# Gaze-independent visual event-related potential decoding in locked-in patients

Study design and experimental protocol

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# Contents

> This document is based on the recommendations in Paul, Govaart, and Schettino (2021) and Govaart et al. (2022)

# 1 Study Description

## 1.1 Introduction

Brain-Computer Interfaces (BCIs) decode brain activity with the aim to establish a direct communication pathway, bypassing speech and other forms of muscular activity and in this way provide solutions for patients devoid of these abilities (Naci et al. 2012; Chaudhary, Birbaumer, and Ramos-Murguialday 2016; Neeling and Van Hulle 2019). The quest for performant and affordable solutions is most evident in EEG-based visual BCIs where it has led to a gamut of increasingly sophisticated decoders, tailored to the needs of specific stimulation paradigms and use contexts. In a visual BCI, the user is presented with a set of flashing targets presented on e.g. a computer screen, each of which correspond to a specific command to be executed. A decoder can then analyze the brain's response to a series of stimulations, and determine which of the target the user attended. However, most visual BCIs cannot operate efficiently without redirecting one's gaze onto the desired target (overt attention). The case were the user does not focus gaze at the desired target but only mentally attends it is denoted as covert attention (Posner and Petersen 1990; Posner and Dehaene 1994; Saenz, Buracas, and Boynton 2002).

Covert attention paradigms have applications in communication interfaces for patients with limited eye motor control, e.g., ALS patients in a progressed stage of the disorder or stroke patients with LIS. While communication enabling BCIs are most useful for patients with limited eye motor control that cannot communicate trough eye movements, most visual BCI spellers are to some degree dependent on eye gaze (Brunner et al. 2010; M. S. Treder and Blankertz 2010; Frenzel, Neubert, and Bandt 2011). A BCI that does not depend on covert visual attention is one of the only ways to reliably communicate if a Locked-In patient suffers from involuntary eye movements and drifts or is completely unable to control their gaze. Additionally, covert attention clears the field of view of the user and allows them to perceive other visual elements. This is particularily useful in VR and AR applications where the stimulated cues can be moved to the visual periphery, and the central field of view can be used to present an immersive display. The usual covert attention paradigms are, however, still to some degree dependent on eye motor control, since they require the user to fixate their gaze at the center of the screen, which might be a hard task for some patient populations.

Gaze-independent BCIs (Riccio et al. 2012) can be realized in three ways: First, visual stimulation can be avoided alltogether by the modality of stimulus presentation when choosing for auditory or somatosensory stimulation. However, these modalities often have a lower information transfer rate, require high mental effort or suffer from high variability between users (Reichert, Dürschmid, et al.

2020). Second, gaze-independence can be forced through the manner of visual stimulus presentation (Zhang et al. 2010; Mathias. S. Treder, Schmidt, and Blankertz 2011; Acqualagna and Blankertz 2013; Hwang et al. 2015; Lin et al. 2018; Reichert, Tellez Ceja, et al. 2020; Aggarwal, Chugh, and Balyan 2022; Won et al. 2018), either exploiting overt or covert attention. These paradigms, too, often suffer from a low information transfer rate. Overt or covert attention can also be forced using eye-tracking stabilisation, but experience from our research shows that this can be nauseating. Additionally, it would deprive patients of limited eye motor control of the option to also use the interface in overt attention mode to the best of their abilities. Third, stimuli can be presented in a normal visual paradigm manner, but the covert attention of the user can be identified and decoded seperately from the overt attention (Frenzel, Neubert, and Bandt 2011; Reichert, Dürschmid, et al. 2020; Wang et al. 2022). This allows the user to use a BCI independent of the position of their gaze. This study focusses on the latter implementation. **Hence, this study further explores the idea that a visual BCI can be considered fully independent of gaze, if it is proven to work in an exhaustive range of settings concerning the position of the gaze and the focus of mental attention of the user**. Coincidentally, this also builds towards a solution for the Midas Touch Problem in BCI, where a BCI user sometimes accidentally selects a target while not wanting to give any input. Decoding of mental attention independent of eye gaze, with the option of having visual attention without mental attention, would counteract this.

The event-related potential (ERP) is the EEG response of interest in many visual BCIs. The most prominent ERP is the P3, a positive deflection in EEG amplitude, peaking around 300ms, synchronous with the onset of a rare stimulus (“oddball”) to which the viewer pays attention. Besides P3, other ERP components are evoked in response to a visual stimulus, such as the visual evoked potentials (VEPs) that occur up to 150 – 200 ms post-onset and that reflect the processing of visual stimuli by the occipital cortex (Luck 2014). As a rule, early ERP components (< 150 ms) are less modulated by attention than late components (> 150 ms), the late components are less dependent on the physical appearance of the stimulus but instead more on the task the subject is engaged in (Woodman, Arita, and Luck 2009). This can lead to differences in activated ERP components. For example, Treder and Blankertz (M. S. Treder and Blankertz 2010) showed that P1, N1, P2, N2, and P3 are evoked by overt attention whereas only N2 and P3 by covert attention. Frenzel, Neubert, and Bandt (2011) showed that the N2 component is evoked when covertly focussing on a specific target, even when overtly focussing on another target, while the P3 component is rather present only for the covertly attended target.

These examples, combined with early findings from our experiments with healthy patients, indicate that it is possible to operate an oddball visual BCI paradigm like the Hex-o-Spell interface without the necessity of eye motor control. Aricò et al. (2014) show that with enhancement of the P3 template, decent covert attention performance can be reached. This study aims to apply a similar enhancement procedure to all ERP components to increase covert attention decoding performance in a setting where overt attention to different targets is allowed.

To achieve gaze-independence, a BCI should be able to operate with decent performance in the following discrete settings, which all could occur in patients suffering from eye movement limitations:

- **Overt attention**: The user gazes at the intended target which is periodically stimulated.
- **Covert attention**: The user gazes at an empty portion of the screen while covertly attending the intended target which is periodically stimulated.
- **Split attention**: The user covertly attends the intended target which is periodically stimulated, while gazing at another target wich is also periodically stimulated.

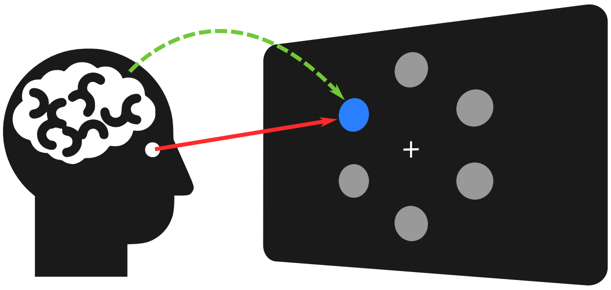

**Figure 1:** Overt attention

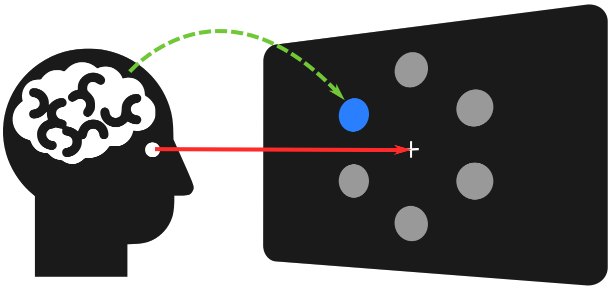

**Figure 2:** Covert attention

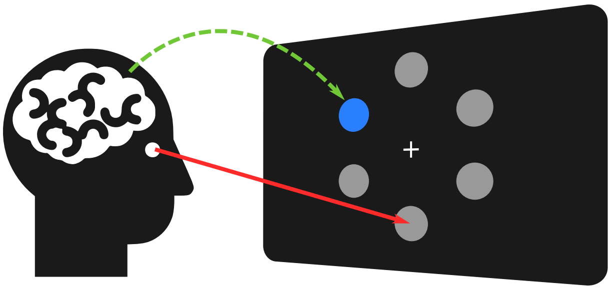

**Figure 3:** Split attention

## 1.2 Study end goal

The end goal of this study is to develop brain–computer communication interfaces with high usability for disabled patients. Patients with Locked-In Syndrome due to neurodegenerative diseases like ALS or brain injuries due to stroke or trauma often suffer from limited eye motor control. Gaze independent BCIs allow these patient populations to comfortably use BCIs.

## 1.3 Study objective

The objective of this study is to develop and validate a fully gaze-independent BCI that has a sufficiently high accuracy (> 80%) in a population of patients with severely limited motor control and limited eye motor control.

## 1.4 Hypothesis

We predict that is possible to construct a classifier that accurately classifies ERPs in a BCI setting from the target group of patients, evoked by an attended stimulus, independent of whether the attention was overt, covert or split.

# 2 Design Plan

## 2.1 Stimuli

Six round white full-contrast circular targets will be presented in a hexagonal pattern on a black screen as in Figure 4, resembling the Hex-o-Spell interface (M. S. Treder and Blankertz 2010; Mathias. S. Treder, Schmidt, and Blankertz 2011). A Hex-o-Spell type interface with empty middle is apt since the low number of targets counteracts crowding, and, as long as the subject's gaze is whithin the hexagon of targets, there can be no other target in line between the subject's gaze and a covertly attended target. Targets have a diameter of 4.15° visual angle and are layed out on a hexagon with a radius of 12.28° of visual angle conforming to the interface proposed by M. S. Treder and Blankertz (2010). Targets are full-contrast white and will be intensified by scaling them to a larger size (5.60° of visual angle) as in Figure 5, instead of changing the contrast to avoid Troxler-fading[1] (Troxler 1804; M. S. Treder and Blankertz 2010) in the peripheral vision.

[1] https://en.wikipedia.org/wiki/Troxler%27s_fading

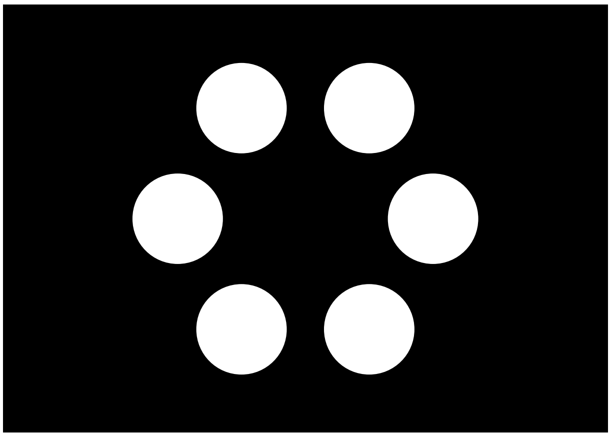

**Figure 4:** Hexagonal target layout

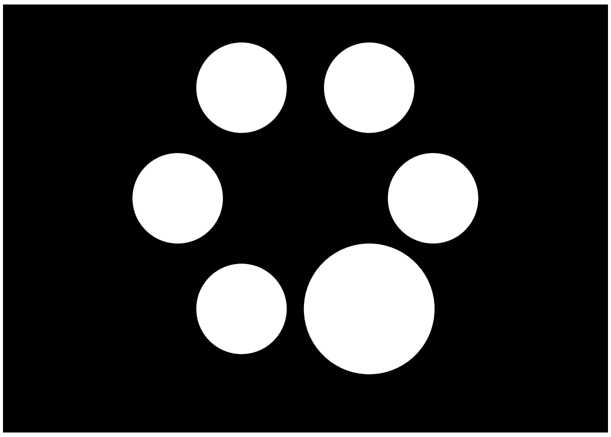

**Figure 5:** Intensified target

An experiment block starts by cuing one of the targets. A target is cued by intensifying it as in Figure 6. A block of stimulations will then start. For each stimulation, a random target is chosen which is intensified for a short duration before returning to the interface without intensification for a short duration. In a stimulation block, all 6 targets will be intensified multiple times with a minimum of 10 times and a maximum of 15 times. At least two intensifications of a different target are required before a given target can be intensified again. This results in blocks containing a minimum of $10 \cdot 6 = 60$, a maximum of $15 \cdot 6 = 90$ and on average $12.5 \cdot 6 = 75$ stimulations of which on average 16.50% ($\frac{1}{6}$) will be attended. The subject is allowed to pause after each block.

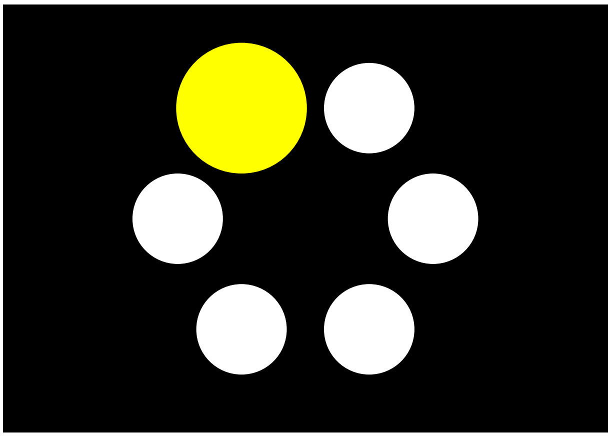

**Figure 6:** Cue for the mental attention

## 2.2 Study Design

## 2.3 Experimental design

An information letter will be provided to participants at least one week before the experiment. These documents will explain how the entire experiment will be conducted, as well as how the data will be processed and the full anonymization procedure. These documents will be as clear and pedagogical as possible.

**In contrast to the experiments with healthy subjects who can freely control their eye gaze, the overt, covert and split conditions are not cued in the experiment. Instead, the subject is asked to normally operate the interface as is most comfortable for them, and an eye tracking device will determine in which of the conditions apply to the subject's attention at each trial.**

The subject is seated at a distance of 60 cm (M. S. Treder and Blankertz 2010) before a computer screen displaying the stimuli. If the subject cannot hold their head in a suitable position to observe the screen, the subject's head will be stabilized or fixated in the usual manner for that subject.The cued target will then be intensified for 5 seconds, and the subject is instructed to count the number of intensifications of the cued target during the following block of stimulations. After a pause of 5 seconds, the stimulation block will start. Stimuli will be presented for 100ms with a 300ms inter-stimulus interval with 200ms uniform jitter (Sellers et al. 2006; McFarland et al. 2011). On average, a block of stimulations will last 22.5 seconds. After each block of stimulations, a pause of 5 seconds is introduced before cueing the next target.

Inter-stimulus intervals are jittered to counteract steady-state effects and residue in averaging. A longer inter-stimulus interval will increase component amplitude and aid in counteracting temporal autocorrelation for a higher statistical test precision.

The experiment will consist of two sessions, each on a different day. In the first session, a target will be cued for each block and the user is instructed to count the intensifications of that block. The objective of the first session is to collect labeled ERP data to train and to tune the classification algorithms. After the first session, offline classification performance will be established. If the offline classification accuracy for our algorithm is not significantly above random chance for a patient, we will not continue with that specific patient. In the second session, a pre-trained classifier will be used to realize an on-line BCI that determines the selected target. The objective of the second session is to determine the accuracy of the BCI in a condition where feedback effects are present, and to test the robustness of the decoder to real-time processing constraints.

In each session, 24 blocks will be presented with a 5 minute pause after each sequence of 6 blocks, resulting in an experiment length of 30 minutes, a duration chosen to limit patient exhaustion. Assuming experiment setup will take about 30 minutes and teardown another 15 minutes, a session should be finished in about 1h15.

### 2.4 Randomization

Each target will be cued exactly 6 times once per subject-session in a per subject-session pseudo-random order.

### 2.5 Blinding

After the experiment and during preprocessing and analysis, the experimenter will be blind to the subject. Subjects will be assigned a numeric identifier. Before analysis, the unique identifiers will be shuffled. After the analysis, results can be related to the subjects medical information.

## 3 Sampling Plan

### 3.1 Existing data

This study design has been established prior to creating the data and does not use existing data.

### 3.2 Participants

Participants will be recruited from phycisal medicine departements and can include (but not strictly limited to) patients diagnosed with:

- ALS
- MS
- Locked-in Syndrome
- tetra- or hemiplegia due to neurotrauma
- tetra- or hemiplegia due to brainstem stroke
- Duchenne myopathy
- cerebral palsy
- muscular dystrophy
- chronic peripheral neuropathy

Participant selection will rather be based on the extent of the disability than the exact diagnosis (Wolpaw et al. 2006; Neeling and Van Hulle 2019).

### 3.2.1 Inclusion criteria

All subjects must:

1. be at least 18 years old and no older than **TODO** years. Subjects should be relatively young to avoid decline in P3 (Dinteren et al. 2014) or other ERP component amplitude and jitter and visual and spatial attention.
2. belong to class 2 or 3 according to Wolpaw's BCI patient selection criteria (Wolpaw et al. 2006).
3. have functional vision and hearing (normal or corrected to normal)
4. have limitations to the extent or comfort of eye motor control
5. have given their informed consent before the start of the experiment
6. be able to understand the experiment instructions

### 3.2.2 Exclusion criteria

Subjects will be excluded from the study if they:

1. have a diagnosis of a major medical condition, including any major neurological of psychiatric disorder, including motor, oculomotor or communication deficits.
2. have a predisposition to or have a history of any kind of epileptic seizures, including photosensitive epilepsy.
3. have a severe loss in vision, hearing, or communicative ability that would significantly impair participation in the experiment
4. are currently using specific psychoactive medications or substances that could affect the outcome.
5. have any other limitations preventing them from performing the given task.

### 3.2.3 Sample size

We intend to recruit 10 patients. This number is in line with usual patients BCI studies and is chosen for practical reasons.

# 4 Variables

## 4.1 Manipulated variables

None

## 4.2 Measured variables

The following variables are measured during experiment:

1. The EEG as a 16-channel time series for the duration of the experiment
2. The eye gaze position as a time series of $(x, y)$-position relative to the computer screen
3. Age
4. Handedness
5. Sex
6. Relevant medical diagnosis

The following variables are analyzed statistically:

2. The condition of the eye gaze, either overt, covert or split per epoch.
3. Cross-validated classifier accuracy for each of the tested classifiers.

# 5 Acquisition

## 5.1 Electroencephalogram

EEG will be recorded at 2048Hz and 16 Ag/AgCl active electrodes arranged in the international 10-20 layout. Using gel, electrode impedances will be brought down to below 5k$\Omega$. The electrodes `TP9` and `TP10` used for off-line re-referencing will be attached directly to the skin using stickers for better contact.

### 5.2 Eye Tracking

In addition to EEG, eye movements will be recorded.

## 6 Preprocessing

### 6.1 Software

**TODO: Recording software**. The dataset will be organized and stored conforming to the BIDS specification (Pernet et al. 2019) and imported in Python using MNE-BIDS (Appelhoff et al. 2019). Data processing will be performed using MNE-BIDS-Pipeline Data analysis will be performed in Python using the MNE software package (Gramfort 2013).

### 6.2 Pipeline

The EEG will be processed as follows:

1. **Re-referencing**: The EEG data will be re-referenced to the average of the mastoid electrodes `TP9` and `TP10`.
2. **Filtering**: The EEG data will be band-pass filtered between 0.1Hz and 32Hz using forward filtering with an IIR filter. A higher frequency than the usual 16Hz for oddball paradigm data is chosen because we are also interested in the early visual components with a shorter duration, as well as in the latencies of some components, and a low low-pass filter can reduce temporal precision.
3. **Epoching**: The contiuous EEG data will be cut into epochs from 0.2 seconds before stimulus onset to 1.0 seconds after stimulus onset. We include data up to 1.0 seconds after stimulus onset to ensure all components (including the late negativity)(Blankertz et al. 2011; Luck and Kappenman 2011) are included.
4. **Artifact reparation**: No artifact reparation will be applied.
5. **Baseline correction**: No baseline correction will be applied.
6. **Resampling**: the epochs will be downsampled for analysis to 1024Hz.
7. **Decoding**: the selected classifier will be trained on a set of training epochs as processed above and collected eye tracking data, and will for each block be applied to the average of a variable number of testing epochs per target.

# 7 Data management plan

Pseudonymized EEG and eye tracking data will be stored in EEG-BIDS (Pernet et al. 2019) format, accompanied by the experiment log files (text).

# 8 Analysis Plan

## 8.1 Statistical model

The data from session 1 is used to compare our decoder with other decoders in an offline settting. We will compare the performance of our classifier with different alternative classifiers and evaluate the accuracy after 6-fold cross validation for the different attention modes (overt, covert and split), and compare accuracies statistically using a Wilcoxon rank-sum test at significance level $\alpha = 0.05$, corrected for multiple comparisons.

The data from session 2 is used to prove our classifier can reach sufficient decoder performance. A test (to be defined) is used to determine if decoding accuracy is significantly ($\alpha = 0.05$) above 80%, a generally accepted usability threshold for BCIs.

## 8.2 Data exclusion

No data are excluded.

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# 10 Notes

## 10.1 TODO

- Include letters on targets
- Figures
- Data management plan

## 10.2 To be decided

- Either use longer inter-stimulus interval and colored intensification, but this means doing a separate series of healthy subject experiments; or keep same inter-stimulus interval and intensification.
- Maybe use each of the four sequences of 6 blocks of session 1 to ask patient to do respectively overt, covert, split and most comfortable attention, and default to most comfortable attention if they are not able to perform one of the first 3 conditions.
- Which age groups?
- Which hardware?