

CLOSED-LOOP DEEP BRAIN STIMULATION SYSTEM FOR AN ANIMAL MODEL OF PARKINSON'S DISEASE: A PILOT STUDY

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ABSTRACT: Deep Brain Stimulation (DBS) is a standard clinical tool for treating refractory stages of Parkinson's Disease (PD). While current chronic DBS systems apply constant stimulation patterns, improved clinical effects are expected from adaptive DBS (aDBS) systems, which stimulate only when required, and for which single-trial methods developed in the field of BCI may prove fruitful. The development of aDBS systems requires (among others) two key ingredients: neural markers informative about the state of the patient's motor system, and algorithmic control strategies which translate the observed markers into stimulation patterns. While both start to be investigated in human patients, animal models of PD may drive aDBS research forward at substantially higher speed and lower risks. In this regard, we present a prototype setup of a closed-loop aDBS system. It enables online recording, signal analysis and stimulation for a rodent model of PD. Our preliminary analyses show that the system – in accordance to the literature – is able to evoke spectral power changes of cortical and subcortical LFPs, and thus provides the experimental basis to systematically investigate informative markers and control strategies.

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a standard therapy for treating refractory stages of Parkinson's disease (PD) [1]. Clinical applications of DBS usually rely on open-loop technology, which means that the stimulation is uninterruptedly delivered, disregarding the motor state of the patient or his/her related brain activity signatures, also called neural markers (NM). This type of DBS is termed continuous DBS (cDBS). Despite proven clinical benefits, cDBS systems are energetically inefficient, leading to a reduced battery life, and are also known to cause side effects like tolerance to treatment [2], [3], [4] which may be related to the continuous stimulation. In recent years, first closed-loop adaptive DBS (aDBS) systems have been presented in research environments [5], [6], [3]. They pursue the goal to provide stimulation

on-demand only, for example, by reducing or stopping stimulation during periods of inactivity or when the motor performance of the patient does not require it. The envisioned effect of aDBS is an improvement of the PD symptoms which is at least comparable to that of a cDBS approach, while simultaneously minimizing the energy input to the brain. Determining when and how to deliver stimulation in closed-loop aDBS systems could directly be based upon the observed motor ability of the patient. For practical reasons, however, current approaches try to replace the behavioral measurements by NMs which describe the current motor state of the patient. Such NMs can be extracted from local field potentials (LFPs) recorded via electrodes which have been implanted in the STN for delivery of the DBS pulses [7], [8]. Although the identification of PD-relevant NMs has been studied in recent years, the high intersubject variability of the signal features makes the characterization of such NMs a difficult task [9], [10], [11]. In addition, the development of closed-loop control algorithms poses a great challenge as (a) non-stationarities govern the dynamics of measured brain activity, (b) artifacts of biological and non-biological origin are contained in the data, (c) the amount of labeled data per patient to learn from is limited. Further studies on investigating the mechanisms of the DBS [12] and on the optimization of stimulation parameters [13], are additional examples of the efforts done in this regard. Along these lines, several studies on closed loop DBS in both computational and experimental neuroscience — such as by [14], [15] and [16] — have been published, where the development of systems that can record, analyze and stimulate in an online closed-loop scenario seemed key to scientific progress. The development of such systems can be addressed using an experimental setup based on animal models, as introduced in [17], [18], [19]. The 6-hydroxydopamine (6-OHDA) PD rat model is an example of a neurotoxic model. It makes use of 6-OHDA injected into the substantia nigra pars compacta (SNc), medial forebrain bundle (MFB), or the caudate-putamen complex CPu [20] to generate Parkinsonian-like biomarkers and behavior. In the present work,

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we introduce our initial work on a novel closed-loop DBS stimulation system that allows recording, analysis and stimulation of cortical and subcortical structures in hemi-Parkinsonian rats, which has not been reported so far in the literature. We also present preliminary results on the spectral effects evoked by DBS when applied to the STN of 6-OHDA PD rats.

METHODS

Animal Preparation

Stereotactic surgery was carried out for high precision lesioning and electrode implantation. All protocols were approved by the Animal Care Committee of the University of Freiburg (permit G-15/31). Female Sprague-Dawley rats (300-320g) received inhalation anaesthesia with isoflurane. A freshly prepared 6-hydroxydopamine according to [21], kept in the dark and on ice, was injected unilaterally into the ventrolateral CPu. The flow rate of the injection was $0.5 \mu\text{l}/\text{min}$ and the injection was carried out for 10 min using a microperfusion pump.

Four weeks after the operation, a rotational test was carried out on each rat. Each animal was habituated to the test environment for around 30 minutes. Then, the animal was taken out, subcutaneously administrated with apomorphine to evaluate the success of the lesioning operation with drug-induced rotation, as explained in [21]. The animals were placed back in the experiment environment and the rotation was measured for 40 minutes. The animals showing drug-induced rotation (PD rats from now on) were chosen for the electrode implantation surgery.

The week after, electrodes implantation surgery was carried out on 6 PD rats. Two electrodes were implanted in two different regions of the brain. One tetrode in the subthalamic nucleus (STN) with four contacts (two stimulation and two recording), made from $50\mu\text{m}$ micro wires (Science Products GmbH, Germany) and a bitrode with two recording contacts in the motor cortex with the same micro wires. Two anchors were placed on the rat's skull as reference and ground contacts, respectively. After a week of recovery the closed loop experiment was executed.

Signal Acquisition

The stimulation device used in this study was designed and built in the Neuroelectronic System group (NES STiM) of the University Medical Center Freiburg, Germany [22],[23]. An Alphaslab SnR (Alphaomega Co., Israel) recording device was utilized to capture the LFPs of the rat's brain during the experiment. The schematic of the closed loop setup is depicted in Fig. 1. The signals were recorded at 1395 Hz sampling frequency. For the offline analysis, a frequency filter with a pass band of 0.7-90 Hz was applied before signals were downsampled to 250 Hz.

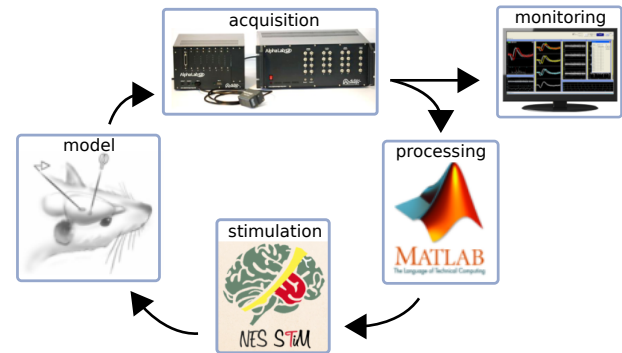


Figure 1. Schematic of the closed loop utilized in this study. The signal of local field potentials (LFPs) is captured using an Alphaslab SnR device and streamed out for visualization and into Matlab. Analysis of the acquired signals, as well as the stimulation control was performed online.

Experimental Design

The timeline of one experimental session is depicted in Figure 2. Each rat was recorded for 10 mins after being placed in the experimental environment (pre-stimulation phase), followed by a stimulation phase of 10 min duration. Prior to the subcutaneous injection of apomorphine and directly after it, the LFP baseline activity was recorded for 10 s each. During the following 10 minutes, closed loop DBS stimulation was carried out (stimulation phase). In this stage, the stimulation onset was triggered when the power of the beta band (13-25 Hz) activity averaged across channels surpassed a threshold defined as the median of the power recorded in the post-injection baseline interval. Once the stimulation was triggered, it was delivered with constant intensity for one minute. For later offline analysis of the stimulation effect, two time intervals of LFP signals of 10 s duration each were extracted from the stimulation-free periods directly before and after the stimulation. After a washout period of 60 s, the threshold criterion became active again and the next stimulation block could be delivered. Within the 10 min stimulation phase, an average of 4.6 stimulation blocks were delivered per animal.

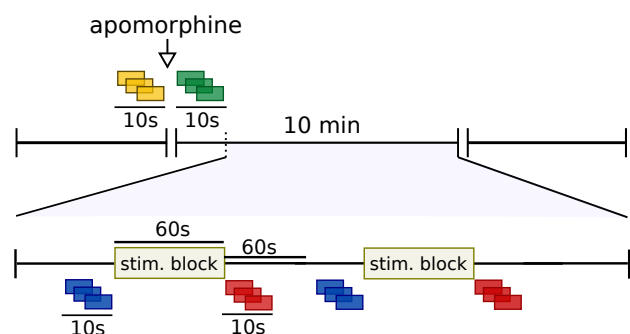


Figure 2. Schematic of the recording sessions with a depiction of the segments analyzed: baseline prior to apomorphine delivery ●, baseline following apomorphine delivery ●, pre-stimulation ●, post-stimulation ●.

Segments analyzed: Recorded signals were analyzed under two different setups.

- 1) To determine the effects of DBS in the spectra of the motor cortex and the STN, signals before and after each stimulation interval were analyzed. The 10 s of data before and after DBS stimulation were segmented using 2 s rectangular windows with 90% overlap. Pre-stimulation and post-stimulation spectra were compared using the Wilcoxon rank-sum test to determine the statistical significance of observed differences. For reference, the spectra of two baseline recordings were also computed, i.e., 10 s segments immediately before and after apomorphine delivery, but prior to any DBS stimulation. Refer to Figure 2 for an schematic representation.
- 2) To analyze potential washout effects of the apomorphine, as well as cumulative effects caused by repeated delivery of DBS periods over 10 minutes, the 10 s segments of data collected before each DBS stimulation (windowed as described above) were correlated with the timestamp (time since apomorphine delivery) of each window using the Spearman's rank correlation.

In all scenarios, PSD of the signals was computed using a multitaper estimate with a multitaper windowing bandwidth of 4 Hz. The frequency components around 30 Hz were disregarded in the analysis due to a hardware-related artifact in that frequency band.

RESULTS

Effects of DBS onto the spectrum

Figure 3 depicts spectra of all animals, four recording locations and the four conditions: baseline prior (yellow) and after (green) apomorphine, and the average of the spectra prior (blue) and after (red) each DBS stimulation block, according to the setup shown in Figure 2. It is observed, that the administration of apomorphine causes an increment in the signal power particularly in the low frequency range. This phenomenon can be observed in all the channels for subjects 2, 3, 4 and 6. DBS effects are assessed by comparing pre and post segments of each stimulation block (blue vs. red). Various, subject-specific effects were observed: For subject 1 synchronization of activity in the 5-10 Hz range was observed (mainly visible in channels m1, m2, and stn1). Subject 2 shows a contrary effect upon stimulation, where power in the low frequency range decreases, as observed in m2 and stn2. An even stronger power decrement can be observed in the beta band (around 15 Hz) of this subject, particularly evident in channels m2, stn1, and stn2. Subject 3 shows a much more smooth spectrum, with no specific frequency peaks standing out from the background in either conditions, except for a low frequency desynchronization present in stn2 and a beta band synchronization detected in stn1. Subject 4 shows a behavior similar to subject 1, presenting power decrease in the lower part of the frequency spectrum for m2,

stn1, and stn2. Subject 5 shows the smallest spectral changes caused by DBS stimulation, with a subtle power decrement of the alpha-range component in channel m2. Similarly to subject 3, power spectra of subject 6 do not show any evident frequency components standing out from the background, with the effects of the stimulation decreasing the signal energy of the entire analyzed spectrum.

Effects of time in PSD

Spearman's rank correlation between the energy of each of the frequency bins and the corresponding timestamp are provided in Figure 4. Subject 1 shows rather heterogeneous changes in the spectra of m1 and m2, however both stn1 and stn2 show a clear desynchronization (marked in blue) in the lower frequency range. Subject 3 shows a consistent power decrement in the lower part of the spectrum for m1 and m2, and a generalized increment of the power (marked in red) in stn2. Subjects 4 and 5 show a generalized decrease in the signal energy along time. It is worth pointing out that for subject 4, alpha band was stable for m1, m2 and stn1, whereas beta was stable only for m1 and m2. On the other hand, the time-related desynchronization for subject 5 is present in the whole spectrum, although a stronger desynchronization in stn1 beta band can also be observed. Finally, subject 3 reveals a weak power decrement in the lower part of the spectrum for m2, having stn1 the contrary effect. Channel stn2 presents a power decrement, which is homogeneous across the spectrum.

DISCUSSION

In this contribution, we presented (1) a closed loop aDBS system allowing acquisition, analysis and stimulation of subcortical and cortical structures of PD animal models and (2) preliminary results on the individual effects observed upon DBS on spectral characteristics of LFP signals.

- i Our system provides a suitable platform for acquisition of subcortical and cortical signals in an on-line scenario. Although, the real-time requirements of the system have not been defined, its modular construction allows for a flexible setup, that is easy to customize. As future work, the exact temporal characteristics of the system will be assessed.
- ii DBS-evoked cortical and subcortical desynchronization and synchronization effects in alpha and beta bands have been observed. As the effects varied between animals, relevant NMs should be determined individually for each subject. This finding underlines the potential benefit of data-driven approaches for driving aDBS methods forward.
- iii We have shown that the experimental setup divided in pre-, during, and post-stimulation phases is appropriate to carry out the intended analysis.
- iv Temporal structure of the spectral features confirms the existence of non-stationary dynamics. While in

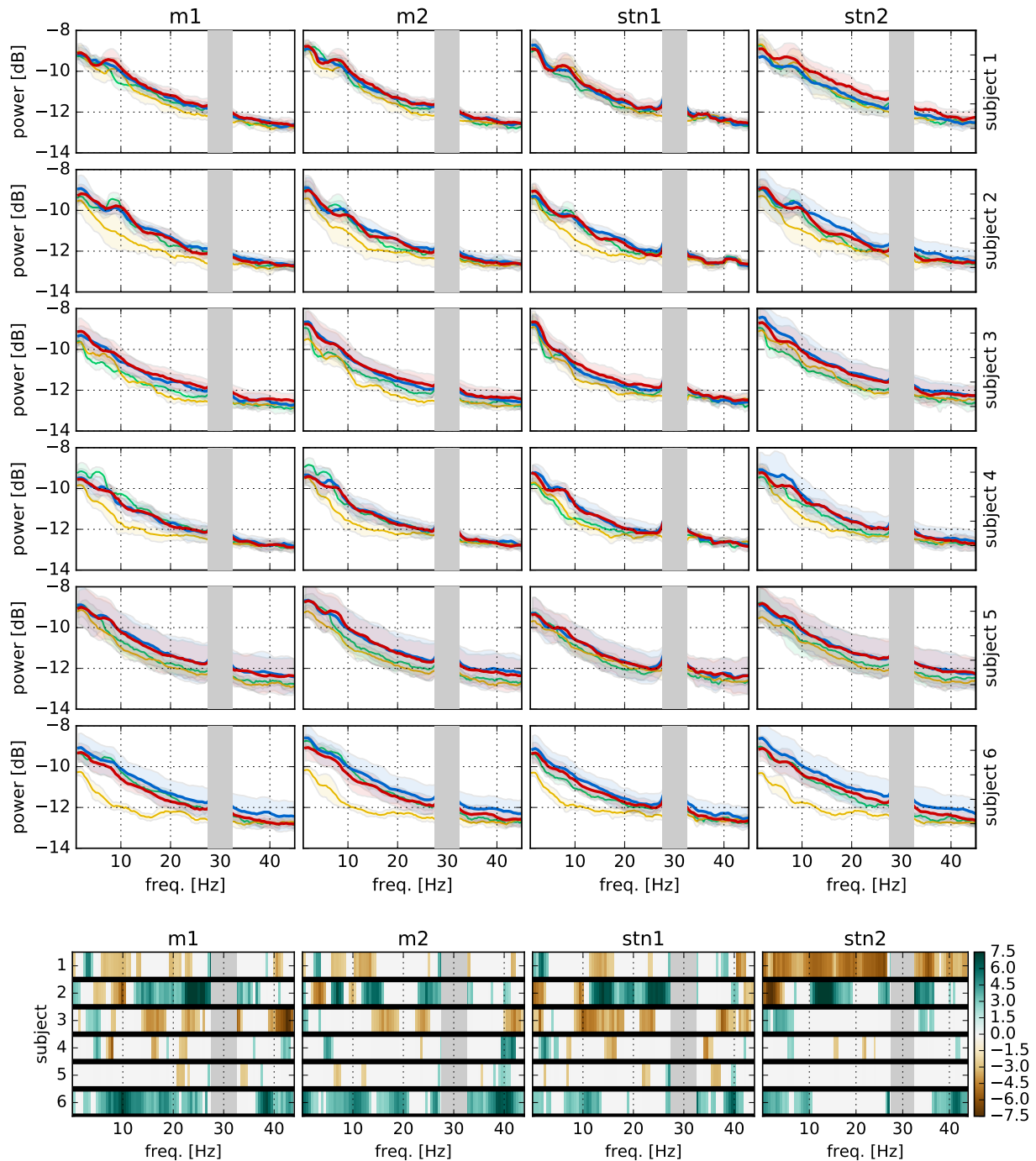


Figure 3. **Top:** spectra of recorded channels displaying DBS- and apomorphine-evoked changes: baseline prior to apomorphine ●, and baseline following apomorphine ●, pre-stimulation block ●, post-stimulation block ●. **Bottom:** Graded scores of the ranksum test are provided in green to brown colors. They compare pre- ● vs. post-stimulation ● spectra. In both figures, gray areas mark the spectral band affected by a technical artifact.

our setup, it could not be determined, if this non-stationarity is caused by repeated DBS or by the washout of the apomorphin, the results strongly indicate, that non-stationarities must be considered in analyses and aDBS systems.

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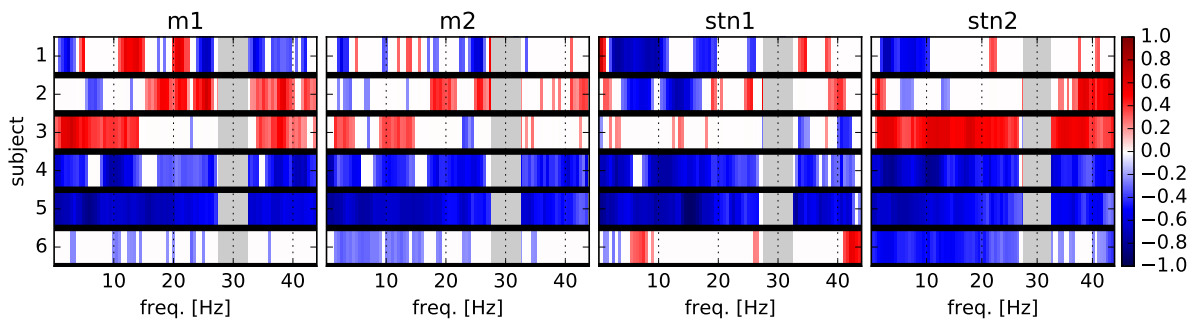


Figure 4. Correlation of power spectrum with time. Red means that the power of the corresponding frequency bin increased during the stimulation phase, whereas blue signals a decrease in power. For each bin, correlations are colored if the p-value of the correlation was > 0.02 . Statistical tests were not corrected for multiple testing.

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