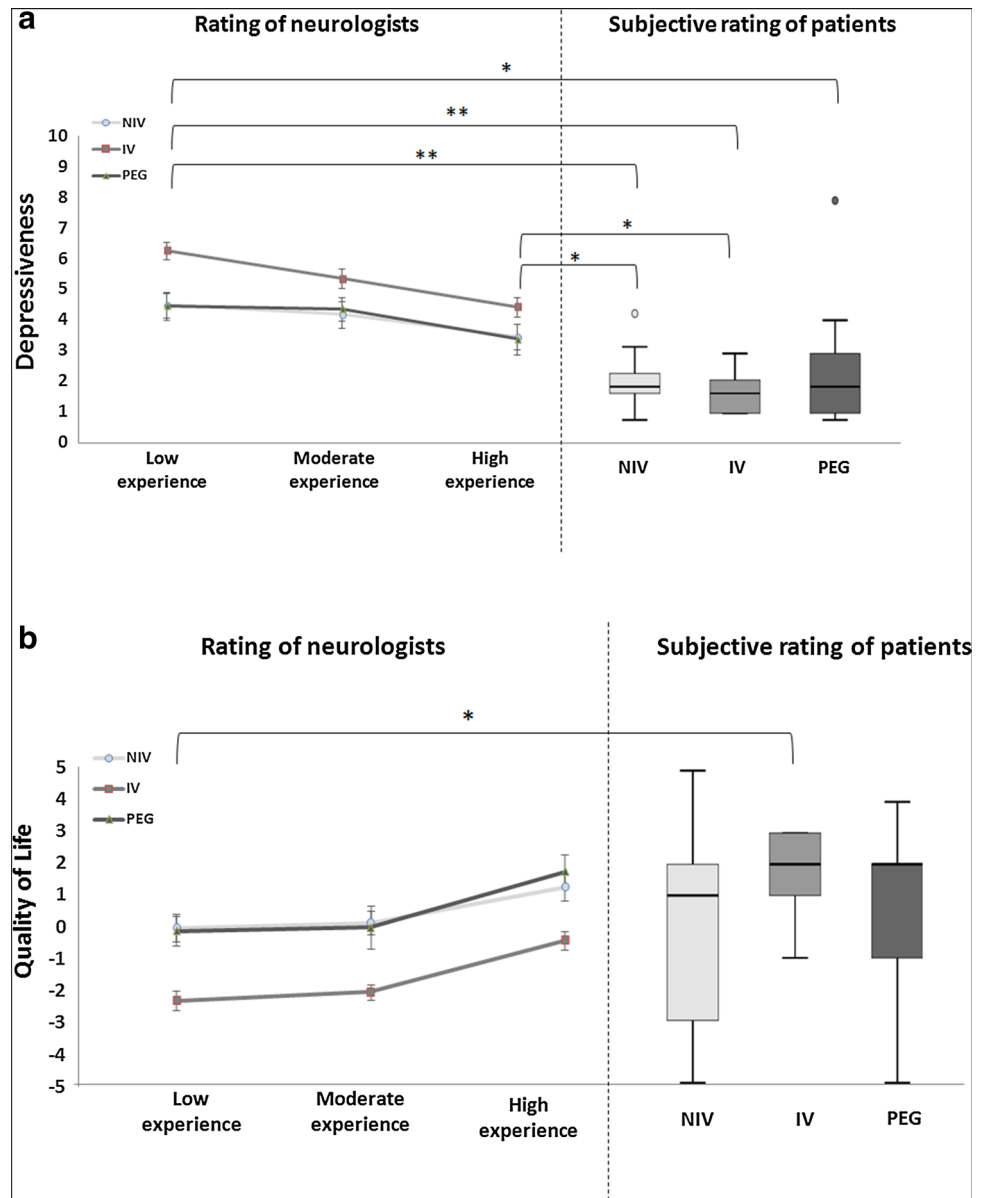

attitudes toward living and dying with fatal illness [27]. Similarly, our results show that neurologists with completed palliative care training rated lower depressiveness and higher quality of life for ALS patients with life-prolonging measures, thus being close to the subjective rating of patients. Therefore, also our results support the importance of training and knowledge on palliative care when treating patients with fatal illnesses.

More difference was seen between rating of less experienced neurologists and subjective rating of patients. The depressiveness of patients with life-prolonging measures was rated higher and the quality or life lower by the neurologists with low experience in ALS. Also, rating of neurologists without completed palliative care training mostly differed from the patients. Discrepancy between the rating of patients and neurologists was present especially for the well-being of patients with IV, which neurologists also overall rated more negatively than PEG and NIV. Similarly, it has been shown that IV might be associated with negative attitudes among some physicians [28, 29]. Additionally, IV is a less desired option also among many ALS patients and caregivers who do not have experience with it [21, 30–32].

There might be some reasons given to the rather negative associations related to IV. Besides the facts that IV is an invasive measure [28] and might increase caregiver burden [29, 33] as well as dependency of the patient [34], rareness of IV might contribute to the associations related to the measure. Physicians see relatively rarely patients with IV, as it is not as commonly employed as NIV or PEG

Fig. 3 Estimation of patients' depressiveness (**a**) and the quality of life (**b**) by neurologists with and without completed palliative care training compared to patients' [21] subjective rating Depressiveness was estimated on a Likert scale ranging from 0 to 10 and the quality of life on a Likert scale ranging from −5 to 5. Box plots show the comparison of the neurologists' (with completed palliative care training: $n = 12$; without completed palliative care training: $n = 93$) estimation on patients' well-being as well as patients' [21] own reports. Medians, first and third quartiles, range and the outliers are shown. * Indicates the statistical significance with $p < 0.01$ and ** with $p < 0.001$ in Mann–Whitney U test. NIV = non-invasive ventilation, IV = invasive ventilation, PEG = percutaneous endoscopic gastrostomy
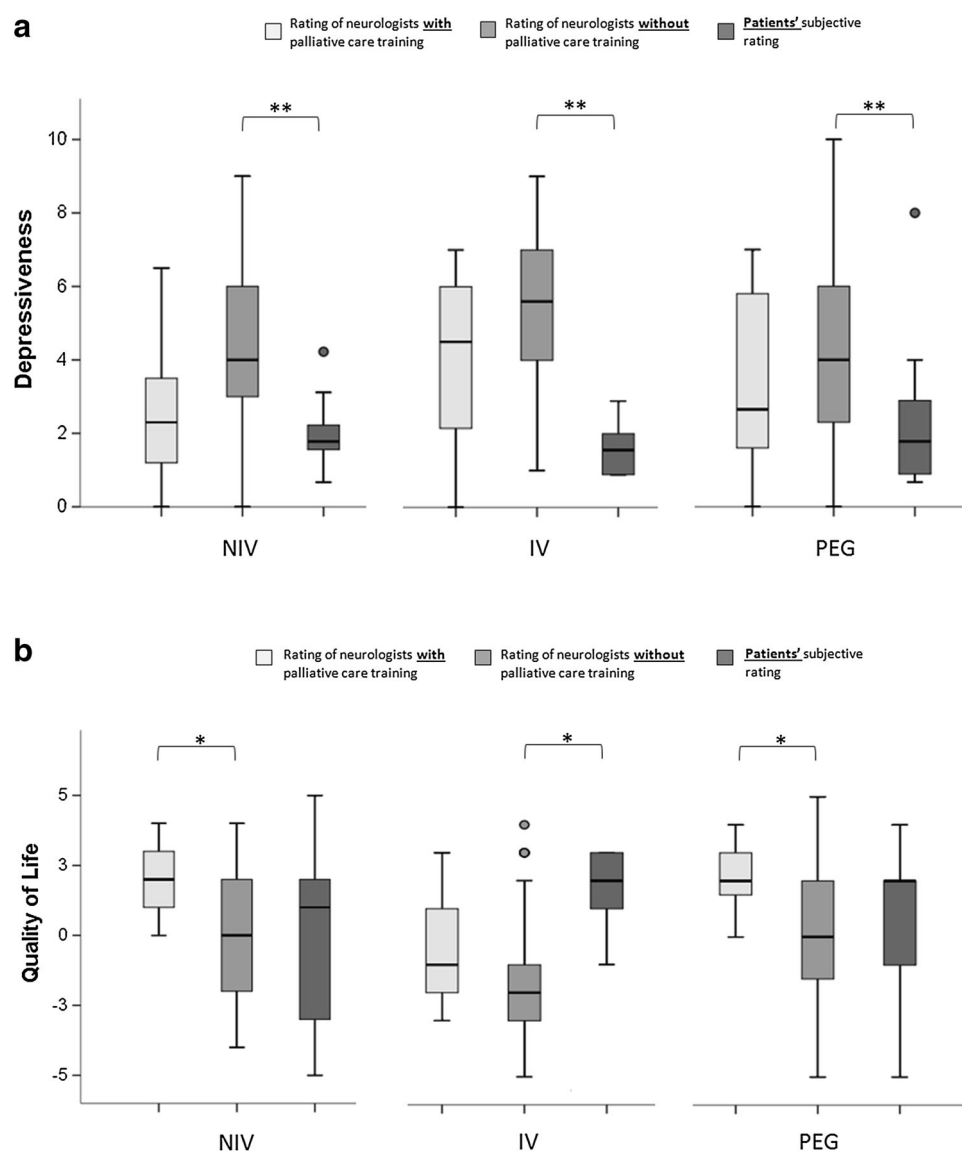
especially in some Western countries [31, 35, 36]. However, again both experience in palliative care and experience in dealing with ALS patients were strongly associated with neurologist's more positive rating of well-being with IV. Thus, experienced neurologists' rating was closer to the subjective rating of patients [21] and earlier findings, showing that patients with IV have rather good quality of life and low depressiveness [37] and do not significantly differ from patients with other life-prolonging measures [21, 33]. Accordingly, it has also been frequently shown that satisfaction in life does not necessarily decline with reduced physical functioning [13, 16, 30, 32, 38].

Finally, it can be speculated whether high empathy on the physician's side for the patient's well-being is even favorable for every medical encounter, as a certain emotional distance might be preferable in a professional relationship. Also, our results show that instead of complete empathy with patients' condition, neurologists, and especially neurologists with significant experience in ALS, are able to empathize with patient's well-being as seen in the accurate estimation of patients' depressiveness and quality of life.

Limitations

First, in such a diverse disease as ALS, only very rough estimations can be made as patients' progression as well as their psychological well-being varies greatly between individuals, which is known especially among experienced neurologists. Ideally, pairwise comparisons allowing the neurologists to evaluate each patient individually and comparing this estimation with patient's subjective estimation would have been done. However, owing to the

anonymity, such a study design was not possible. Moreover, a larger patient cohort would be preferable but due to the rareness of employment of invasive ventilation in Germany [17, 21], it is hard to accomplish. Furthermore, to strengthen the reliability of the conclusions made of the patient–neurologist comparisons, a conservative level of $p < 0.01$ was chosen for statistical significance.

Additionally, a direct comparison of different depression scales filled by the neurologists and patients might be problematic. Patients filled out a proper validated questionnaire with 15 items giving a depression score between 0 and 60, whereas neurologists were only asked to estimate the depressiveness on a visual analog scale between 0 and 10. However, time-consuming questionnaires are not desirable in physician surveys and we believe that comparison and a suggestive conclusion are justifiable through the adjustment of the scales and strict statistical analyses.

Finally, the results of our study may be influenced by a possible selection bias owing to the relatively low response rate which, however, has been reported also earlier [39]. Furthermore, the environment where the patient is met might partly account for the estimation difference between patients and neurologists. In contrast to the caregivers who see the patient at home, physicians meet patients in a clinical setting (in- and outpatient clinics). This should be taken into account as it has been suggested earlier that diverging views on the provision of life-prolonging measures of medical health-care professionals and allied health-care professionals might be partly due to the context where they see ALS patients, either in the clinic or in their home [4]. Similarly, the patient cohort from Lulé et al. [21] used for comparison was not interviewed in the clinic but in the patients' home, where patients might generally be more satisfied with their condition. Therefore, further studies with larger patient groups and reduced biasing environmental factors are needed.

Conclusion

Our results emphasize the importance of neurologist's experience in ALS care, as significant experience was strongly associated with better estimation of patients' well-being. Additionally, not just experience in ALS, but also experience in palliative care and engagement in ALS research, might refine the ability to echo psychological well-being of patients with ALS, thus possibly improving the quality of the therapeutic relationship. However, flawed judgment of the well-being of patients with disability (disability paradox) [15], which was previously reported for non-professionals such as caregivers [17], might also be present in some physicians with low experience in ALS.

As decisions regarding therapies usually have to be backed by family and health professionals [28, 40, 41], it is crucial to consider any possible personal bias in the perception of patient's psychological well-being [28]. Therefore, patients with a rare disease such as ALS would be ideally treated by experienced neurologists, when they might receive both more advanced medical expertise and better understanding of their condition with regard to psychological well-being. This is particularly true for end-of-life decisions for which empathy of the professional environment is mandatory.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The study was approved by the ethics committees of the University of Ulm and the University of Berlin and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave informed consent prior to their inclusion in the study.

References

1. Connolly S, Galvin M, Hardiman O (2015) End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurol 14(4):435–442. doi:10.1016/S1474-4422(14)70221-2
2. McDonald ER, Hillel A, Wiedenfeld SA (1996) Evaluation of the psychological status of ventilatory-supported patients with ALS/MND. Palliat Med 10(1):35–41
3. Dorst J, Dupuis L, Petri S et al (2015) Percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis: a prospective observational study. J Neurol 262(4):849–858. doi:10.1007/s00415-015-7646-2
4. Ruffell TO, Martin NH, Janssen A et al (2013) Healthcare professionals' views on the provision of gastrostomy and noninvasive ventilation to amyotrophic lateral sclerosis patients in England, Wales, and Northern Ireland. J Palliat Care 29(4):225–231
5. Wilson F, Gott M, Ingleton C (2013) Perceived risks around choice and decision making at end-of-life: a literature review. Palliat Med 27(1):38–53. doi:10.1177/0269216311424632
6. Sullivan KE, Hébert PC, Logan J et al (1996) What do physicians tell patients with end-stage COPD about intubation and mechanical ventilation? Chest 109(1):258–264. doi:10.1378/chest.109.1.258
7. Sulmasy DP, Hughes MT, Thompson RE et al (2007) How would terminally ill patients have others make decisions for them in the event of decisional incapacity? A longitudinal study. J Am

Geriatr Soc 55(12):1981–1988. doi:10.1111/j.1532-5415.2007.01473.x

8. Martin NH, Lawrence V, Murray J et al (2016) Decision making about gastrostomy and noninvasive ventilation in amyotrophic lateral sclerosis. Qual Health Res 26(10):1366–1381. doi:10.1177/1049732315583661

9. Uhlmann RF, Pearlman RA (1991) Perceived quality of life and preferences for life-sustaining treatment in older adults. Arch Intern Med 151(3):495–497

10. Junod Perron N, Morabia A, de Torrente A (2002) Quality of life of Do-Not-Resuscitate (DNR) patients: how good are physicians in assessing DNR patients' quality of life? Swiss Med Wkly 132(39–40):562–565

11. Greenaway LP, Martin NH, Lawrence V et al (2015) Accepting or declining non-invasive ventilation or gastrostomy in amyotrophic lateral sclerosis: patients' perspectives. J Neurol 262(4):1002–1013. doi:10.1007/s00415-015-7665-z

12. Kiernan MC, Vucic S, Cheah BC et al (2011) Amyotrophic lateral sclerosis. Lancet 377(9769):942–955. doi:10.1016/S0140-6736(10)61156-7

13. Neudert C, Wasner M, Borasio GD (2004) Individual quality of life is not correlated with health-related quality of life or physical function in patients with amyotrophic lateral sclerosis. J Palliat Med 7(4):551–557. doi:10.1089/jpm.2004.7.551

14. Simmons Z (2015) Patient-perceived outcomes and quality of life in ALS. Neurotherapeutics 12(2):394–402. doi:10.1007/s13311-014-0322-x

15. Hoppe S (2013) Chronic illness as a source of happiness: paradox or perfectly normal? hcs 5(1). doi:10.5195/hcs.2013.138

16. Grehl T, Rupp M, Budde P et al (2011) Depression and QOL in patients with ALS: how do self-ratings and ratings by relatives differ? Qual Life Res 20(4):569–574. doi:10.1007/s11136-010-9781-7

17. Lule D, Ehlich B, Lang D et al (2013) Quality of life in fatal disease: the flawed judgement of the social environment. J Neurol 260(11):2836–2843. doi:10.1007/s00415-013-7068-y

18. Hogden A, Greenfield D, Nugus P et al (2012) Engaging in patient decision-making in multidisciplinary care for amyotrophic lateral sclerosis: the views of health professionals. Patient Prefer Adherence 6:691–701. doi:10.2147/PPA.S36759

19. Bernheim JL (1999) How to get serious answers to the serious question: "How have you been?": subjective quality of life (QOL) as an individual experiential emergent construct. Bioethics 13(3–4):272–287

20. Ludolph A, Drory V, Hardiman O et al (2015) A revision of the El escorial criteria—2015. Amyotroph Lateral Scler Frontotemporal Degener 16(5–6):291–292. doi:10.3109/21678421.2015.1049183

21. Lule D, Nonnenmacher S, Sorg S et al (2014) Live and let die: existential decision processes in a fatal disease. J Neurol 261(3):518–525. doi:10.1007/s00415-013-7229-z

22. Hautzinger M, Bailer M, Hofmeister D et al (2012) ADS—allgemeine depressionsskala. Tests infoHogrefe, Göttingen

23. Cedarbaum JM, Stambler N, Malta E et al (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 169(1–2):13–21

24. Pelayo M, Cebrian D, Areosa A et al (2011) Effects of online palliative care training on knowledge, attitude and satisfaction of primary care physicians. BMC Fam Pract 12:37. doi:10.1186/1471-2296-12-37

25. Anderson WG, Williams JE, Bost JE et al (2008) Exposure to death is associated with positive attitudes and higher knowledge about end-of-life care in graduating medical students. J Palliat Med 11(9):1227–1233. doi:10.1089/jpm.2008.0058

26. Fischer SM, Gozansky WS, Kutner JS et al (2003) Palliative care education: an intervention to improve medical residents' knowledge and attitudes. J Palliat Med 6(3):391–399. doi:10.1089/109662103322144709

27. Long AC, Downey L, Engelberg RA et al (2016) Physicians' and nurse practitioners' level of pessimism about end-of-life care during training: does it change over time? J Pain Symptom Manag 51(5):890.e1–897.e1. doi:10.1016/j.jpainsymman.2015.11.024

28. Moss AH, Casey P, Stocking CB et al (1993) Home ventilation for amyotrophic lateral sclerosis patients: outcomes, costs, and patient, family, and physician attitudes. Neurology 43(2):438–443

29. Heritier Barras A, Adler D, Iancu Ferfoglia R et al (2013) Is tracheostomy still an option in amyotrophic lateral sclerosis? Reflections of a multidisciplinary work group. Swiss Med Wkly 143:w13830. doi:10.4414/smw.2013.13830

30. Trail M, Nelson ND, Van JN et al (2003) A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. J Neurol Sci 209(1–2):79–85. doi:10.1016/S0022-510X(03)00003-0

31. Lemoignan J, Ells C (2010) Amyotrophic lateral sclerosis and assisted ventilation: how patients decide. Palliat Support Care 8(2):207–213. doi:10.1017/S1478951510000027

32. Rabkin JG, Wagner GJ, Del Bene M (2000) Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. Psychosom Med 62(2):271–279

33. Kaub-Wittemer D, Nv Steinbuchel, Wasner M et al (2003) Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. J Pain Symptom Manag 26(4):890–896

34. Oliver DJ, Turner MR (2010) Some difficult decisions in ALS/MND. Amyotroph Lateral Scler 11(4):339–343. doi:10.3109/17482968.2010.487532

35. Albert SM, Murphy PL, Del Bene ML et al (1999) A prospective study of preferences and actual treatment choices in ALS. Neurology 53(2):278–283

36. Chio A, Calvo A, Ghiglione P et al (2010) Tracheostomy in amyotrophic lateral sclerosis: a 10-year population-based study in Italy. J Neurol Neurosurg Psychiatry 81(10):1141–1143. doi:10.1136/jnnp.2009.175984

37. Vianello A, Arcaro G, Palmieri A et al (2011) Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. J Crit Care 26(3):329.e7-14. doi:10.1016/j.jcrc.2010.06.003

38. Matuz T, Birbaumer N, Hautzinger M et al (2010) Coping with amyotrophic lateral sclerosis: an integrative view. J Neurol Neurosurg Psychiatry 81(8):893–898. doi:10.1136/jnnp.2009.201285

39. Viera AJ, Edwards T (2012) Does an offer for a free on-line continuing medical education (CME) activity increase physician survey response rate? A randomized trial. BMC Res Notes 5:129. doi:10.1186/1756-0500-5-129

40. Ho A (2008) Relational autonomy or undue pressure? Family's role in medical decision-making. Scand J Caring Sci 22(1):128–135. doi:10.1111/j.1471-6712.2007.00561.x

41. Ruhnke GW, Wilson SR, Akamatsu T et al (2000) Ethical decision making and patient autonomy: a comparison of physicians and patients in Japan and the United States. Chest 118(4):1172–1182