A Brain-Computer Interface Based on Self-Regulation of Gamma-Oscillations in the Superior Parietal Cortex

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Abstract. **Objective:** Brain-computer interface (BCI) systems are often based on motor- and/or sensory processes that are known to be impaired in late stages of amyotrophic lateral sclerosis (ALS). We propose a novel BCI designed for patients in late stages of ALS that only requires high-level cognitive processes to transmit information from the user to the BCI. **Approach:** We trained subjects via EEG-based neurofeedback to self-regulate the amplitude of gamma-oscillations in the superior parietal cortex (SPC). We argue that parietal gamma-oscillations are likely to be associated with high-level attentional processes, thereby providing a communication channel that does not rely on the integrity of sensory- and/or motor-pathways impaired in late stages of ALS. **Main results:** Healthy subjects quickly learned to self-regulate gamma-power in the superior parietal cortex by alternating between states of focused attention and relaxed wakefulness, resulting in an average decoding accuracy of 70.2%. One locked-in ALS patient (ALS-FRS-R score of zero) achieved an average decoding accuracy significantly above chance-level though insufficient for communication (55.8%). **Significance:** Self-regulation of gamma-power in the superior parietal cortex is a feasible paradigm for brain-computer interfacing and may be preserved in late stages of ALS. This provides a novel approach to testing whether completely locked-in ALS patients retain the capacity for goal-directed thinking.
1. Introduction

Brain-computer interfaces (BCIs) hold the promise of enabling communication with completely locked-in (CLI) patients in late stages of amyotrophic lateral sclerosis (ALS). Despite intensive research efforts spanning four decades [1–6], this promise has yet to be fulfilled [7]. The reasons for the present inability of CLI patients to communicate with a BCI remain largely unknown. It has been argued that long-term paralysis leads to the extinction of goal-directed thinking [8], with CLI patients residing in a state-of-mind similar to REM sleep [7]. An alternative explanation is that BCIs are often based on processes known to be impaired in ALS. For instance, volitional modulation of sensorimotor rhythms (SMRs) [5] is one of the most prevalent BCI paradigms [9], even though ALS is known to be associated with a degeneration of neurons in the primary motor cortex [10] and a decrease in resting-state SMRs [11]. Visual P300 speller systems [4, 12], on the other hand, require subjects to fixate target letters for optimal decoding performance [13]. This is not practicable for patients in late stages of ALS due to impaired oculomotor control [14]. To address this issue, novel BCI paradigms based on covert attention shifts have been developed. These require subjects only to fixate one spot, while covertly shifting attention to different peripheral locations of the visual field [15] or attending to various aspects, e.g. color or form, of visual stimuli [16]. As CLI patients are by definition unable to fixate any location of the visual field, they are unlikely to benefit from these developments. Tactile P300 systems [17] may suffer from similar problems, as vibrotactile stimulation in one ALS patient in the CLI state was not found to result in any changes in cortical activity [18]. Auditory BCIs may provide a viable alternative [19–21], as processing of auditory stimuli has been found to remain intact in the CLI state [18]. Despite promising results of auditory paradigms with severely paralyzed patients [22, 23], no successful communication attempt with a CLI patient has been reported. It thus remains unclear whether CLI patients are unable to use a BCI due to the extinction of goal-directed thinking, or because available systems are based on neural and/or cognitive processes that are impaired in late stages of ALS.

We argue that in order to decide this question, it is essential to develop BCI paradigms that are not based on sensory- and/or motor-processes known to be impaired in ALS. Specifically, we propose to train subjects to self-regulate spontaneous activity in high-level brain areas that are not known to be directly affected by ALS and that are likely to remain engaged during states of reduced consciousness. This approach is conceptually similar to the self-regulation of slow cortical potentials (SCPs) pioneered by Birbaumer et al. in the 1990s [3, 24, 25]. However, self-regulation of SCPs requires extensive training [24] and has not been demonstrated in the CLI state [7]. Moreover, the cognitive correlates of SCPs remain debated [26, 27]. This raises the question which neural signals representing high-level cognitive processes are amenable to self-regulation by severely paralyzed patients. In this work, we investigate the utility of γ-oscillations in the superior parietal cortex (SPC) for this purpose. Oscillations in the γ-range (> 40 Hz) are an indicator of local information processing by inhibitory interneurons [28–30].
and are known to be involved in a variety of cognitive tasks [31, 32]. Due to their potential contamination by electromyogenic artifacts, they have long been shunned in EEG research [33]. However, a variety of groups have demonstrated that spatial filtering allows the observation of cortical oscillations in the $\gamma$-range in EEG recordings [34–37].

We have provided empirical evidence that $\gamma$-oscillations originating in the SPC can be observed in EEG recordings, and argued that they are likely to be generated by a high-level attention network that modulates sensorimotor areas [36,38]. As such, we consider them less likely to be affected by ALS than brain activity more closely linked to the peripheral nervous system. Furthermore, as the SPC has been found to remain engaged during REM sleep [39], we consider it a primary target for interacting with patients who may be in a state-of-mind akin to REM sleep. It is an open question, however, whether $\gamma$-oscillations in the SPC can be self-regulated and thus employed to transmit information. In this work, we show that it can based on experimental data from eleven healthy subjects and one (not yet completely) locked-in ALS patient. We emphasize that it is not our goal at this stage to design an assistive communication device with a high information transfer rate for patients with residual muscle activity. Rather, we aim to establish a BCI paradigm for basic yes/no-communication that offers a novel approach to challenging the thought-extinction hypothesis in CLI patients in late stages of ALS.

2. Methods

Sections 2.1 to 2.4 focus on the experimental setup and analysis procedures for the healthy subjects. Section 2.5 is devoted to the feedback sessions carried out with the locked-in ALS patient.

2.1. Experimental Paradigm

Subjects were placed in a comfortable chair in a dimly lit room approximately 1.25 m away from a computer screen. Prior to each feedback session, a five-minute resting-state EEG was recorded. The subject was instructed to let their mind wander while fixating a gray cross displayed centrally on the computer screen. Data recorded during the resting-state baseline was used to calibrate a beamformer employed in the subsequent feedback session. The beamformer was aimed at a region of the superior parietal cortex (SPC) that we found to predict performance in an SMR-based BCI [36]. The details of the beamforming procedure are described in Section 2.3.

Following the resting-state baseline, subjects performed three feedback blocks with brief intermissions in between. In each block, subjects received continuous feedback on their current state of $\gamma$-power in the SPC. Specifically, log-bandpower in the range of 55–85 Hz in the SPC, as estimated by the beamformer, was linearly mapped to the vertical position of a white ball displayed on the computer screen (Figure 1). Subsequently, log-bandpower of $\gamma$-oscillations in the SPC is referred to as $\gamma_{SPC}$. The vertical center of
Figure 1. Visual feedback shown to subjects during neurofeedback training. Subjects employed self-regulation of $\gamma_{SPC}$ to move the ball vertically towards the current target, indicated by the yellow rectangle.

The screen was chosen to represent the mean of $\gamma_{SPC}$ during the resting-state baseline. The top and bottom of the screen were chosen to represent two positive and negative standard deviations of resting-state $\gamma_{SPC}$, respectively. The vertical movement of the white ball was constrained to the limits of the computer screen. The ball’s horizontal position was fixed at the center of the screen.

Each of the three blocks consisted of 20 trials, in which subjects had to either enhance or attenuate $\gamma_{SPC}$. Every trial began with a baseline during which a fixation cross and two gray blocks were shown at the top and bottom of the screen. After 5 s, the white ball appeared and one of the gray blocks turned yellow, instructing the subject to move the ball to this target. To reinforce successful self-regulation of $\gamma_{SPC}$, the target block turned green whenever it was touched by the ball. After 60 s, the ball disappeared and the target-color changed back to gray. This indicated the end of the trial and start of the subsequent trial’s baseline. We chose a trial length of 60 s, as we reasoned that successful self-regulation of attentional states is likely to require more time than typically allotted to subjects in BCI paradigms. For each block, the number of trials per condition was balanced and the order of trials was pseudo-randomized. No instructions were given to the subjects in order to obtain unbiased reports on the cognitive strategies employed to self-regulate $\gamma_{SPC}$. Following each recording session, subjects were asked to note down the thoughts and feelings associated with control of the feedback signal.
2.2. Experimental Data

Twenty-one healthy subjects participated in this study (10 female; mean age of 31.9 years with a standard deviation of 11.4 years). Two subjects were excluded from the analysis due to medication-related issues. The remaining 19 subjects are referred to as S1 to S19. Following the initial feedback session, three subjects were re-invited to receive four additional training sessions. These subjects were chosen based on their decoding accuracy in the first recording session, with one subject performing very well in the initial session (S3), one subject showing a moderate performance (S8), and one subject having no initial control of the feedback signal (S10). The additional training sessions were carried out at the same time of the day and on the same day of the week on four consecutive weeks. Four subjects had previous experience with either motor-imagery or P300-based BCIs (S1, S8, S10 & S11). All subjects gave informed consent in agreement with guidelines of the Max Planck Society.

Throughout all sessions a 121-channel EEG was recorded at a sampling frequency of 500 Hz using actiCAP active electrodes and a QuickAmp amplifier (both provided by BrainProducts GmbH, Gilching, Germany). Electrodes were placed according to the extended 10-20 system with electrode Cz as the initial reference. All recordings were converted to common average reference.

2.3. Online Feedback

In order to provide each subject with online feedback on their current level of $\gamma$-power in the SPC, EEG data recorded during the subject’s resting-state baseline was used to compute a linearly-constrained-minimum-variance (LCMV) beamformer [40]. We chose beamforming because it has been shown to achieve decoding results competitive with other state-of-the-art spatial filtering methods for non-invasive BCIs [41]. The resting-state EEG was first bandpass-filtered between 55 and 85 Hz using a third-order Butterworth filter before computing a subject-specific spatial covariance matrix $\Sigma \in \mathbb{R}^{N \times N}$ with $N = 121$ (the number of EEG channels). The beamformer was then computed by solving the LCMV-optimization problem

$$w^* = \arg\min_w \{w^T \Sigma w\} \text{ s.t. } w^T a = 1,$$

with $a \in \mathbb{R}^N$ the scalp topography generated by the targeted dipoles in the SPC. This scalp topography was obtained by generating a forward model, described by a leadfield matrix $L \in \mathbb{R}^{N \times K}$ for $K = 15028$ dipoles distributed throughout the cortex, and taking the mean of $L$ over the subset of 300 dipoles found to be most predictive of performance in an SMR-based BCI [36]. This resulted in the topography $a$ displayed in Figure 2, exhibiting a focus over right superior parietal cortex. The leadfield matrix $L$ was generated with the BrainStorm toolbox [42], using standardized electrode locations and a standardized four-shell spherical head model. The solution to the optimization problem in (1) is given by $w^* = (a^T \Sigma^{-1} a)^{-1} a^T \Sigma^{-1}$ [40]. The resulting spatial filter
$w^*$ was then applied to the EEG data $x[t] \in \mathbb{R}^N$ to obtain a 1D-signal $y[t] = w^T x[t]$. In this signal, EEG sources in the targeted region are represented with unit gain, while the variance of all EEG sources outside the targeted area is optimally attenuated.

In order to estimate the beamformer’s spatial transfer function, i.e. the gain with which activity at each cortical location is passed into the spatially filtered EEG signal, the EEG data can be modeled as $y[t] = w^T x[t] = w^T Ls[t]$, with $s[t] \in \mathbb{R}^K$ the (unknown) time-course of cortical sources. The beamformer’s spatial transfer function is then given by $g = w^T L$. This gain vector can be plotted in 3D to obtain a visualization of the cortical areas used for online feedback (cf. Figure 3 in Section 3.1). For each subject, the beamformer computed from the resting-state data was held constant throughout all feedback sessions, as dynamic adaptation of beamformers has been found to have little influence on decoding performance [41].

During the feedback sessions, the current estimate of $\gamma_{SPC}$ was obtained by first applying the beamformer to the recorded data and then computing log-bandpower between 55 and 85 Hz of the spatially filtered signal. Bandpower computation was based on a Fast Fourier Transform (FFT) in conjunction with a Hanning window, using the past 5 s of recorded data. This estimate of $\gamma_{SPC}$ was then standardized by the mean and standard deviation of $\gamma_{SPC}$ observed during the resting-state baseline. Visual feedback of $\gamma_{SPC}$ was updated every 40 ms, i.e. at a frame rate of 25 Hz. Online signal processing and visual feedback was implemented in BCI2000 [43] and its extension BCPy2000 (http://bci2000.org/downloads/BCPy2000/).
2.4. Offline Data Analysis

Following the online training sessions, we analyzed the recorded data offline to identify and attenuate potential confounding by electromyogenic activity (Section 2.4.1), analyzed the discriminability of up- and down-regulation of $\gamma_{\text{SPC}}$ (Section 2.4.2), and investigated the spectral- and spatial specificity of the observed effects (Section 2.4.3).

2.4.1. Attenuation of Electromyogenic Artifacts  
EEG recordings in the $\gamma$-range are likely to be contaminated by electromyogenic (EMG) activity arising from scalp muscles [33, 44]. While source localization methods such as beamforming are robust against a moderate contamination by electromyogenic activity [37], subjects might have been able to influence the feedback signal by altering the tonus of scalp muscles. In order to identify and attenuate potential confounding by EMG activity, we employed independent component analysis (ICA) [45, 46]: We first high-pass filtered each subject’s data using a 3rd order Butterworth filter with a cut-off frequency of 3 Hz, reduced it to 64 dimensions by principal component analysis (PCA), and then separated it into independent components (ICs) using the SOBI-algorithm [47]. We then inspected the topography, spectrum, and time-series of each IC, and rejected those ICs as non-cortical for which at least one of the following four criteria applied [36]: (1) The spectrum did not show the $1/f$-behaviour typical of a cortical source. In particular, we rejected ICs that displayed a monotonic increase in spectral power starting around 20 Hz, as this is characteristic of muscular activity [33]. (2) Eye blinks were detectable in the time-series. (3) The topography did not show a dipolar pattern. (4) The time-series appeared to be contaminated by other noise sources such as 50 Hz line noise or large spikes. We then reprojected the remaining ICs to the scalp.

While this procedure attenuates the extent of EMG confounding, it would be unreasonable to expect a full elimination of electromyogenic activity. As described in detail in the following sub-section, we thus compared the decoding accuracy for each subject prior to and following artifact attenuation. We excluded subjects from further analysis if the ICA-based attenuation of EMG activity resulted in a decrease in decoding accuracy. Conversely, we argue that if an attenuation of EMG signals does not impede - or even enhance - decoding accuracy, it is unlikely that this subject employed muscular activity to control the online feedback. We describe how we validated this artifact-attenuation procedure in Section 2.4.3.

2.4.2. Decoding  
We used Linear Discriminant Analysis (LDA) to estimate the accuracy in discriminating up- and down-regulation of $\gamma_{\text{SPC}}$, with trial-averaged $\gamma_{\text{SPC}}$ as the one-dimensional feature space. In order to avoid overfitting effects, we employed a leave-one-trial-out cross-validation procedure. As subjects had to explore how to self-regulate $\gamma_{\text{SPC}}$ during the first 20-minute feedback block, only trials from the last two blocks were used for classification. The classification procedure was carried out on each subject’s data once before and once following ICA-based artifact attenuation. Subjects were only
kept for further analysis if the artifact attenuation procedure did not result in a decrease in cross-validated decoding accuracy.

2.4.3. Spectral & Spatial Specificity of Bandpower Modulation To investigate the spectral specificity of bandpower modulation in the SPC, we computed $r^2$-values for each subject’s beamforming signal across the whole frequency range, using a sliding window of 3 Hz width with center-frequencies ranging from two to 249 Hz. These $r^2$-values range from zero to one and quantify the amount of variance in each frequency band across trials that can be explained by the class labels (up- or down-regulation of $\gamma_{SPC}$). We then multiplied each $r^2$-value by the sign of the correlation between class-labels and trial-averaged bandpower, such that positive $r^2$-values indicate an increase in bandpower when subjects are asked to up-regulate $\gamma_{SPC}$ and a decrease in bandpower when subjects are asked to down-regulate it. We refer to this measure as the signed $r^2$.

To investigate whether subjects learned to focus self-regulation of $\gamma$-power to the SPC, we used a beamformer to scan each subject’s brain for $\gamma$-modulation. Specifically, we successively pointed a LCMV-beamformer at each of the $K$ cortical dipoles modeled by the leadfield matrix $L$ (cf. Section 2.3) and estimated the signed $r^2$-value of the resulting signal in the $\gamma$-range (55–85 Hz). We thereby obtained a cortical map that displays, for each subject, cortical locations at which $\gamma$-power was modulated in accordance with the experimental conditions. We refer to this map as the cortical $r^2$-map.

In order to validate the ICA-based artifact attenuation procedure we repeated this scanning procedure. Instead of retaining the non-artifactual ICA-components, however, we only reprojected those ICA-components that we identified as being of electromyogenic origin (cf. Section 2.4.1). In this way, we obtained a cortical map of signed $r^2$-values that indicates how our estimates of $\gamma$-modulation are confounded by electromyogenic activity. We refer to this map as the electromyogenic $r^2$-map. We argue that observed effects should only be interpreted as being of cortical origin if they appear in the cortical—but not in the electromyogenic $r^2$-map.

As we argued in Section 1, modulation of $\gamma_{SPC}$ is likely to be linked to attentional processes. As such, it is reasonable to expect that up- and down-regulation of $\gamma_{SPC}$ also affects various other neural processes. In particular, we expected self-regulation of $\gamma_{SPC}$ to modulate sensorimotor rhythms [36]. To investigate this issue we scanned the spatial distribution of signed $r^2$-values, in the same manner as described earlier in this sub-section, in the $\theta$- (4–8 Hz), $\alpha/\mu$- (8–12 Hz), and $\beta$-range (20–30 Hz).

2.5. Training of a Locked-in ALS Patient

2.5.1. Subject Following the training sessions with the healthy subjects, we recruited one female locked-in ALS subject for this study. At the time of the recordings this patient, subsequently referred to as LEK, was 53 years old. She was diagnosed with ALS 15 years ago. On the revised ALS functional rating scale (ALSFRS-R), a metric to
quantify disease progression [48], she scored zero out of a maximum of 48 points. She had no control of her limbs, was artificially ventilated, and was provided with nutrition via a PEG tube. LEK did, however, retain intermittent oculomotor control, allowing her to answer yes/no questions by moving her eyes to the left or to the right. Communication by gaze control was used to obtain informed consent, in agreement with guidelines of the Max Planck Society. Due to the low level of gaze control, answering a question required roughly ten seconds. Oculomotor control rapidly diminished from question to question, requiring her to rest after about five questions before attempting further answers.

LEK participated in 18 feedback sessions, carried out at the same time of day and on the same day of the week. While the first four feedback sessions were carried out in consecutive weeks, there was a disease-related intermission of four months before the last 14 sessions could be recorded. LEK quit five sessions prematurely due to mucus building up within her throat, causing painful pharyngeal reflexes. These sessions were excluded from the analysis. All recordings were carried out in the patient’s home.

2.5.2. Online Feedback As LEK retained very little oculomotor control, the visual feedback was replaced by feedback in the auditory domain. Two publicly available sound samples were selected from the freesound repository for this purpose (http://www.freesound.org). The first sample consisted of a group of people humming (http://www.freesound.org/people/freesound/sounds/50168/). The second sample was recorded in a forest with wind rustling in the trees and birds chirping (http://www.freesound.org/people/homejrande/sounds/17383/). Both samples were edited to play as continuous loops at constant volume.

During the feedback sessions, the current level of $\gamma_{SPC}$ was mapped to the volume of these sound samples in analogy to the ball’s position used for visual feedback (cf. Section 2.1). The humming sound was only played when $\gamma_{SPC}$ exceeded its mean during the resting-base baseline, with the volume linearly increasing from zero to its maximum value when $\gamma_{SPC}$ reached two positive standard deviations of resting-state $\gamma_{SPC}$. Conversely, the wind-rustling sound was only played when $\gamma_{SPC}$ fell below its mean during the resting-base baseline, with the volume linearly increasing from zero to its maximum value when $\gamma_{SPC}$ reached two negative standard deviations of resting-state $\gamma_{SPC}$. Instructions to the subject were recorded by a male speaker and automatically read out by the computer system when appropriate. The mental strategies employed by the healthy subjects to control $\gamma_{SPC}$ (cf. Section 3.4) were read out to LEK prior to the first feedback session. Following the fourth feedback session, the length of each trial was reduced from 60 s to 30 s, while the number of trials per block was increased from 20 to 30. This resulted in an increase in the total number of trials per session from 60 to 90, while slightly reducing the time needed to complete each session.
3. Experimental Results

We first describe the experimental results obtained with the healthy subjects in Sections 3.1 to 3.5. The decoding results achieved with the locked-in ALS patient are reported in Section 3.6. Statistical tests are only reported for the initial hypothesis that subjects can learn to regulate $\gamma_{\text{SPC}}$. Results of exploratory post-hoc analyses are discussed qualitatively.

3.1. Decoding Results

The group-average gain vector $g$ of the beamformer is shown in Figure 3 (cf. Section 2.3). This figure indicates that, as intended, the beamforming procedure focused on $\gamma$-power originating in the right superior parietal cortex. For eight of the 19 subjects decoding accuracy decreased due to the artifact-attenuation procedure (cf. Sections 2.4.1 & 2.4.2). These subjects were excluded from further analyses due to potential contamination of the feedback signal by electromyogenic activity. Decoding results obtained for the remaining eleven subjects are shown in the second column of Table 1.

On a group-level, subjects scored an average classification accuracy of 70.2%. Single-subject results ranged from 47.5% to 95%. A Wilcoxon signed rank test rejected the null-hypothesis of median classification accuracy of 50% (chance-level) across subjects at $p = 0.002$. On the individual subject level, a decoding accuracy of 62.5% (70% with Bonferroni correction for multiple (11) comparisons) would be required for the present setup to reject the null-hypothesis of chance-level accuracy at a significance-level of $\alpha = 0.05$ [49]. However, above chance-level decoding accuracy is of little use in brain-computer interfacing, as a classification accuracy $> 70\%$ is usually considered necessary for communication. Five out of eleven subjects achieved this level of performance after a training period of 20 minutes.
Table 1. Decoding performance of healthy subjects following a 20-minute training session in percentage of correctly decoded trials.

<table>
<thead>
<tr>
<th>Subject</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
<th>S8</th>
<th>S9</th>
<th>S10</th>
<th>S11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy [%]</td>
<td>47.5</td>
<td>72.5</td>
<td>95.0</td>
<td>60.0</td>
<td>92.5</td>
<td>92.5</td>
<td>55.5</td>
<td>80.0</td>
<td>62.5</td>
<td>57.5</td>
<td>57.5</td>
</tr>
</tbody>
</table>

Figure 4. Group-average spectral profile of $r^2$-values in the superior parietal cortex, displaying a bandpower modulation in a broad $\gamma$-range (cf. Section 2.4.3 for details).

3.2. Spectral & Spatial Specificity of Bandpower Modulation

Figure 4 displays the group-average spectral $r^2$-profile of bandpower modulation in the SPC (cf. Section 2.4.3). This plot indicates that subjects employed a broad-band modulation in the $\gamma$-range to control the feedback signal with a peak $r^2$-value at 121 Hz.

Figure 5 displays group-average cortical maps of $r^2$-values in the $\gamma$-band (cf. Section 2.4.3). A distinct modulation of $\gamma$-power is evident in a fronto-parietal network with a focus in the SPC, which is in agreement with the region targeted by the beamformer (cf. Figure 3). Importantly, this network of $\gamma$-modulation is only evident in the cortical-but not in the electromyogenic $r^2$-map (Figure 6), providing empirical support for a cortical origin of $\gamma$-modulation in the SPC. This is in contrast to modulation of $\gamma$-power in the occipital cortex, which is found in both the cortical- and the electromyogenic $r^2$-map. We suspect this to result from a low coverage of the occipital cortex by EEG.
channels at the edge of the EEG cap, resulting in a poor attenuation of EMG artifacts generated by neck muscles.

3.3. Secondary Effects of $\gamma_{SPC}$-Modulation in other Frequency Bands

Consistent with our previous findings on the relationship of $\gamma_{SPC}$ and sensorimotor rhythms [36], we found that instructing subjects to up- and down-regulate $\gamma_{SPC}$ led to a bilateral decrease and increase of $\mu$-rhythms in sensorimotor areas, respectively (Figure 7). In addition, the amplitude of frontal $\alpha$-rhythms decreased when subjects were instructed to up-regulate $\gamma_{SPC}$ and increased when they were told to down-regulate it. Both secondary effects are not evident in the corresponding electromyogenic $r^2$-map (Figure 8), indicating that estimates of bandpower modulation in the $\alpha/\mu$-range are not confounded by EMG activity. We found no consistent effects of $\gamma_{SPC}$-regulation across subjects in the $\theta$- or the $\beta$-band.
3.4. Subject Reports

Following the feedback training, subjects were given a questionnaire in which they were asked to describe how they controlled the feedback signal and note down any feelings induced by up- and down-regulation of $\gamma_{\text{SPC}}$. As neurofeedback is an implicit form of learning, these reports should be interpreted with caution.

Subjects explored a wide range of strategies, ranging from various visual imagery tasks to alternating between different attentional states. Only reports of subjects with a decoding accuracy greater than 70% are discussed here (S2, S3, S5, S6 & S8). Subject S2 noted that she simply moved the feedback ball into the desired direction, as is common in neurofeedback paradigms [50]. Subjects S3, S6 & S8, however, stated that they alternated between states of focused attention, e.g. involving a complex ice-skating choreography (S8), and relaxed wakefulness, e.g. by trying not to think (S3 & S6), to enhance and decrease $\gamma_{\text{SPC}}$, respectively. Subject S5 indicated that she imagined driving up and down within my body to increase or decrease $\gamma_{\text{SPC}}$. 
### Table 2. Classification performances in percent of correct trials for the additional training sessions.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>Session 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>90.0</td>
<td>95.0</td>
<td>95.0</td>
<td>91.7</td>
</tr>
<tr>
<td>S8</td>
<td>61.7</td>
<td>63.3</td>
<td>45.0</td>
<td>43.3</td>
</tr>
<tr>
<td>S10</td>
<td>33.3</td>
<td>46.7</td>
<td>56.7</td>
<td>61.7</td>
</tr>
</tbody>
</table>

**Figure 9.** Spectral profiles of $r^2$-values in the superior parietal cortex for all training sessions of subjects S3, S8, and S10 (cf. Section 2.4.3 for details).

### 3.5. Results of Additional Training Sessions

Results of decoding for the additional four training sessions are listed in Table 2. As subjects were already familiar with the experimental setup, all three blocks of each session (60 trials) were used for decoding.

Subject S3 consistently performed at or above 90% accuracy in all feedback sessions. This high level of performance is also reflected in the $r^2$-profile of bandpower modulation in the SPC (Figure 9, left column), showing a consistent modulation in the 55–85 Hz feedback range. In terms of the cortical $r^2$-map, subject S3 generated a broad fronto-parietal modulation of bandpower in the $\gamma$-range during the last two feedback sessions (Figure 10). In all five feedback sessions, subject S3 indicated that she alternated between states of relaxed wakefulness and focused attention to regulate $\gamma_{SPC}$ down and up, respectively.

Subject S8 performed reasonably well in the first three feedback sessions (cf. Tables 1 & 2), alternating between relaxed wakefulness and focusing on complex tasks to decrease and increase $\gamma_{SPC}$, respectively. During subsequent training sessions, however, S8 indicated that she changed her cognitive control strategy to motor-imagery (having previously participated in a motor-imagery BCI study). This was accompanied by a drop in decoding accuracy to chance-level (Table 2) and the absence of distinct $\gamma$-modulation in the SPC (Figure 9, middle column) or any other part of cortex (Figure 11).

Subject S10 initially proved to be incapable of self-regulating $\gamma_{SPC}$. With repeated training, however, S10 learned to control $\gamma_{SPC}$, resulting in a decoding accuracy of
61.7% in the last training session. This learning effect is also reflected in the $r^2$-profile of bandpower modulation in the SPC (Figure 9, right column), leading to a fronto-parietal $\gamma$-modulation in the last two training sessions (Figure 12) that is consistent with the ones observed on the group-level and in subject S3 (cf. Figures 5 & 10). In terms of cognitive control strategies, S3 indicated after every training session that she did not use any explicit control strategy.

Over the course of the five feedback sessions, all three subjects developed secondary effects of $\gamma_{SPC}$-regulation in various other frequency bands, including the $\theta$-, $\alpha/\mu$- and $\beta$-band. We did not find these effects to be consistent across subjects, however, potentially due to different cognitive control strategies. An in-depth analysis of the subject-specific effects of $\gamma_{SPC}$-regulation on other frequency bands is beyond the scope of the present article.

### 3.6. Decoding Results of the Locked-in ALS Patient

In five out of the 13 training sessions completed by LEK, decoding accuracy decreased due to the ICA-based artifact-attenuation procedure (cf. Sections 2.4.1 & 2.4.2). These sessions were excluded from further analysis due to potential confounding by EMG...
activity. Offline decoding results for the remaining eight sessions are listed in Table 3.

LEK achieved an average decoding accuracy of 55.8%. A Wilcoxon signed rank test rejected the null-hypothesis of median classification accuracy of 50% (chance-level) across sessions at $p = 0.012$. LEK did not, however, reach a decoding accuracy greater than 70%, which is considered necessary for communication, in any of the training sessions.

Before discussing the spectral and spatial $r^2$-profiles for LEK, we would like to point out that these measures, contrary to the beamforming signal used for decoding, do not integrate over a wide frequency range and a large cortical area. In combination with the low decoding accuracy achieved by LEK, we found this to result in $r^2$-profiles with a very low signal-to-noise ratio (SNR). We have thus chosen to present LEK’s $r^2$-profiles averaged over the three best-performing sessions only (sessions 1, 2 & 10). The resulting $r^2$-profiles should be interpreted with the appropriate caution.

Figure 13 displays LEK’s spectral $r^2$-profile in the SPC. This profile exhibits a similar shape to the ones found in healthy subjects after repeated training sessions, with a positive peak in the $\gamma$- and a negative peak in the $\alpha$-range (cf. Figure 9). In terms of the cortical $r^2$-map in the $\gamma$-range, we again found a fronto-parietal modulation of $\gamma$-power (Figure 14). In contrast to the healthy subjects, however, LEK displayed a focus of $\gamma$-modulation in frontal- rather than in parietal areas. This modulation pattern is apparent only in the cortical- and not in the electromyogenic $r^2$-map (Figure 15). Despite the low SNR, this supports the interpretation that in the best three sessions LEK was capable of self-regulating fronto-parietal $\gamma$-power. Consistent with our initial argument that SMRs are impaired in ALS, we found no spatially coherent effects in LEK’s cortical $r^2$-maps in the $\mu$-range (not shown).

4. Discussion

We argued in the introduction that in order to challenge the thought-extinction hypothesis in ALS patients, it is essential to develop novel BCI paradigms that directly
Table 3. Decoding results of eight recording sessions with the locked-in ALS patient (cf. Section 3.6). Accuracy is given in percentage of correctly decoded trials.

<table>
<thead>
<tr>
<th>Session</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>10</th>
<th>13</th>
<th>15</th>
<th>18</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>56.7%</td>
<td>60.0%</td>
<td>55.0%</td>
<td>55.6%</td>
<td>57.8%</td>
<td>55.6%</td>
<td>50.0%</td>
<td>55.6%</td>
<td>55.8%</td>
</tr>
<tr>
<td>Trials</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>630</td>
</tr>
</tbody>
</table>

Figure 13. Spectral profile of $r^2$-values in the superior parietal cortex of ALS patient LEK, averaged across the first, second, and tenth training session (cf. Sections 2.4.3 & 3.6 for details). While bandpower modulation is very weak in LEK, the spectral profile resembles that of healthy subjects with a positive peak in the feedback range (55–85 Hz) and negative values in the α-range.
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Figure 14. Cortical $r^2$-map of LEK in the $\gamma$-range, averaged over the first, second, and tenth training session (cf. Sections 2.4.3 & 3.6 for details). Despite very low $r^2$-values, a coherent pattern of $\gamma$-modulation is apparent in fronto-parietal areas, overlapping with regions also engaged by healthy subjects (cf. Figure 5).

Figure 15. Electromyogenic $r^2$-map of LEK in the $\gamma$-range, averaged over the first, second, and tenth training session (cf. Sections 2.4.3 & 3.6 for details). In contrast to the cortical $r^2$-map in the $\gamma$-range (cf. Figure 14), no coherent pattern of $\gamma$-modulation is apparent.

target high-level cognitive processes. In the following, we discuss the available evidence that self-regulation of $\gamma_{SPC}$ is indeed associated with high-level cognitive control and consider the significance of our findings.

In previous work, we have shown that $\gamma$-power during rest in a fronto-parietal network including the SPC predicts the ability of subjects to modulate their sensorimotor $\mu$-rhythm [36]. This led us to hypothesize that $\gamma$-power in the SPC is an indicator of information processing in a fronto-parietal attention network that modulates sensorimotor-rhythms [38]. In agreement with this hypothesis, we found here that self-regulation of $\gamma_{SPC}$ leads to a bilateral modulation of $\mu$-rhythms in the sensorimotor cortex (cf. Figure 7). Importantly, we did not find any evidence for a distinct modulation of $\gamma$-power in sensorimotor areas, which is known to accompany changes in $\mu$-power when subjects engage in motor tasks or motor-imagery [34, 51–53] (cf. Figure 5). We interpret this as evidence that the observed changes in $\mu$-power are not movement-related but are a result of self-regulation of $\gamma_{SPC}$. This interpretation
is consistent with the subjects’ reports on their cognitive control strategies. Three out of the five most successful subjects alternated between states of focused attention and relaxed wakefulness to control $\gamma_{\text{SPC}}$. Furthermore, one subject’s (S8) change in cognitive control strategies from attention-regulation to motor-imagery resulted in a loss of the ability to self-regulate $\gamma_{\text{SPC}}$. Our interpretation, that $\gamma_{\text{SPC}}$ in an indicator of a high-level cognitive process, is further supported by previous reports on the relevance of the SPC [54] as well as of $\gamma$-oscillations [55, 56] for top-down attentional control. While several BCI systems based on attentional paradigms have been proposed in the past, these paradigms require subjects to modulate the brain’s response to external stimuli [16, 20–22, 57]. Even though the paradigm presented here also relies on sensory feedback during the initial training phase, the actual transmission of information from the subject to the BCI does not require sensory processing.

Regarding the performance of our system, we note that while the group-average decoding accuracy of 70.2% is comparable to a simple motor-imagery BCI [58], the long trial-time of our paradigm results in a low information transfer rate. As we have indicated in the introduction, however, we did not aim to design a BCI with a high information transfer rate. Instead, our goal was to establish a novel paradigm that will allow us to investigate whether CLI patients in late stages of ALS retain the capacity for goal-directed thinking. As such, the crucial question is whether subjects in late stages of ALS are able to modulate $\gamma_{\text{SPC}}$. While only a small percentage of healthy subjects appear incapable of operating a BCI [58, 59], successful decoding results with severely paralyzed ALS patients are scarce. Only two ALS patients with a severity of impairment comparable to that of LEK have been reported to achieve above chance-level decoding accuracy in a BCI task [8]. In a recent study with three locked-in ALS patients, none learned to successfully operate the BCI [60]. This underscores the importance of developing novel BCI paradigms for patients in late stages of ALS. While the decoding results obtained by LEK are encouraging, we note that throughout all training sessions residual eye-movement was the most reliable form of communication. It thus remains an open question whether ALS patients in general and LEK in particular may benefit from our work when entering the CLI state.

This raises the question how our system may be further improved. Firstly, we note that computation of $\gamma_{\text{SPC}}$ was based on a group-level template derived from previous work [36]. Substantially higher performances may be expected by learning subject-specific spatial filters that also incorporate frequencies beyond the $\gamma$-range [61, 62]. Secondly, the long trial-length limits the number of training trials that can be recorded in one session, thereby restricting the maximum size of the feature space. Addressing this issue may require more advanced machine-learning techniques such as multi-task learning to exploit structure in the feature space that is shared across sessions [63]. Thirdly, the motivational aspect of operant conditioning has largely been neglected in this study [64, 65]. A feedback scheme that provides more engaging rewards may result in enhanced training effects. Finally, we note that LEK was already in the locked-in state at the start of training. In order to improve the chances of falsifying the thought-
extinction hypothesis, we consider it essential to start training patients at an early stage and accompany them throughout disease progression into the CLI state.

5. References

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