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Electroencephalography of completely locked-in state patients with amyotrophic lateral sclerosis

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ABSTRACT

Patients in completely locked-in state (CLIS) due to amyotrophic lateral sclerosis (ALS) lose the control of each and every muscle of their body rendering them motionless and without any means of communication. Though some studies have attempted to develop brain-computer interface (BCI)-based communication methods with CLIS patients, little information is available of the neuroelectric brain activity of CLIS patients. However, because of the difficulties with and often loss of communication, the neuroelectric signature may provide some indications of the state of consciousness in these patients. We recorded electroencephalography (EEG) signals from 10 CLIS patients during resting state and compared their power spectral densities with those of healthy participants in fronto-central, central, and centro-parietal channels. The results showed significant power reduction in the high alpha, beta, and gamma bands in CLIS patients, indicating the dominance of slower EEG frequencies in their oscillatory activity. This is the first study showing group-level EEG change of CLIS patients, though the reason for the observed EEG change cannot be concluded without any reliable communication methods with this population.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease that affects patients' motor control. ALS patients suffer from progressing impaired motor control, and often their options for communication methods become limited. In the advanced stage of ALS called locked-in state (LIS), patients lose most voluntary body movements but still can communicate using their eye movements or any other muscular response. However, in the further advanced stage called completely locked-in state (CLIS), patients lose all muscular control including their eyes and thus all communication methods are lost, although cognitive function of CLIS patients is assumed to be functioning (Kotchoubey et al., 2003; Fuchino et al., 2008).

Some studies have attempted to establish brain-computer interface (BCI)-based communication methods with CLIS patients using brain signals such as electrocorticography (ECoG), electroencephalography (EEG), and functional Near-Infrared Spectroscopy (fNIRS) (Kübler and Birbaumer, 2008; Murguialday et al., 2011; Gallegos-Ayala et al., 2014; Okahara et al., 2018; Ardali et al., 2019; Han et al., 2019). Though some of such attempts partly succeeded in communication (Okahara et al., 2018; Han et al., 2019), it is still a quite challenging problem. Characterization of EEG in CLIS patients can assist in the development of EEG-BCI-based communication methods with CLIS patients because the knowledge of the EEG frequency characteristics is crucial in the correct selection and exclusion criteria of classification algorithms for BCIs (Nicolas-Alonso and Gomez-Gil, 2012).

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Though EEG of non-late-stage ALS patients during resting state have been reported in some studies (Mai et al., 1998; Santhosh et al., 2005; Iyer et al., 2015; Jayaram et al., 2015; Fraschini et al., 2016, 2018; Nasseroleslami et al., 2019) and reviews (Kellmeyer et al., 2018; Proudfoot et al., 2019), little EEG information is available of late-stage ALS patients such as LIS and CLIS. Only one case study investigated power spectral densities (PSDs) of 2 ALS-CLIS patients (Hohmann et al., 2018). This study quantitatively reported shifts of the alpha peak frequencies in the CLIS patients toward the lower frequency ranges compared with healthy participants and ALS patients who showed ALSFRS-R (The Revised ALS Functional Rating Scale) (Cedarbaum et al., 1999) scores larger than 0. Other single case studies also reported dominance of low EEG frequencies in ALS-CLIS patients (Hayashi and Kato, 1989; Kotchoubey et al., 2003). However, group-level comparison between ALS-CLIS and healthy people has not been performed yet.

In this study, therefore, to describe the EEG characteristics of ALS-CLIS patients at group level, we investigated the resting-state PSDs of ALS-CLIS patients. The PSD analysis was performed for signals recorded from fronto-central, central, and centro-parietal sensors that could be placed over the scalp of the bedridden patients.

2. Materials and methods

The Institutional Review Boards of the Medical Faculty of the University of Tübingen and Tokyo Institute of Technology approved the study reported in this study. This study is in full compliance with the ethical practice of Medical Faculty of the University of Tübingen and follows the criteria of the Helsinki Accords. Written informed consent for this study was obtained from the patients' legal representatives and the healthy participants.

2.1. Participants

We recorded EEG signals from 10 ALS-CLIS patients and 7 healthy participants. The number of healthy participants was decided so that mean and variance of age were not significantly different in each comparison, considering the different numbers and positions of sensors between the patients due to clinical needs. Table 1 shows the demographic data and EEG measurement conditions. The mean age (standard deviation) was 47.1 (19.7) in patients and 45.7 (12.6) in healthy participants. All patients were in home care and bed-ridden, artificially ventilated and fed. CLIS was defined as inability to communicate with eye movements or any other voluntary muscle with use or non-use of eye trackers for more than 6 months. (After failure of eye-trackers caretakers tried to "read" "yes"- signals from eye or face muscles, in none of the patients any reliable communication was possible. A detailed description of the patients can be found in Malekshahi et al., 2019). All patients showed regular circadian patterns of slow wave sleep and waking (Malekshahi et al., 2019).

2.2. EEG acquisition

In the EEG measurement, the CLIS patients and the healthy participants were instructed to relax, try not to think anything, and refrain from sleeping. Eyes of the CLIS patients were closed (they can only be opened actively by caretakers). Healthy participants were additionally instructed to keep their eyes closed and not to move throughout the measurement.

Table 1
Demographic data and EEG measurement conditions of the participants.

Participant ID	Gender	Age (years)	ALS duration (years)	Recording time (seconds)	EEG sensor positions
ALS-CLIS Patients					
P1	F	72	10	311	FCC3, FCC4, FCC5, FCC6, Cz [a]
P2	M	62	4	603	AF3, AF4, FC1 [a], FC5 [a], FC6 [a], CP1 [a], CP5 [a], CP6 [a]
P3	F	79	7	584	FC3, FC4, FC5 [a], FC6 [a], Cz [a]
P4	F	26	4	487	FC1 [a], FC2, FC5 [a], FC6 [a], CP1 [a], CP2, CP5 [a], CP6 [a]
P5	M	58	7	600	FC1 [a], FC2, FC5 [a], FC6 [a], CP1 [a], CP2, CP5 [a], CP6 [a]
P6	M	37	8	623	FC5 [a], FC6 [a], C5, C6, Cz [a], T9, T10
P7	F	56	7	753	FC3, FC4, FC5 [a], FC6 [a], Cz [a]
P8	F	33	6	630	FC1 [a]
P9	M	23	4	1032	F3, F4, C3, C4, Cz [a]
P10	M	25	5	641	FC5 [a], FC6 [a], C5, C6
Healthy Participants					

Table 1 (*Continued*)

Participant ID	Gender	Age (years)	ALS duration (years)	Recording time (seconds)	EEG sensor positions
H1	M	26	N.A. [c]	684	AF3, AF4, FC1 [a], FC2, FC3, FC4, FC5 [a], FC6 [a], C5, C6, Cz [a], CP1 [a], CP2, CP5 [a], CP6 [a], Oz
H2	F	29		1166	
H3	F	51		682	
H4 [b]	M	50		1268	
H5	M	65		1258	
H6	M	49		1272	
H7	M	50		1214	

[a] EEG sensors used in the analysis.
[b] Data of H4 was excluded from the analysis due to recording failure and artefact contamination.
[c] Not applicable.

EEG sensors were attached according to the 10-5 system, with one reference channel attached to their right mastoids. EEG signals were recorded using a V-Amp amplifier and passive electrodes (Brain Products GmbH, Gilching, Germany). In the measurement of the patients, electrooculogram (EOG), chin electromyogram (EMG), and Near-Infrared Spectroscopy (NIRS) sensors were also attached to faces and heads for other clinical and research purposes. Due to clinical needs, the numbers and positions of sensors were different between the patients, while they were identical across the healthy participants (Table 1). The EEG data was measured in the afternoon for all the CLIS patients and healthy participants to equalize their conditions in terms of the circadian rhythm. The EEG data from one of the healthy participants (H4) was excluded from the analysis due to recording failure of EEG sensors and artefact contamination.

2.3. EEG processing

EEG signals were processed using Matlab R2016b (The MathWorks, Inc., Natick, Massachusetts, U.S.A.) and EEGLAB 14.1.1 software (Delorme and Makeig, 2004). In the preprocessing, a high-pass finite impulse response (FIR) filter at 0.5 Hz and a low-pass FIR filter at 45 Hz were applied to the raw EEG signals, followed by down-sampling to 100 Hz to save computational cost. Subsequently, we extracted five 1-minute epochs (i.e., 5-minute data in total) containing minimal artefacts such as muscle activities and body movements by visual inspection.

Considering the difference of sensor positions in CLIS patients due to clinical limitation, we decided to use 7 sensors FC5, FC6, Cz, FC1, CP1, CP5, and CP6 (Table 1) for the PSD comparison analysis. Specifically, FC5 and FC6 were used for 7 patients (patient ID: P2, P3, P4, P5, P6, P7, and P10), Cz was used for 5 patients (patient ID: P1, P3, P6, P7, and P9), FC1 was used for 4 patients (patient ID: P2, P4, P5, and P8), and CP1, CP5, and CP6 were used for 3 patients (patient ID: P2, P4, and P5). For these 7 sensors (FC5, FC6, Cz, FC1, CP1, CP5, and CP6), PSDs of these patients were compared with PSDs of all the 6 healthy participants (H1, H2, H3, H5, H6, and H7), respectively. For each sensor, PSD for each 1-minute epoch was calculated by Fast Fourier Transform (FFT) of 1-second time window with 0.25-second overlap, and each participant's PSD was obtained by averaging five 1-minute PSDs. Hann window was applied as the window function. We averaged 1185 PSDs (237 PSDs per 1-minute epoch × 5 epochs) to get each participant's representative resting-state PSD. From the PSD, delta (1–3 Hz), theta (4–7 Hz), low alpha (8–10 Hz), high alpha (11–13 Hz), beta (14–30 Hz), and gamma (31–40 Hz) band power was calculated by averaging power in the corresponding frequencies.

2.4. Statistical analysis

Statistical tests were performed in free software R (R Core Team, 2018). Due to small sample sizes, we applied a two-tailed Wilcoxon rank sum test to test the power difference between the CLIS patients and the healthy participants for each frequency band and sensor. The obtained p-values were False Discovery Rate (FDR) corrected using the Benjamini-Hochberg method to compensate for the multiple comparison of 6 frequency bands and 7 sensors (Benjamini and Hochberg, 1995). Additionally, at sensors where significant difference of frequency band power was observed in the above comparison, correlation between frequency band power and ALS duration in the CLIS patients was tested based on Spearman's rank correlation coefficient for each frequency band. The obtained p-values were FDR corrected for the multiple comparisons (Benjamini and Hochberg, 1995).

3. Results

For each comparison the mean and the variance of age were not significantly different between the CLIS patients and the healthy participants (two-tailed *t*-test and *F*-test).

On Fig. 1A and B, we show filtered EEG time series of a representative CLIS patient (Fig. 1A) and a healthy participant (Fig. 1B) at sensor Cz. Fig. 1C and D show PSDs at Cz for the 5 CLIS patients who could use Cz for the recording (patient ID: P1, P3, P6, P7, and P9 as described above and in Table 1) and the 6 healthy participants, and their mean PSDs are compared in Fig. 1E. These figures show the dominance of slow oscillations in the CLIS patients. In the same manner, we also calculated PSDs of the other sensors (FC1, FC5, FC6, CP1, CP5, and CP6), and frequency band power of the CLIS patients and the healthy participants at all of the sensors are statistically compared and summarized in Fig. 2. Fig. 2A–F show power in the delta, theta, low alpha, high alpha, beta, and gamma bands, respectively. In the high alpha band (Fig. 2D), power between the two groups was significantly different at sensor FC5 ($p = 0.044$). In the beta and gamma bands (Fig. 2E and F), power between the two groups was significantly different at sensors FC1, FC5, FC6, and Cz ($p = 0.044$, 0.016, 0.016, and 0.030 respectively in the beta band and $p = 0.044$, 0.016, 0.024, and 0.030 respectively in the gamma band).

In the correlation analyses, we included only sensors FC1, FC5, FC6, and Cz because significant differences of frequency band power between the CLIS patients and the healthy participants were observed at these sensors. Relationships between frequency band power and ALS duration in the CLIS patients at these 4sensors are depicted in Fig. 3A–F. Spearman's rank correlation coefficients at sensors FC1, FC5, FC6, and Cz were −0.32, 0.17, −0.24, and −0.82 respectively in the delta band, −0.32, −0.37, −0.71, and −0.87 respectively in the theta band,

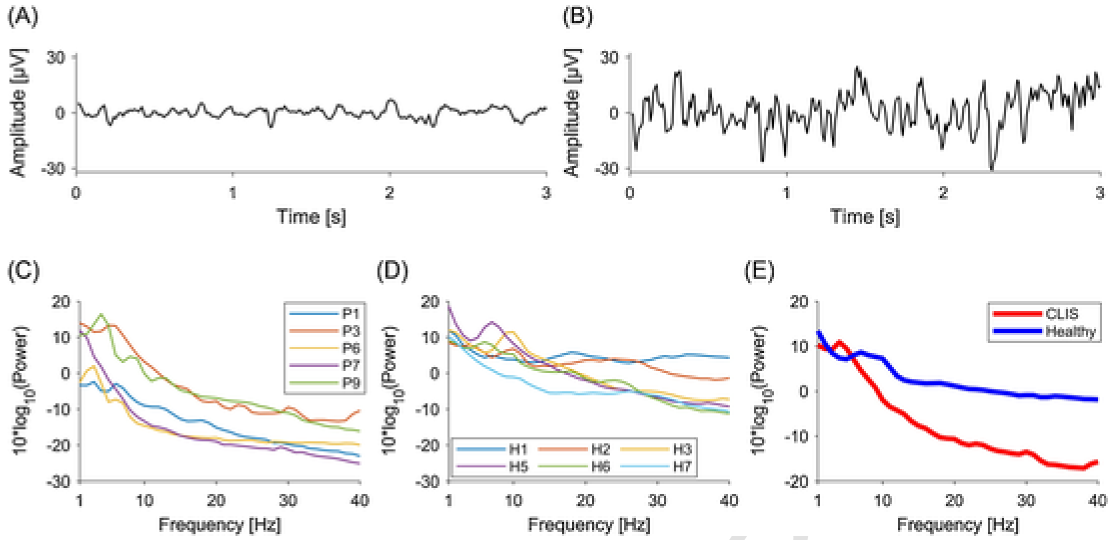

Fig. 1. EEG time series and power spectral densities of the CLIS patients and the healthy participants at sensor Cz. (A) EEG of a CLIS patient (P1). (B) EEG of a healthy participant (H3). (C) PSDs of the 5 CLIS patients (P1, P3, P6, P7, and P9). (D) PSDs of the 6 healthy participants (H1, H2, H3, H5, H6, and H7). (E) Mean PSDs of the 5 CLIS patients and the 6 healthy participants.

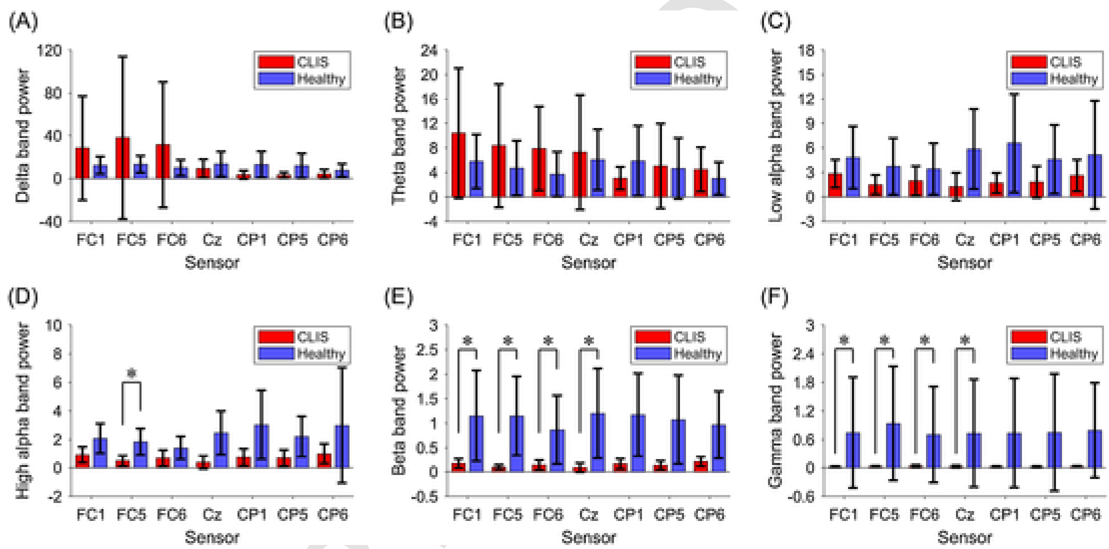

Fig. 2. Mean frequency band power at sensors FC1, FC5, FC6, Cz, CP1, CP5, and CP6. Error bars represent standard deviations. Significant power differences between the CLIS patients and the healthy participants in two-tailed Wilcoxon rank sum test with False Discovery Rate correction are marked: *$p < 0.05$. (A) Delta band (1–3 Hz). (B)Theta band (4–7 Hz). (C) Low alpha band (8–10 Hz). (D) High alpha band (11–13 Hz). (E) Beta band (14–30 Hz). (F) Gamma band (31–40 Hz).

−0.63, −0.51, −0.88, and −0.46 respectively in the low alpha band, −0.95, −0.51, −0.88, and −0.46 respectively in the high alpha band, −0.95, −0.75, −0.73, and −0.46 respectively in the beta band, and −0.95, 0.15, −0.47, and −0.41 respectively in the gamma band. No correlation coefficients were statistically significant after FDR correction.

4. Discussion

We investigated resting-state EEG of ALS-CLIS patients to provide insight into their electric brain activities and possible state of consciousness. The CLIS patients showed significant power decrease in the high alpha band at sensor FC5 and in the beta and gamma bands at sensors FC1, FC5, FC6, and Cz. This group-level comparison using EEG data of CLIS patients and healthy participants demonstrated clear EEG power differences.

Different state of consciousness and arousal is the most discussed reason for the power decrease in the alpha and beta bands. Patients with Alzheimer's dementia show a decrease of the absolute power in the alpha and beta bands together with an increase in the delta and theta bands in comparison with healthy participants during eyes-closed resting state (Pucci et al., 1998). Some ALS patients may also show cognitive impairment in various domains such as executive function, language, and fluency (Phukan et al., 2007; Raaphorst et al., 2010; Goldstein and Abrahams, 2013; Beeldman et al., 2016). Mild cognitive deficits are more frequently observed in the advanced stage of ALS than in the early stage (Crockford et al., 2018). However, there is also a report with LIS patients suffering from ALS who showed no signs of cognitive decline during testing using an eye-tracking system (Linse et al., 2017). None of the studies cited here found a significant relationship between the reduction of band power and cognitive performance. At present, testing of cognitive capacities becomes increasingly difficult with progressing paralysis and finally impossible in LIS and CLIS. Thus, any conclusion about such a relationship remains highly speculative. However, a decreased state of central

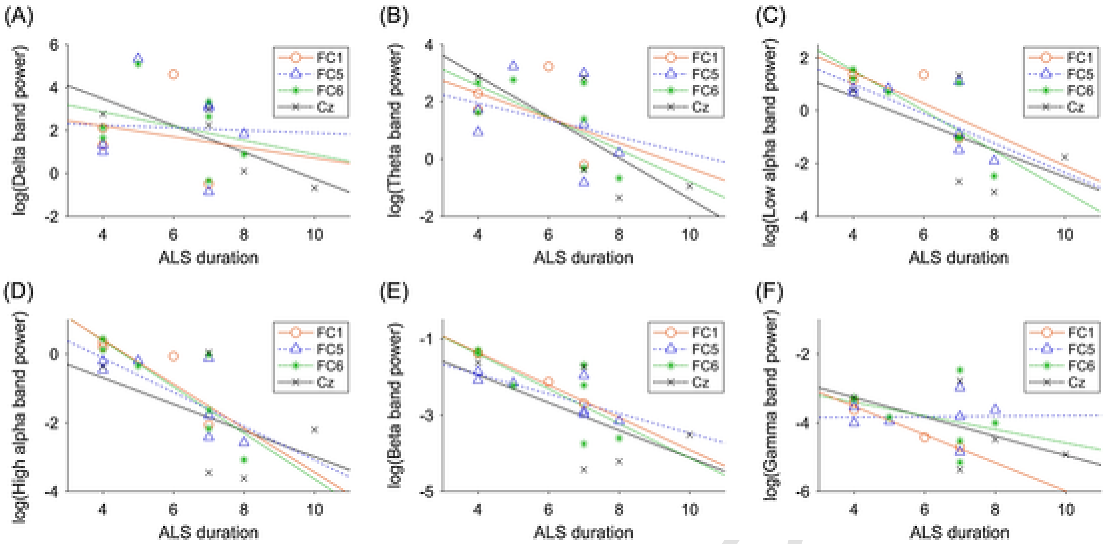

Fig. 3. Scatter plot of ALS duration and frequency band power at sensors FC1, FC5, FC6, and Cz. Red circles, blue triangles, green stars, and black crosses represent individual patients' data for FC1, FC5, FC6, and Cz, respectively. The corresponding lines represent linear approximation calculated by a least-squares method. (A) Delta band (1–3 Hz). Spearman's correlation coefficients (ρs) were −0.32, 0.17, −0.24, and −0.82 at sensors FC1, FC5, FC6, and Cz respectively. (B)Theta band (4–7 Hz). ρs were −0.32, −0.37, −0.71, and −0.87 at sensors FC1, FC5, FC6, and Cz respectively. (C) Low alpha band (8–10 Hz). ρs were −0.63, −0.51, −0.88, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (D) High alpha band (11–13 Hz). ρs were −0.95, −0.51, −0.88, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (E) Beta band (14–30 Hz). ρs were −0.95, −0.75, −0.73, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (F) Gamma band (31–40 Hz). ρs were −0.95, 0.15, −0.47, and −0.41 at sensors FC1, FC5, FC6, and Cz respectively (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

arousal during waking seems plausible associated with the complete immobility and consequent deprivation of environmental stimulation.

There are inconsistent reports about the relationship between the decrease of the gamma band power and cognitive impairment. Herrmann and Demiralp suggested relationship between the alteration of the gamma band activity and disturbed cognitive function (Herrmann and Demiralp, 2005), while van Deursen et al. reported that patients with Alzheimer's dementia showed power increase in the gamma band during eye-open resting state in comparison with healthy participants (van Deursen et al., 2008). In comparison with healthy people, we should not ignore the effect of absence of muscle activities in CLIS patients because high frequency bands such as the gamma band are easily contaminated by muscle activities (Pope et al., 2009). Though we instructed the healthy participants not to move during the EEG recordings, the decrease of the gamma band power in the CLIS patients in comparison with the healthy participants can be partly due to the loss of muscle activity. Accordingly, it is premature to associate the gamma band power reduction with cognitive impairment without reliable findings from a cognitive testing procedure.

Another reason for the power decrease in the alpha band could be reduced vigilance and outward attention, since the alpha peak frequency is suggested to be associated with the activities in brain regions modulating attention in healthy people (Jann et al., 2010). The "extinction of goal-directed thinking" hypothesis formulated by Kübler and Birbaumer predicts the reduction of arousability and vigilance in CLIS patients due to suppressed social-cognitive interaction (Kübler and Birbaumer, 2008). However, it is also impossible to affirm a reduced vigilance and outward attention in CLIS patients without any existing behavioral evidence. To investigate the attentional and cognitive function in CLIS patients and their relationship with the EEG characteristics, functioning BCI systems allowing more flexible communication than simple yes/no responses are necessary (Ardali et al., 2019).

Both, the decrease of the alpha and gamma band power may be in part due to loss of motor control. Most EEG-based BCIs use power changes in the alpha band in accordance with preparation and start and stop of imagined or executed body movements. These phenomena are called event-related desynchronization (ERD) for movement and event-related synchronization (ERS) for stopping movements, and are commonly observed in EEG signals recorded from central area (Pfurtscheller and Aranibar, 1979). Although the exact neuro-physiological mechanisms of the phenomena have not been clarified yet, CLIS patients may have less neural activation in the motor related areas, which may be related to the power decrease in the alpha band. Gamma band power is also reported to be involved in action execution in studies using ECoG (Pistohl et al., 2008; Nakanishi et al., 2013; Babiloni et al., 2016). On the other hand, some BCI studies reported that LIS and non-late-stage ALS patients succeeded in controlling a speller or a web browser using neuronal signals from intracortical electrodes placed in the hand area of dominant motor cortex (Vansteensel et al., 2016; Pandarinath et al., 2017; Nuyujukian et al., 2018). Considering the success of the BCI-use in these studies, the power decrease in the frequency bands may just indicate shifts of alpha frequency to lower frequencies such as theta or delta, which has been suggested in previous studies (Hohmann et al., 2018; Malekshahi et al., 2019). Our results may also indicate this tendency of a shift of alpha as shown in Fig. 1.

We calculated the correlation coefficients between the EEG power and the disease duration. Though we found no significant correlation in this study and it is difficult to reach a conclusion with such a limited number of patients, the frequency band power at most sensors tended to decrease as the ALS duration was long. In addition to the disease duration, other factors such as progression rate of the disease, age, and medication may be responsible for such hypothetical relationships with the demonstrated power reduction. An important factor affecting the difference between CLIS patients and healthy participants may result from artificial respiration over extensive time periods, a rule in CLIS patients. Hyper- as well as hypoventilation is strongly related with EEG-slowing (Hoshi et al., 1999). However, both, long-term hyperventilation and lack of oxygen lasting minutes or more, are causing reduced central and subjective arousal and are thus compatible with our conclusion of lowered arousal level in CLIS. If resting-state EEG of ALS patients progressing toward CLIS can be recorded longitudinally before and after artificial respiration, it will reveal the relationship between the EEG power and ALS progression and respiration-related changes. Furthermore, if ALS patients would use a BCI-based communication method already in the early stage of the disease, the BCI-use might play a role as a device to prevent the power decrease in the higher frequency bands due to continued cognitive demands and increased environmental stimulation. For stroke patients, an ERD-based BCI has been used as a rehabilitation to restore or reorganize their neural processing for their partially paralyzed body (Ramos-Murguialday et al., 2013). To investigate whether the use of BCI-based communication has the effect of preventing the power decreases and/or changing subjective arousal and activation in ALS patients, studies applying BCI for ALS patients from the early stage are needed. In addition, although the population of CLIS is small, a study with more CLIS patients in comparison with non-late-stage ALS patients is necessary to further quantify their EEG signatures.

In conclusion, this study showed altered oscillatory brain activities of CLIS patients compared with healthy participants. We found significant power decrease in the high alpha, beta, and gamma bands at fronto-central and/or central channels in the CLIS patients suggesting reduced central arousal. We think the observed EEG change may indicate a shift of the alpha band toward lower frequencies. This overall slowing may indicate a different state of vigilance and attention and may not allow the application of comparable cognitive tasks as in healthy subjects for which most BCI paradigms were developed. Thus, BCIs that entail tasks that seem difficult for LIS and CLIS patients should be replaced. In addition, many BCIs that rely on the classification of ERD/ERS using the defined frequency band of 8–15 Hz will not function because in LIS and CLIS frequency bands below 8 Hz seem to be relevant. Changes of the target frequencies may be needed because the target brain activities may be represented in the slower frequency ranges in CLIS patients. Further investigation using longitudinal recordings and use of BCIs are required to clarify the effect of BCI-use as a rehabilitation method and if the power decrease correlates with loss of motor control, cognitive changes, reduced vigilance, and/or emergency treatment effects such as artificial respiration and feeding.

Author contributions

NY, NB, and UC conceptualized and designed the study. AR, AM, AT, AJ, and UC collected the data. YM performed analysis. NY supervised analysis. YM, NY, NB, and UC wrote the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neures.2020.01.013.

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