Abstract. Objective. Electroencephalographic (EEG) brain-computer interfaces (BCIs) hold promise in restoring communication for patients with completely locked-in stage (CLIS) amyotrophic lateral sclerosis (ALS). However, these patients cannot use existing EEG-based BCIs, arguably because such systems rely on brain processes that are impaired in the late stages of ALS. In this work, we introduce a novel BCI designed for patients in late stages of ALS based on high-level cognitive processes that are less likely to be affected by ALS. Approach. We trained two ALS patients via EEG-based neurofeedback to use self-regulation of theta or gamma oscillations in the precuneus for basic communication. Because there is a tight connection between the precuneus and consciousness, precuneus oscillations are arguably generated by high-level cognitive processes, which are less likely to be affected by ALS than processes linked to the peripheral nervous system. Main results. Both patients learned to self-regulate their precuneus oscillations and achieved stable online decoding accuracy over the course of disease progression. One patient achieved a mean online decoding accuracy in a binary decision task of 70.55% across 26 training sessions, and the other patient achieved 59.44% across 16 training sessions. We provide empirical evidence that these oscillations were cortical in nature and originated from the intersection of the precuneus, cuneus, and posterior cingulate. Significance. Our results establish that ALS patients can employ self-regulation of precuneus oscillations for communication. Such a BCI is likely to be available to ALS patients as long as their consciousness supports communication.
1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that is mainly characterized by loss of motor neurons [1]. As the disease progresses, patients gradually lose the ability to move their limbs, talk, swallow, move their eyes and eyelids, and breathe. Eventually, the patients enter a completely locked-in state (CLIS) in which they cannot communicate. It has long been believed that ALS is purely a motor disease, but recent evidence suggests that ALS eventually affects the whole brain. Schmidt et al. found that, even in early ALS, the alterations in functional and structural connectivity are spread beyond the motor cortices, with the degree of those alterations decreasing with distance from the motor cortex [2]. Braak et al. connected ALS with misfolding of the pTDP-43 protein [3]. They also found that agglomerates of the misfolded proteins are spread beyond the motor cortex with disease progression. It is not clear how these structural alterations affect cognitive functions and whether patients residing in a CLIS for a prolonged time are still conscious. Kübler and Birbaumer have suggested that long-term paralysis might disable a patient’s ability for goal-directed thinking [4] and that CLIS patients reside in a state of mind similar to REM sleep [5]. If ALS patients in a CLIS remain conscious, however, they would benefit from restoring communication. To communicate, they would need a method that does not depend on peripheral nerves or muscles. One such method could be a brain-computer interface (BCI) [6].

In clinical settings, BCI systems based on an electroencephalogram (EEG) are particularly advantageous due to their mobility, safety, and low price. Various EEG-based BCI-systems have been proposed, yet none has been shown to enable communication with CLIS ALS patients [5]. Current BCI paradigms are often based on low-level cognitive processes that are likely impaired in ALS. For example, BCIs based on volitional modulation of sensorimotor-rhythms (SMRs) in motor and sensory cortices or tactile BCIs [7] are unsuitable for CLIS ALS patients because of the degenerated neurons in their primary motor [1] and sensory [8] cortices. P300 speller systems [9,10] are also unsuitable for these patients because of their impaired gaze fixation [11]. However, some BCIs are based on low-level processes that are likely unaffected by ALS [12], including auditory BCIs [13,14], but they do not yet provide decoding accuracies sufficient for communication when used by severely paralyzed patients [15].

Communication is needed only as long as patients remain conscious. If they are conscious, their brain structures supporting consciousness are probably not yet affected by ALS. We propose to use activity in those brain structures for communication with CLIS ALS patients. One brain area connected with consciousness and self-referential processing is the precuneus, a part of the superior parietal cortex [16]. Activation of the precuneus has been shown to correlate with one’s degree of self-relevance of retrieved judgements [17], and connectivity in the precuneus has been shown to correlate with one’s degree of consciousness [18]. In contrast, precuneus deactivation has been observed in various stages of sleep [19,20] and in vegetative states [21]. These correlations
suggest that altering the precuneus would likely alter one’s conscious state to a state close to sleep or a vegetative state, making communication impossible. Though we do not know to what extent ALS affects the precuneus, previous research suggests that a conscious patient who has the capacity for communication might have normal precuneus function. Thus, we propose to communicate with CLIS ALS patients by using the neural oscillations in their precuneus.

In this work, we investigate the possibility of basic communication with ALS patients by using self-regulation of brain rhythms in the precuneus. We have two hypotheses: First, ALS patients in early disease stages are able to gain control of brain rhythms in the precuneus. Second, they can maintain this skill as their disease progresses.

We tested these hypotheses by training two ALS patients (with a revised ALS functional rating scale (ALSFRS-R [22]) of 33 and 36 out of 48 in the beginning and 10 and 33 by the end of the study) to self-regulate their precuneus oscillations. One patient used the \(\theta\) frequency range (2–5 Hz), building on our previous work with the same patient [23]. The other patient used the \(\gamma\) frequency range (55–85 Hz), as motivated by our previous work with another subject [24]. We trained them by neurofeedback, which was derived by beamforming from high-density EEG recordings. With the resulting BCI the two patients achieved a mean online accuracy of 70.55\% (over 26 sessions) and 59.44\% (over 16 sessions), respectively.

We were not able to assess the performance of our BCI in the CLIS: One of the patients died before entering the CLIS. The other patient moved away, making further training infeasible.

2. Methods

2.1. Subjects

Two male ALS patients were recruited from the local community. At the beginning of the training, the first patient, GH, was 59 years old. He was diagnosed with bulbar ALS eight months before, with his first symptoms appearing 18 months prior to the study. Throughout the study, his ALSFRS-R score decreased from 33 to 10. We conducted 29 training sessions with GH over 18 months. GH had been trained to modulate his posterior \(\gamma\) (55–85 Hz) power in an earlier study [23]. At the beginning of the training, the second patient, LS, was 63 years old. He was diagnosed with bulbar ALS four years before. Throughout the study, his ALSFRS-R score decreased from 36 to 33. We conducted 22 training sessions with LS over 8 months. Prior to the training, LS participated in a pilot study that was unrelated to the paradigm reported in the present work. On sessions 12 and 13, LS had a broken rib. All recordings were carried out in the patients’ homes. Both patients gave informed consent. The study was approved by the Max Planck Society’s ethics committee.
2.2. Overview of experimental setup

We introduced the patients to our BCI in several steps. First, we trained the patients to modulate brain rhythms by providing them with continuous neurofeedback (Section 2.3). During this training, we only evaluated their performance offline (Section 2.5). Once the offline decoding accuracy was stable and the topography of bandpower modulation was consistent between sessions, we introduced an online classification procedure (Section 2.4). At this stage, the patients received two types of feedback during each session: continuous neurofeedback during each trial (Section 2.3) and discrete classifier decisions at the end of each trial (Section 2.4). From there on, we used both online and offline classification accuracies for performance evaluation. The offline decoding accuracy allowed us to evaluate performance within one session, while the online decoding accuracy characterized consistency of the brain rhythms and generalization power of the classifier across sessions. Once online performance was sufficient and stable, we introduced the final BCI, which patient GH used for answering yes-no questions (Section 2.3.2).

During all steps, we continuously improved the BCI by adjusting the frequency band and spatial location of the neurofeedback procedure, as well as by re-training the classifiers to compensate for individual differences and non-stationarity of the brain signals. The details of these adjustments are provided in further sections. We note that statistical tests of our hypotheses are based on online decoding results only.

2.3. Neurofeedback training

2.3.1. Hardware

EEG recordings were done with an EEG cap with 121 actiCAP active electrodes at a sampling frequency of 500 Hz with a QuickAmp amplifier (BrainProducts GmbH, Gilching, Germany). Electrodes were placed according to the 10-5 system, using electrode located over left mastoid (TPP9h in 10-5 system) as the initial reference. All recordings were converted to a common average reference.

2.3.2. Experimental paradigm

Every training session consisted of three blocks. Each block started with a five-minute resting phase, during which the subject was instructed to keep eyes open, focus on a cross in the middle of a computer screen and let his mind wander. The data acquired in this phase were used to calibrate a beamformer that we aimed at the precuneus. The details of the beamforming procedure are described in Section 2.3.4. These data were also used to estimate the natural variations of resting log-bandpower over the ranges of 2–5 Hz for GH and 55–85 Hz for LS. To do so, we spatially filtered the recorded data with the precomputed beamformer (as described in Section 2.3.4) and applied a fast Fourier transform (FFT) with a sliding Hann window of 5 s with a step length of 40 ms. We used this estimate to calibrate the feedback, as described below.

In each of the three blocks, the resting phase was followed by the neurofeedback training phase, which consisted of 20 trials, each lasting 1 min with a pause of $5 \pm 0.5$ s
between one and the next. In every trial the patient was asked in pseudorandom order either to up-regulate or to down-regulate his $\theta$ (GH) or $\gamma$ (LS) log-bandpower in his precuneus. The number of trials per condition was balanced in each block. The patient received continuous feedback on the current state of the log-bandpower in his precuneus (the log-bandpower computations are described in Sections 2.3.3 and 2.3.4).

In this training, the patient received simultaneous visual and auditory feedback. While visual feedback is more intuitive, patients with progressing ALS eventually lose oculomotor control, making visual feedback useless. Once this happens, patients must rely only on auditory feedback. The patient received both types of feedback to allow for a smooth transition. For visual feedback, the estimated log-bandpower was mapped to the vertical position of a white ball displayed on the computer screen in front of the subject (Figure 1). The screen’s center position represented the median resting-state bandpower (baseline), and the blocks in the top and bottom of the screen represented the median minus two and plus two standard deviations, respectively. For auditory feedback, we used two distinct sounds from a publicly available sound repository (http://freesound.org): If the estimated log-bandpower exceeded the baseline, a humming sound played continuously (http://freesound.org/people/freesound/sounds/50168); otherwise, a wind sound played continuously (http://freesound.org/people/homejrande/sounds/17383). The volume of each sound increased linearly as the difference increased between the current log-bandpower and the baseline. Both, the auditory and the visual feedback signal, were updated at 25 Hz. All online signal processing and stimuli presentation was performed with BCI2000 [25] and its extension BCPy2000.

The patient was prompted to up- and down-regulate with both auditory and visual instructions. Auditory instructions were given at the beginning of each trial: The name of the sound corresponding to the trial task was read out in German by a male voice (“Summen” for up-regulation; “Windrauschen” for down-regulation). Visual instructions were shown throughout the trial: A yellow box at the top or the bottom of the screen indicated the target for up- or down-regulation, as shown in Figure 1.

Beginning in session 14, we did not provide GH with targets, but instead asked him questions, which he answered with our BCI. A decrease in $\theta$ bandpower meant ”yes”, and an increase in $\theta$ bandpower meant ”no”. GH had provided twenty personal questions (ten with a ”yes” answer and ten with a ”no” answer), which we presented to him in each block in pseudorandom order.

In the training trials, every time the ball was in the target area (log-bandpower of two standard deviations or more away from the baseline in the desired direction for three cumulative seconds, a ”winning” sound was played (http://freesound.org/people/fins/sounds/171670/) and one point was awarded. The patient’s number of collected points was shown on the screen throughout training. At the end of the trial, additional points were awarded for successful online classification (Section 2.4).

The patients did not receive any instructions on how to control the feedback signal. Following each session, they were asked to write down their thoughts and feelings.
associated with up- and down-regulation of the feedback signal.

Due to technical problems, only two blocks of the experiment are available for GH’s sessions 1, 6, 12, 25, 28 and LS’ sessions 3, 11, 22, resulting in 20 trials for each condition; only one block of experiment is available for LS’ session 12, resulting in 10 trials per condition.

2.3.3. Feedback  We provided feedback in the $\gamma$ band to LS and in the $\theta$ band to GH. The $\gamma$ feedback frequency band for LS was set to 55–85 Hz to avoid contamination by 50 Hz line noise. For GH, we chose an initial feedback range of 2–5 Hz (based on a previous study with GH [23]). We adjusted the feedback frequency band, in order to capture the strongest observed modulations, first to 2–4 Hz (sessions 4–12) and then to 1–5 Hz (sessions 13–29). We validated that this feedback range captured GH’s $\theta$ rhythm by comparing resting state EEG with eyes closed (5 min long) and eyes open (5 min long) that we recorded prior to session six. We employed the established observation that there is more power in the $\alpha$ frequency band in the eyes-closed state than in the eyes-open state (Klimesch, 1999). We computed the log-bandpower (fast Fourier transform (FFT) with a Hann window of five-minute width) of the channel Oz, overlapped the two log-bandpower spectra and determined the intersections around the $\alpha$ peak. GH’s individual $\alpha$ peak was located at 10 Hz. We identified the upper $\theta$ boundary as the integer nearest to the first intersection point before the $\alpha$ peak at 5 Hz, i.e., in agreement with the chosen feedback range.

To estimate the current log-bandpower, we spatially filtered the recorded data with the precomputed beamformer (as described in Section 2.3.4) and applied a FFT with a sliding Hann window of 5 s with a step length of 40 ms. The estimate was standardized by using the median and standard deviation of the estimated log-bandpower from the
resting state.

2.3.4. Beamforming To estimate the bandpower in the precuneus, we used linearly constrained minimum-variance (LCMV) beamforming [27], because LCMV beamforming has been previously validated in an online BCI study [28]. LCMV beamforming is an adaptive spatial filter that attenuates the activity of sources outside the region of interest (ROI), while preserving the activity from sources within the ROI. The ROI activity \( y[t] \) is estimated as the dot product between the spatial filter \( \mathbf{w}^* \) and measurements of the electrical potential on the surface of the scalp at \( N \) electrode locations \( \mathbf{x}[t] \in \mathbb{R}^N: \ y[t] = \mathbf{w}^T \mathbf{x}[t] \). The spatial filter is obtained by solving the optimization problem

\[
\mathbf{w}^* = \arg\min_{\mathbf{w}} \{ \mathbf{w}^T \Sigma_{\text{EEG}} \mathbf{w} \} \text{ s.t. } \mathbf{w}^T \mathbf{a} = 1,
\]

which has the analytic solution [27]

\[
\mathbf{w}^* = (\mathbf{a}^T \Sigma_{\text{EEG}}^{-1} \mathbf{a})^{-1} \mathbf{a}^T \Sigma_{\text{EEG}}^{-1}.
\]

Here, \( \Sigma_{\text{EEG}} \in \mathbb{R}^{N \times N} \) is a spatial covariance matrix of EEG data computed for every subject and session from the five-minute eyes-open resting-state data directly preceding each training block (pre-filtered for 1–100 Hz with a 3-rd order Butterworth filter); \( \mathbf{a} \in \mathbb{R}^N \) is the topography of the ROI dipole projection on the scalp. This topography can be determined in a model-driven approach, e.g., by manually selecting dipoles in the precuneus and using a biophysical forward model to compute their projection on the scalp, or in a data-driven approach. We used a data-driven approach that allows to compensate for inter-subject differences in cortex anatomy. In particular, we
first performed two independent component analyses (ICA, for the details see Section 2.5.1), one for GH and one for LS, on previously recorded data. For GH, we used data described in a previous study [23]. For LS, we used data from a pilot study unrelated to the paradigm reported in the present work. For each patient, we then fitted a single dipole to every cortical independent component (IC), using the BrainStorm toolbox for standardized electrode locations and a standardized three-shell spherical head model [29], and chose the beamforming topography as the IC topography whose single-dipole fit was closest to the precuneus. The resulting topographies are shown in Figure 2A and Figure 2C for GH and LS, respectively. Their dipole fits are displayed in Figure 2D. We note that dipole A (corresponding to the initial GH beamformer topography) lies slightly outside the precuneus. During the first 12 sessions, GH thus received feedback from the intersection of the cuneus and the precuneus. We updated the beamformer topography before session 13, using the same approach described above but on the concatenated data from all previous sessions. The final beamformer topography is shown in Figure 2B. We investigate the effects of this change in feedback topography in Section 3.3.

2.3.5. Safety There are no studies on how neurofeedback affects ALS progression. To avoid abnormal $\theta$ and $\gamma$ powers, and to ensure the safety of the neurofeedback procedure for the patients, we did not further reward the patients for up- or down-regulating bandpower beyond plus or minus two standard deviations of their resting-state bandpower (cropped feedback). This way patients were trained to modulate oscillations within their natural range of variations. Additionally, after every session the patients were asked if they had noticed any negative effects of the training. None of the patients reported any negative effects of the study.

2.4. BCI: Online classification

Beginning in session four for GH and in session seven for LS, we performed online classification. The data corresponding to each trial were classified online with a pre-trained classifier, providing one bit of information per trial.

To accomplish this, a linear $\nu$-support vector machine ($\nu$-SVM) classifier [30] was trained on all previously collected data by using the lib-svm toolbox [31]. To prevent the classifier from focusing on artefacts, we pre-processed the data prior to the classifier training. We performed ICA (as explained in Section 2.5.1), manually selected the artefactual ICs, and then randomly permuted the trial-order of these ICs within each session. Then, we re-projected all ICs back on the scalp and used this data to train the classifier. In this way, we ensured that artefactual ICs did not carry any information on the class labels without altering the overall power of the EEG. We used the trial-averaged $\theta$ (GH) or $\gamma$ (LS) log-bandpower on all channels as the 121-dimensional feature vector. The optimal $\nu$-parameter was estimated by ten-fold cross validation (CV): The $\nu$-parameter was changed from 0.05 to 1 in steps of 0.05 and the mean CV classification
accuracy was estimated for every value. The $\nu$-parameter yielding maximal CV accuracy was used for training the final $\nu$-SVM.

Feedback on online classification was provided to the patient after each trial. For a successful classification, a "winning" sound (http://freesound.org/people/fins/sounds/171670/) was played and 10 points were added to the final score.

For GH, prior to session 15 the classifier was retrained using the three most-recent sessions. For LS, prior to session 11 the classifier was retrained using his five most successful previous sessions. From session 18 onward we classified the trial by the sign of the difference between the baseline and the median $\gamma$ bandpower in the precuneus (as estimated by the beamformer). The details of the classifier change are discussed in Section 3.3.

We tested whether online decoding accuracy was significantly above the chance-level by a binomial test [39].

2.5. Offline analysis

2.5.1. ICA-based artefact attenuation EEG recordings are often contaminated by muscle (EMG) [32] and ocular (EOG) artefacts [33]. To attenuate the effects of these artefacts, we used second-order blind identification (SOBI) independent component analysis (ICA) [34]. Specifically, the data from each session were first high-pass filtered with a third-order Butterworth filter with cutoff frequency of 0.1 Hz, then reduced to 64 dimensions by principle component analysis (PCA), and finally separated into independent components (ICs). The ICs were then visually inspected and rejected as artefactual if they fulfilled any of the following criteria [35]: (1) The IC spectrum did not follow the cortical $\frac{1}{f}$-behaviour; (2) The IC topography was not dipolar; (3) The IC time series contained EOG-like activity (eyelid blinks, eye movements); (4) The IC time series contained any other artefacts (50-Hz line noise, large spikes). The remaining ICs were re-projected on the scalp to obtain the data cleaned from artefacts of muscular and ocular activity.

2.5.2. Topography of bandpower modulation To investigate the topographies of the bandpower modulations, we computed the signed $R^2$ for every EEG channel. First, we estimated log-bandpower for each trial by using a FFT with a Hann window of 1 min (trial length). Then we averaged the log-bandpower over the feedback frequency range. Lastly, we computed signed $R^2$, i.e., the percentage of variance in the data that is explained by the class labels, for every channel in every session and then averaged it over sessions.

2.5.3. Offline classification To estimate how discriminable the up- and down-regulated states are, we employed a linear discriminant analysis (LDA). For every session, the block-specific precomputed beamformer was applied to the ICA-cleaned data, and then the log-bandpower for each trial was estimated by using a FFT with a Hann window of 1
min (trial length). We then averaged the log-bandpower over the frequency range of the feedback. The resulting one-dimensional vector was used for offline leave-one-trial-out crossvalidation (LOOCV) accuracy estimation with the LDA classifier.

2.5.4. Spectral specificity of bandpower modulation We analyzed the spectral specificity of the neurofeedback training using both the ICA-cleaned data and the raw data. For that, we first applied the block-specific precomputed beamformer to the data and then computed the log-bandpower for each trial by using a FFT with a Hann window of 1 min (trial length). Then, we computed the signed $R^2$ for all training sessions and all frequencies from 1 Hz to 250 Hz in non-overlapping windows of 1 Hz width. Lastly, we averaged the signed $R^2$ across all training sessions.

2.5.5. Spatial specificity of the bandpower modulation: Dynamic statistical parametric maps and statistical testing To test whether the bandpower modulation arose from the precuneus, we employed noise-normalized minimum norm estimate dynamic statistical parametric maps (dSPM) [36]. We spread $K = 3 \cdot 15028$ current dipoles over 15028 cortical locations, with three dipoles at every location being mutually orthogonal. Then, we generated the leadfield matrix $A$ specifying the projection of dipole activity $s[t] \in \mathbb{R}^K$ on the $N = 121$ electrodes $x[t] \in \mathbb{R}^N$. The leadfield matrix was generated with the BrainStorm toolbox [29] for standardized electrode locations and a standardized three-shell spherical head model. The ICA-cleaned data was filtered in the $\gamma$ (55–85 Hz, LS) or $\theta$ (2–5 Hz, GH) band. Then the activity of each source was estimated from the ICA-cleaned EEG measurements at $N$ electrode locations, as described in [36]:

$$\tilde{s}[t] = Wx[t], \text{ with } W = \Sigma_d A^T (A\Sigma_d A^T + C)^{-1}. \quad (3)$$

Here, $\Sigma_d$ is the spatial covariance of the dipole strength vector, approximated by the identity matrix, and $C$ is the sensor noise covariance matrix, computed for each session from the resting-state data. We then estimated a noise-normalized current dipole power $\tilde{q}_i[t]$ at each time point $t$ and location $i$ by averaging the three dipoles for each location,

$$\tilde{q}_i[t] = \frac{\sum_{j \in G_i} \tilde{s}_j^2[t]}{\sum_{j \in G_i} w_j C w_j^T} \quad (4)$$

where $w_j$ is the $j$th row of the unmixing matrix $W$ and $G_i$ is the set of dipole indices located at $i$.

To estimate the effect of the neurofeedback training, we then averaged the current dipole power estimate over all trials from all sessions of each condition and computed the difference $D$ between the up- and down-regulation conditions. To test the null hypothesis $H_0$: $D = 0$ that there is no difference in activity between the two conditions, we estimated a $p$-value for each cortical location. To do this, we randomly permuted the condition labels of the trials $10^3$ times. We then counted the number of times the
resulting $|D_{H0}|$ exceeded $|D|$ and divided this number by the number of permutations to obtain a $p$-value for each source location. Lastly, we corrected the significance level by using a false discovery rate (FDR) of $\alpha_{FDR} = 0.05$ [37] to compensate for the multiple comparisons at each of the 15028 cortical locations. To plot the results, we set $D = 0$ for the locations at which we did not reject the null hypothesis.

2.5.6. Spatial specificity of the bandpower modulation: Functional magnetic resonance imaging (fMRI) Following the fifth neurofeedback session, patient GH participated in an additional fMRI study. This fMRI study followed the same design as the neurofeedback training, except that no feedback was provided. Instead, GH was asked to carry out the same thought patterns he previously used to control the EEG-based neurofeedback. Eighteen trials per condition were recorded in pseudorandomized order in a 3T Siemens TRIO (Erlangen, Germany), using a multi-band gradient echo planar sequence with 48 slices (3 mm isotropic voxel, MB 3, TR 1500 ms, TE 30 ms). The BOLD data was then motion-corrected, high-pass filtered at 0.01 Hz, and spatially smoothed with a kernel of 7 mm using the LIPSIA software package [38]. We then employed a linear SVM with leave-one-trial-out cross-validation to compute voxel-wise decoding accuracy in differentiating the experimental conditions that correspond to up- and down-regulation of precuneus $\theta$ power in the neurofeedback sessions. Here, trial-averaged BOLD signals of the center voxel and its six adjacent voxels were used as features. Parameter tuning of the SVM was carried out by an inner-loop cross-validation. We tested each voxel for a decoding accuracy significantly above chance-level by a binomial test [39], using a false discovery rate (FDR) of $\alpha_{FDR} = 0.05$. We could not do the fMRI study with LS, because he could not formulate an explicit strategy for controlling the BCI and was thus unable to control his precuneus $\gamma$ in the absence of continuous feedback.

3. Experimental Results

The results section is structured as follows. First, we report the general results: average neurofeedback training performance (offline classification accuracy), BCI performance (online classification accuracy), patients’ strategies and the resulting bandpower modulation topographies. Then, we describe changes in performance across sessions. We note that our setup does not enable us to distinguish between effects that are due to disease progression and those that result from repeated training. In Sections 3.4–3.5, we provide further evidence of the precuneus origin of the modulations by analysing spectral and spatial specificity of the modulations.

3.1. Neurofeedback training and BCI performance

GH and LS achieved an average online decoding accuracy of 70.55% and 59.44% across all sessions, respectively. Their offline decoding accuracies across all sessions are 70.09%
and 75.87%, respectively. GH performed 29 sessions (820 trials per condition), with 26 sessions (710 trials per condition) classified online. LS performed 29 sessions (610 trials per condition), with 26 sessions (440 trials per condition) classified online. For both patients, we rejected the null hypothesis of online chance-level performance with $p = 1.76 \cdot 10^{-55}$ (GH) and $p = 2.43 \cdot 10^{-8}$ (LS) [39].

We note that online- and offline classification accuracies can not be directly compared: Offline classification accuracy is computed on individual sessions, while online classification accuracy depends on the ability of the pre-trained $\nu$-SVM classifier to generalize from previous sessions to the current one. Thus, a high offline accuracy does not necessarily imply a high online accuracy, because it is possible that the patient induces activation patterns that are discriminable within one session but are changing from session to session. We discuss the observed differences in online- and offline decoding accuracy in patient LS in Section 4.

3.2. Patients’ reports and topographies of bandpower modulation

GH reported that he could control his precuneus $\theta$ bandpower by alternating pleasant and sad thoughts, with exception of session 12, when he tried to repeat words "yes" or "no" in his head. GH’s strategy is in agreement with previous studies connecting emotional processing with posterior $\theta$ modulations (for a review, see [40]). LS could not precisely describe how he controlled his precuneus $\gamma$ bandpower, but he reported that he controlled the ball by thinking "yes" or "no" or by wanting the ball to go in the desired direction.

Despite different strategies and different feedback frequency bands, the average signed $R^2$ topographies are similar for both patients (Figure 3). Both topographies resemble the beamformer topographies used for training (Figure 2), indicating successful neurofeedback training. Note that for GH channels in central areas show slight negative correlation, while for LS all the channels are positively correlated with the condition (required direction of precuneus bandpower modulation).

3.3. Performance variations and training effects

For each individual session, an online decoding accuracy of 60.0% is required to reject the null hypothesis of chance-level performance at the significance level $\alpha = 0.05$ [39]. GH performed above this threshold in 22 out of 26 BCI sessions (Figure 4). Despite a fast disease progression, as indicated by a decline of the ALSFRS-R score by 23 points over the course of the study, GH’s offline accuracy remained roughly stable across the whole study. His initially high online accuracy declined to chance-level performance in sessions 10–14, but recovered after updating the online classifier in session 15.

The pattern of bandpower modulation also remained stable, becoming more localized and converging to Figure 3 after an update of the beamformer topography (Figure 5 A–B). The central electrodes showed initially positive correlation with the condition and changed to negative after an update of the beamformer. Changes in the
modulations topography motivated the classifier update, that led to increase in online classification accuracies (Figure 5 C–F). Despite the progress of ALS, the modulations topography remained consistent (Figure 5 F).

LS performed above the decoding accuracy of 60.0%, that is required to reject the
null hypothesis of chance-level performance at the significance level $\alpha = 0.05$ [39], in 10 out of 16 online decoding sessions (Figure 6). LS also showed convergence to the beamformer topography as a result of training (Figure 7, A, B, and D). However, LS’ performance was likely impaired in several sessions by pain from a broken rib. LS broke a rib before session 12, but expressed the desire to continue the training. This event coincided with a drop in online decoding accuracy to chance-level. The averaged $R^2$ topography over those two sessions showed almost no modulation (Figure 7, C). LS performance only recovered after we updated the online decoding algorithm in session 18 (cf. Section 2.4).

3.4. Spectral specificity of the bandpower modulation

Here, we compare modulations of precuneus activation for different frequencies before and after ICA artefact attenuation. Such comparison allows us to estimate the contribution of artefacts to the neurofeedback training.

For both patients the maximum of $R^2$ lies within the feedback frequency range (Figures 8 & 9, shaded area), indicating successful neurofeedback training. Furthermore, ICA-based attenuation of the artefacts increases the $R^2$ within the feedback frequency range. This suggests that the induced modulations are primarily of cortical nature.
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![Graph showing BCI online (yellow) and offline (green) performance and ALSFR-R score (gray) for patient LS. Circles, asterisks, and crosses mark the three classifiers; the red dot marks the sessions when LS had a broken rib. Red line corresponds to chance level classification accuracy (two-class classification).](image)

**Figure 6.** BCI online (yellow) and offline (green) performance and ALSFR-R score (gray) for patient LS. Circles, asterisks, and crosses mark the three classifiers; the red dot marks the sessions when LS had a broken rib. Red line corresponds to chance level classification accuracy (two-class classification).

![Maps showing training effects: Signed $R^2$ topography for the $\gamma$ bandpower modulations of patient LS averaged over A) Sessions 1-5; B) Sessions 7–10 (first sessions classified online); C) Session 12–13 (broken rib); D) Sessions 15–22 (recovery).](image)

**Figure 7.** Training effects: Signed $R^2$ topography for the $\gamma$ bandpower modulations of patient LS averaged over A) Sessions 1-5; B) Sessions 7–10 (first sessions classified online); C) Session 12–13 (broken rib); D) Sessions 15–22 (recovery).

We note that the results of GH also show a modulation in the $\gamma$ range and LS exhibits, to a lesser extent and only visible after ICA-based artefact reduction, regulation of brain rhythms in the $\theta$ range. This finding is consistent with previously reported relations between the $\theta$ and the $\gamma$ band [41].

In GH’s data, we also observed a negative correlation between theta (2 – 5 Hz) and
Figure 8. Spectral specificity of the neurofeedback training for patient GH: signed $R^2$ averaged over all training sessions before and after the ICA artefact attenuation. The shaded area shows the frequency range of the online neurofeedback (1–5 Hz).

Figure 9. Spectral specificity of the neurofeedback training for patient LS: signed $R^2$ averaged over all training sessions before and after the ICA artefact attenuation. The shaded area shows the frequency range of the online neurofeedback (55–85 Hz).
alpha (6 – 12 Hz) rhythms, which is in agreement with previous findings [26]. We did not observe such a negative correlation in LS’ data.

3.5. Spatial specificity of the bandpower modulation: dSPM

Figure 10. Significant bandpower differences, averaged over all of GH’s training sessions.

Figure 11. Significant bandpower differences, averaged over all of LS’ training sessions.

For both patients, the maximum bandpower modulation (Figures 10 & 11) coincides with the precuneus and extends to the cuneus and the posterior cingulate.
According to GH’s reports, he controlled his $\theta$ bandpower by alternating pleasant and sad thoughts. These reports agree with previous studies that found the posterior cingulate cortex to be activated during emotional evaluation [42]. Positively correlated regions in the precuneus and the frontal medial cortex are parts of the Default Mode Network (DMN) [43]. The DMN is known to be activated by self-referential thoughts [44,45]. Deactivation in the pre-motor areas indicates an involvement of the task positive network, which is known to be anticorrelated with the DMN [46].

LS' $\gamma$ bandpower modulation pattern (Figure 11) is in general similar to GH's, with the strongest modulation found in the precuneus. However, it is much less localized: almost the entire cortex shows a significant modulation. While spatial specificity is generally not crucial for controlling a BCI, the broad modulation suggests a spatially unspecific contamination by residual EMG activity.

![Figure 12. fMRI decoding results of patient GH.](image)

3.5.1. Spatial specificity of the bandpower modulation: fMRI The fMRI decoding results (Figure 12) agree with those of the dSPM source localization, with a statistically significant modulation at the intersection of the precuneus, cuneus, and posterior cingulate as well as in the medial prefrontal cortex. Deeper brain structures are unlikely to be detectable by EEG.

4. Discussion

In this work, we proposed a novel BCI for ALS patients based on self-regulation of brain rhythms in the precuneus. In particular, we tested two hypotheses: First, ALS patients in early disease stages are able to gain control of neuronal oscillations in the precuneus. Second, they can maintain this skill as the disease progresses. The available evidence supports both hypotheses. Both patients were able to modulate the posterior brain rhythms and use these modulations to control the BCI online. These modulations originated from the intersection of the precuneus, cuneus, and posterior cingulate and
were specific to the frequency band in which the patients were trained (θ or γ). Patient GH was able to maintain this skill despite the dramatic decrease in his ALSFRS-R score throughout the training. Patient LS showed almost no disease progression throughout training, shortly lost the ability to control the BCI due to a broken rib, but was able to rapidly recover the skill.

While both patients were able to modulate their brain rhythms in the precuneus, GH (trained in the θ range) achieved a higher online performance and exhibited a more consistent topography of bandpower modulation than LS (trained in the γ range). This made it easier to create an online classifier for GH that generalised well across sessions. For LS, we failed to train such an online classifier and had to use a more simple strategy, i.e., we directly used the neurofeedback signal for classification. While it is difficult to generalise observations from two subjects only, these differences might be connected to the prevalence of EMG signals in γ range: A spatially non-specific contamination of γ-range oscillations by EMG activity may hinder the training of classifiers that generalise well across sessions. Therefore, a θ-based BCI may be more stable in early to moderate disease stages than a BCI based on γ rhythms [24]. On the other hand, muscle contaminations naturally decrease in the late stages of the ALS. Thus, it is possible that the γ range could serve as an alternative in LIS and CLIS. Additionally, observed complimentary effects in these frequency bands (modulations in θ for training in γ and visa versa) suggest that a transition between frequency bands during training may be feasible.

Other EEG-based BCIs have been reported to work well for ALS patients in early to moderate disease stages [4, 5, 47]. However, as the disease progresses and ALS gradually affects the whole brain [3, 18], LIS and CLIS patients appear to lose the ability to control conventional BCIs [4, 47]. We were not able to test our novel approach in the CLIS because of the death of one of the patients and a relocation of the other. Nevertheless, we argue that BCIs based on brain activity in the precuneus have the best chance of maintaining communication with CLIS patients for as long as this is supported by their degree of consciousness, because consciousness is required for any type of communication and the precuneus is linked to consciousness [21]. More specifically, the intersection of the precuneus, cuneus, and posterior cingulate is one of the nodes of the DMN [43]. The DMN, comprising the precuneus/posterior cingulate cortex, medial prefrontal cortex, and the temporoparietal junction, is a resting-state network that is active in the absence of any tasks with high cognitive demand. It has been linked to autobiographical memory, envisioning the future, theory of mind and moral decision making (for a review see [48]). Abnormalities in the DMN have been linked to various neuropsychiatric disorders [49]. Failure of precuneus-based BCI in CLIS may indicate alterations in the state of consciousness that prohibit communication.

For conscious CLIS patients, BCIs based on self-regulation of brain rhythms in the precuneus still hold the promise of restoring communication and thus improving ALS patients’ life quality [50]. Thus, further investigation is needed on the performance of BCIs based on self-regulation of brain rhythms in the precuneus in CLIS ALS. Because
our study is limited to two patients with bulbar ALS, it will also be important to investigate whether other patients can control this type of BCI. Training should be started early, because patients’ learning abilities can decline as ALS progresses [51].

In the future, longitudinal studies with ALS patients could be made easier by developing simple and robust neurofeedback systems that can be used by patients and patients’ caretakers and do not require the constant presence of a researcher. Electrocorticography (ECoG) can replace EEG for such purposes. Our work indicates that implanting an ECoG grid between the two hemispheres over the precuneus may be a viable strategy to maintain communication as long as this is supported by patients’ consciousness. This could provide a stable long-lasting interface, eliminate the need for source-localisation and time consuming EEG-cap placement, and potentially increase the classification accuracy due to better signal quality [52].

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6. References


