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Sleep Detection in Completely Locked-in ALS Patients

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Abstract

Patients with amyotrophic lateral sclerosis in completely locked-in state are unable to communicate using motion. Brain–computer interfaces (BCIs) could be a way to overcome this by capturing thought-evoked brain signals. This work aims to improve BCI communication by determining whether patients are awake during BCI experiment sessions. We propose to identify awake periods by measuring the patient's heart rate. In a first study on one patient answering yes–no questions, taking into account only trials in high mean pulse periods improves yes–no classification. In a second study, extending the paradigm by a pulse feedback mechanism, heart rate variability is a better indicator for yes–no discriminability than mean pulse. To extend our method to recording sessions that did not measure heart rate, we attempt to find a heart rate correlate in EEG data. However, none of three explored approaches produces a reliable correlate.

1 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease affecting motor neurons in primary motor cortex and spinal cord [1]. The progressing course of the disease causes more and more movement impairments. In the late stage this may lead to paralysis of the entire body. Since eye movements are often the last preserved actions that patients can control [2], they use visual speller systems as the only way to communicate [3] . The stage when also oculomotor neurons are degenerated is called completely locked-in syndrome (CLIS) [4]. To date, it is not possible to establish reliable communication with CLIS patients due to total lack of controlled movements [3].

There have been attempts to build brain–computer interfaces (BCIs) operating directly with brain signals—for example, by means of electroencephalography (EEG; e.g. [5, 6]). This way, CLIS ALS patients could become able to interact with their environment via yes–no communication. However, Marchetti and Priftis [7] report a vast heterogeneity of BCI effectiveness in ALS patients among studies. Overall, effectiveness has not increased within the past 15 years. Murguialday and colleagues [2] even questioned CLIS ALS patient's ability for goal-directed thinking—that is, their preserved higher-level consciousness. The most persuasive way to rule out these objections would be to show that patients still participate in experiments and reliably answer questions correctly.

In the present work, we aim to gain a more stable communication with CLIS ALS patients through a BCI by incorporating their particular physiological state in our analysis. Thus, instead of assuming that the complete lack of motor control and interaction with the environment may lead to cessation of higher-level consciousness [2], we may conclude that the patient's ability to stay awake for a whole day is impaired. This is, CLIS ALS patients may not be able to focus on their environment constantly anymore because they do not have the incentive of interaction and getting feedback. Instead, they may occasionally drift to a sleepy state for short periods of time during the day. If these periods fall into the time of the experiment, the results may be strongly impaired. This hypothesis gains support from findings from Barthlen and Lange who reported increased daytime fatigue in ALS patients [8].

In both rapid eye movement (REM) sleep and non-REM sleep, heart rate and blood pressure are decreased in comparison to awakeness [9, 10]. Heart beat starts to slow down approximately 30 seconds before onset of

sleep [11]. Decreased heart rate results from an increased parasympathetic and a decreased sympathetic tone [10]. This effect is stable over different age groups [11] and different mammal species [10]. In contrast, heart rate variability (HRV) is higher during sleep than awakeness [12]. Besides, it is also an indicator of stress level [13]—this is, low HRV indicates high stress level.

Sachs et al. report a normal heart rate pattern in ALS patients [14]. However, several studies point towards higher resting state heart rate [15] and impaired parasympathetic activity [16] in ALS patients, compared to control subjects. This may explain increased daytime fatigue and sleeping disorders [8].

To improve the results of yes–no classification experiments, we use heart rate as an indicator to detect whether patients are currently awake and able to participate in the experimental session. Other typical polysomnographical measures like electromyography, electrooculography or observation of breathing movements are not valide due to the disease. However, heart rate could still serve as a stable measure of awakeness detection.

The experimental paradigm we use is adapted from Hohmann et al. [6]. It uses activity modulation in the Default Mode Network (DMN). Using this paradigm, Hohmann et al. could show accuracy rates of 73% for both healthy subjects and ALS patients that have not entered CLIS yet [17].

2 Methods and Results

In the following, we first explain the experimental setup for two datasets we will analyse. Then we describe three different approaches of how pulse can be taken into account as an indicator for sleepiness before doing yes–no classification. Thereafter, three attempts to find a pulse correlate in EEG are shown for the purpose of including more data in the analysis and examining reliability of detected effects.

2.1 Experimental Setup

We recorded EEG and pulse data from one female 61 years old ALS patient that had already entered the completely locked-in state. The EEG system included 124 actiCAP active electrodes and a BrainAmp amplifier (both provided by BrainProducts GmbH, Gilching, Germany). We placed electrodes

according to the extended 10–20 system, with electrode *TP16* as the initial reference. All data was recorded with 500 Hz sampling rate and converted to common average reference. Pulse was measured with a pulse oxymeter (also provided by Brain Products GmbH).

Every experimental session included a 10 minutes long resting state and three experimental blocks of 20 trials each. In every trial the patient heard one question that was randomly selected out of a set of 20 questions (see Appendix A). The set contains 10 questions with a positive answer and 10 questions with a negative answer. Afterwards, the patient was asked to think for 15 seconds of either a positive memory if the correct answer was 'yes' (condition 1, ten trials) or the result of a simple math equation if the correct answer was 'no' (condition 2, ten trials). In every block, every question of the set was asked once. In half of the blocks, the answering key was inverted. Instructions were provided by a male voice.

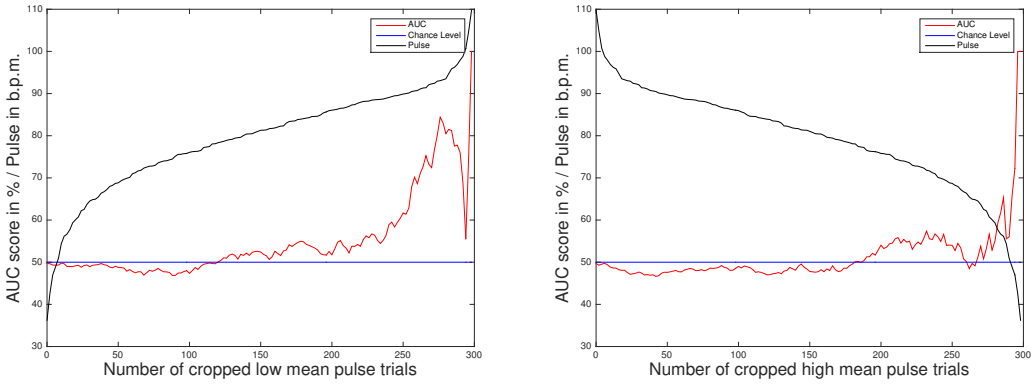
Dataset A consists of five sessions, all recorded with the same patient. For Dataset B, we modified the paradigm slightly by providing feedback after every trial: if mean pulse of a trial was below 87 beats per minute (b.p.m.) or above 91 b.p.m., the patient got auditory feedback that the trial was rejected. Dataset B, too, includes five sessions by three blocks each.

2.2 Mean Pulse as Sleep Indicator

In our first analysis, we aimed at finding evidence that yes–no classification is more accurate when the patient is awake. Assuming higher probability for the patient to be awake when mean pulse is high, we hypothesized better classification for high mean pulse trials.

To classify whether the patient thought of a positive memory or solved the math task, we observed the frequency modulation of the alpha peak in the band-power spectrum in channel *Pz*. We estimated the alpha peak of the spectrum by conducting a Fourier analysis (Hilbert transform) of the trials of all sessions. We express information content of frequency modulation by calculating the area under the curve (AUC) of the distribution of condition 1 versus distribution of condition 2.

For the analysis, we first calculated the AUC for all 300 trials of Dataset A. Then, we identified in both conditions one trial with lowest mean pulse, eliminate them both from the data set, and calculated the AUC for the remaining 298 trials. We repeated this procedure until only two trials remained: we eliminated the n trials with lowest mean pulse and calculated

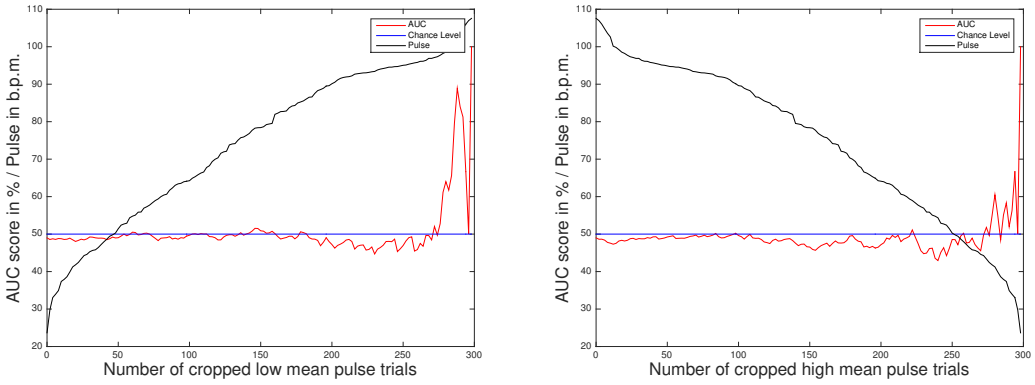


(a) (b)

Figure 1: DATASET A: AUC and mean pulse course depending on number of trials excluded before calculating AUC. (a) Excluding low mean pulse trials. (b) Excluding high mean pulse trials.

the AUC for the remaining 300-n trials. In Figure 1a, we plot the AUC values as function of the number of excluded trials n (red curve). In black, we depict the mean pulse (in b.p.m.) of the two trials with lowest mean pulse—averaged over both conditions. While AUC is at chance level when including all trials, it increases to 80% when including only the 100 trials with the highest mean pulse in the analysis. The concerned pulse range between 89 and 98 b.p.m. fits well to our hypothesis that the patient has to be awake to be able to participate in the experiment. To rule out that this effect is merely an artifact of lower trial sample size, we inverted the procedure, i.e. sorted out trials with high mean pulse and calculated AUC values with the remaining trials of lowest mean pulse (see Figure 1b). Indeed, we also see a slight increase of AUC score here, however it does not come close to the effect in Figure 1a. Note that the late shoot up of AUC for only five included trials is thought to be an artifact, caused by very low sample size.

Figure 2a and Figure 2b show the results of the same analysis for DATASET B. In contrast to DATASET A, you cannot observe a pronounced increase of AUC within a sensible mean pulse range here. Besides, overall mean pulse is increased. A possible reason for that may be a high stress level of the patient, caused by the feedback and a lot of trial rejections in the paradigm of DATASET B.



(a) (b)

Figure 2: DATASET B: AUC and mean pulse course depending on number of trials excluded before calculating AUC. (a) Excluding low mean pulse trials. (b) Excluding high mean pulse trials.

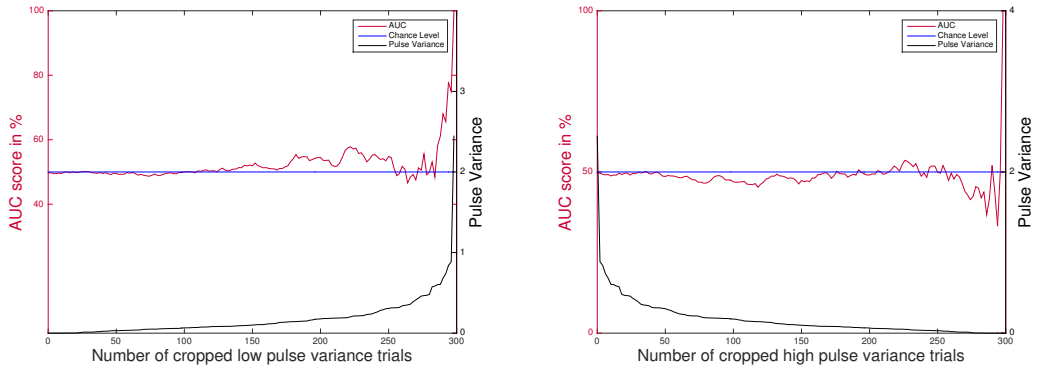
2.3 Heart Rate Variability as Stress Indicator

As HRV is an indicator for stress level [13], we performed the same analysis as described in Section 2.2, but used HRV instead of mean pulse: we eliminated trials with low HRV. HRV was calculated as variance of the peak-to-peak distances in the pulse signal.

While AUC stays close to chance level for the whole course for DATASET A (see Figures 3a and 3b), we see a pronounced deviation in the AUC course for high HRV trials in DATASET B (see Figure 4a; c.f. Figure 4b). This post-hoc observation in DATASET B fits nicely to the assumption that the constraint of the patient's attention was not sleepiness like in DATASET A, but rather high distraction due to increased stress level in the new paradigm with feedback. In Section 3 we discuss how significance of AUC scores can be tested.

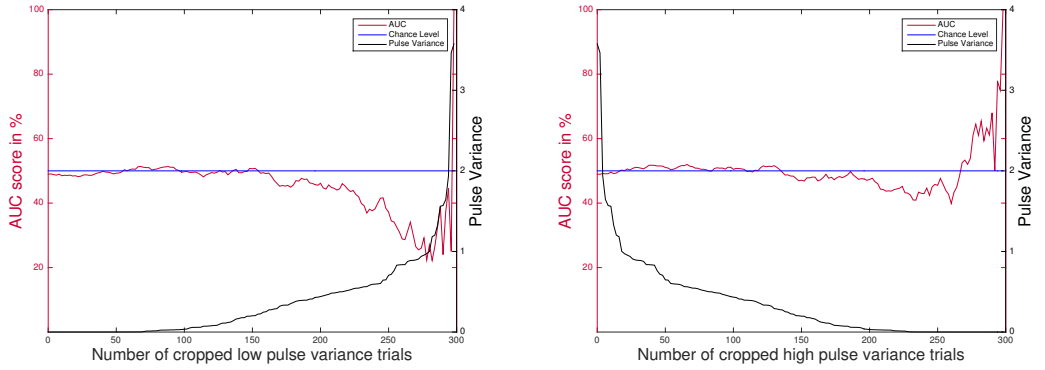
2.4 Mean Pulse as Confound Factor

When analyzing the relationship between frequency modulation of the alpha peak and pulse, we found a slight but significant positive correlation (Spearman's rank-order correlation; $\alpha = .05$) for channel POz in both datasets (DATASET A: $\rho = -0.17$, $p = 0.0024$; DATASET B: $\rho = -0.13$, $p = 0.02$). Based on this finding, we hypothesized that pulse may be a confound fac-



(a) (b)

Figure 3: DATASET A: AUC and pulse variance (variance of pulse in sec) course depending on number of trials excluded before calculating AUC. (a) Excluding low HRV trials. (b) Excluding high HRV trials.



(a) (b)

Figure 4: DATASET B: AUC and pulse variance (variance of pulse in sec) course depending on number of trials excluded before calculating AUC. (a) Excluding low HRV trials. (b) Excluding high HRV trials.

tor in the yes–no classification process. Thus, we cleaned the data before calculating AUC: we predicted frequency modulation with mean pulse and then included only the residuals between measured and predicted frequency modulation scores. However, in both datasets, AUC score, calculated with cleaned data, does not come above chance level.

2.5 Pulse Recognition in EEG

In this section, we aim to develop a method to take mean pulse or HRV into account for EEG data for which explicit heart rate recordings are not available. In the analyses described so far, we laid out the benefits of taking mean pulse or HRV into account. However, for many BCI recording sessions, explicit heart rate recordings are not available. This is the case for a big dataset that is available to us. Thus, using EEG data with heart rate information, we aim to identify a reliable pulse correlate in EEG data. This would allow us to infer mean pulse for EEG data with no heart rate measurement. In the following, we describe three approaches to find such a pulse correlate in Dataset A.

Band-Power Analysis We calculated the Pearson correlation between mean pulse and band-power of 1 Hz in the EEG signal. We expected to observe high correlations in one spot on the topoplot, because this spot may lie above a vein.

The resulting correlation pattern over channels is depicted in Figure 5. In contrast to our expectation, correlations range within medium effect size and are fairly equally distributed over the whole scalp. Furthermore, this pattern is inconsistent between different sessions (see Figure 6).

Pulse-Triggered Median We looked for a typical response in the EEG signal that would always follow one heart beat. To this end, we extracted time points of all peaks in the pulse signal. Then we cut out EEG signals within time windows of one second after every time point and thereafter calculated the median per data point over all time windows and trials of one session. We expected to find one curve caused by one pulse peak—and therefore occurring right after this peak. Figure 7 presents the result of this analysis for *Cz*: there is no consistent pattern visible in all five sessions.

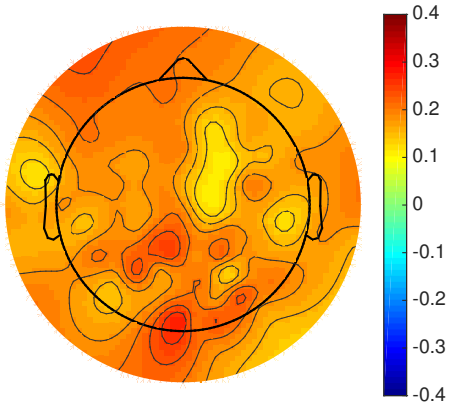


Figure 5: Average correlation pattern between mean pulse and EEG band-power of 1 Hz.

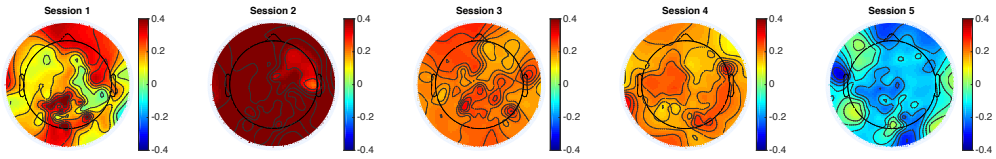


Figure 6: Pattern of correlations between mean pulse and EEG band-power of 1 Hz in session one to five.

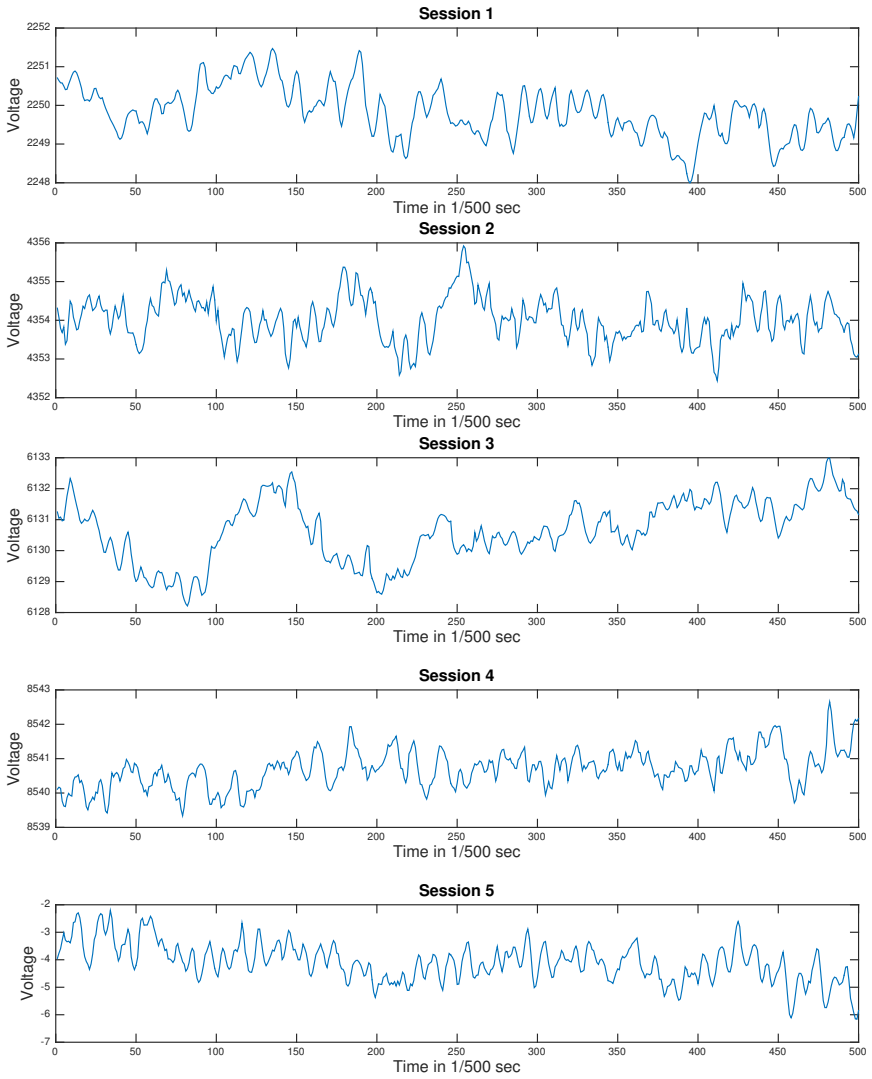


Figure 7: Pulse triggered median in channel *Cz* for sessions one to five.

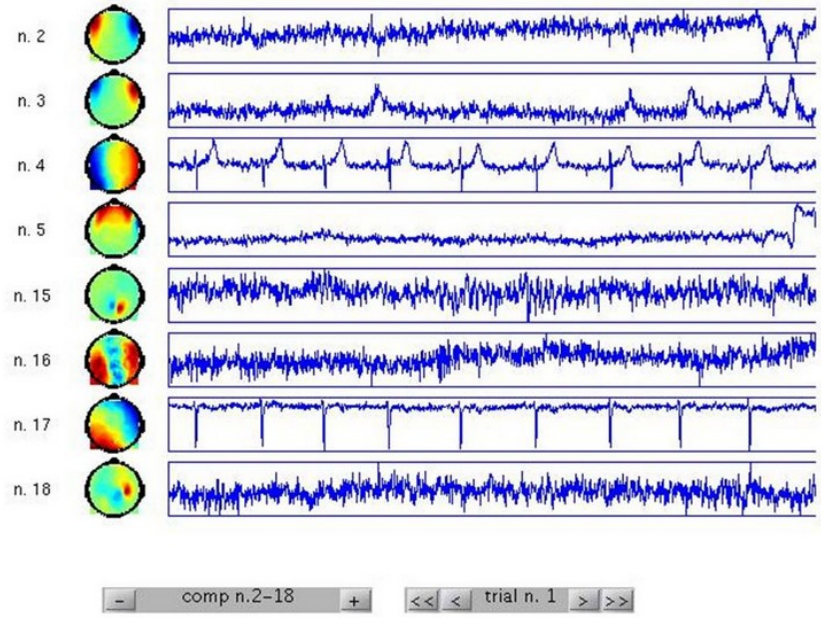


Figure 8: Sample components resulting from ICA of MEG data. Components n. 4 and n. 17 represent pulse artifacts. Retrieved from [18].

Independent Component Analysis We conducted an Independent Component Analysis (ICA) to find the independent components that reflect heart beat. We examined each component visually by screening component weight topoplots and time course of each component. Figure 8 is taken from [18] and depicts several independent components as topoplots and time courses, found in magnetencephalography (MEG) data. Components n. 4 and n. 17 represent pulse artifacts, thus they show a nice periodicity in the time domain and a characteristic pattern in the topoplot. Pulse components in EEG look similar to the ones in MEG. Thus, we tried to find similar patterns in the ICs of Dataset One. However, components seemed to be highly influenced by noise, as we found only few cortical components, if any, and no pulse components at all. We discuss possible reasons for this in Section 3.

3 Conclusion and Discussion

The purpose of the present work was to detect CLIS ALS patients' sleepiness to establish a more reliable yes–no communication with them. To this end, we took pulse as an awakeness indicator. Regressing out mean pulse before calculating AUC score with all trials did not increase AUC. In the study with the original paradigm of Hohmann et al. [6] (Dataset A), classification was better for trials with high mean pulse. This supports our hypothesis that patients only participate in the experiment when being awake. In contrast, when changing the paradigm by giving pulse dependent feedback after every trial (Dataset B), AUC did not depend on mean pulse. Possibly, the patient was distracted by the second task of holding the pulse within a desired range and did not focus on thinking of the correct answer anymore. Furthermore, feedback may have been stressful for the patient, because she got feedback that the trial was rejected for over 50% of the trials. Thus, this may have impaired the patient's ability to participate in the experiment. When we included HRV in the analysis, we observed better AUC scores for trials with high HRV in Dataset B. In further analysis, significance of AUC should be tested. This can be achieved by a *Mann-Whitney-U* or a permutation test.

To be able to include more data in our analysis, we tried to find a pulse correlate in EEG data of Dataset A. Here, we calculated the correlation between 1 Hz band-power and mean pulse, tried to find a curve in EEG data that typically occurs after every heart beat and finally conducted an ICA to find pulse components. Unfortunately, none of the three approaches was able to find a pulse correlate that is stable enough to use it as a reliable method for pulse prediction. A possible reason may be a low signal-to-noise ratio in the data: due to the patient's immobile condition, we took all recordings in the patient's apartment where many noise sources may have been present. Additionally, many trials were distracted by spontaneous uncontrolled swallowing of the patient. Furthermore, a possible factor causing pulse artifacts in EEG are slight pulse-dependent muscle movements, which would be impaired in CLIS ALS patients.

Further research should focus on training patients to stay awake for the whole experiment, while at the same time not stress the patient. This could be achieved by giving directed feedback, e.g. *'Your pulse is too high. Please relax.'*. Furthermore, it is necessary to find a way to keep patients focused on the actual yes–no answering task. Increasing trial length could give patients time to both regulate their heart rate and focus on the answering task.

Finally, other polysomnographical measures or stress measures like thermal regulation or skin conductance could be taken into account.

3.1 Acknowledgements

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Appendices

A Set of Questions

- Waren Sie während Ihres Studiums mehrere Monate in Italien?
- Waren Sie während Ihres Studiums mehrere Monate in Frankreich?
- Haben Sie einen Abschluss in Naturwissenschaften?
- Haben Sie einen Abschluss in Germanistik?
- Waren sie schon einmal in Amerika?
- Waren Sie schon einmal in Israel?
- Ist Ihr Vater in Neresheim aufgewachsen?
- Ist Ihr Vater in Dischingen aufgewachsen?
- Sind Sie in Giengen geboren?
- Sind Sie in München geboren?
- Interessieren Sie sich für Politik?
- Interessieren Sie sich für Fußball?
- Ist der Fernsehsender 3 Sat einer Ihrer Lieblingssender?
- Ist der Fernsehsender RTL einer Ihrer Lieblingssender?
- Mögen Sie Kriminalfilme?
- Mögen Sie Sportsendungen?
- Mögen Sie klassische Musik?
- Mögen Sie Volksmusik?
- Waren Sie schon einmal in Kanada?
- Waren Sie schon einmal in China?