Beta Oscillation-Targeted Neurofeedback Training Based on Subthalamic LFPs in Parkinsonian Patients

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***Abstract*— Increased oscillatory activities in the beta frequency band (13-30 Hz) in the subthalamic nucleus (STN), and in particular prolonged episodes of increased synchrony in this frequency band, have been associated with motor symptoms such as bradykinesia and rigidity in Parkinson's disease (PD). Numerous studies have investigated sensorimotor cortical beta oscillations either as a control signal for Brain Computer Interfaces (BCI) or as target signal for neurofeedback training (NFB). However, it still remains unknown whether patients with PD can gain control of the pathological oscillations recorded from a subcortical site – the STN – with neurofeedback training. We tried to address this question in the current study. Specifically, we designed a simple basketball game, in which the position of a basketball changes based on the occurrence of events of temporally increased beta power quantified in real-time. Participants practised in the game to control the position of the basketball, which requires modulation of the beta oscillations recorded from STN local field potentials (LFPs). Our results suggest that it is possible to use neurofeedback training for PD patients to downregulate pathological beta oscillations in STN LFPs, and that this can lead to a reduction of beta oscillations in the cortical-STN motor network.**

Keywords: **Beta oscillations, neurofeedback training (NFB), local field potential (LFP), Parkinson's disease (PD).**

I. Introduction

Brain computer interfaces (BCI) translate brain activity directly into commands for controlling external devices [1]. As one of the earliest applications of BCI, neurofeedback (NFB) enables the self-regulation of neural activity, and has the potential to alter pathological brain oscillations which play a role in different disorders [2]. Enhanced beta oscillations (13-30 Hz) have been consistently observed in the subthalamic nucleus (STN) in patients with Parkinson's disease (PD). Suppression of this activity, either through dopaminergic medication or deep brain stimulation (DBS), is associated with improvement of motor symptoms [3]. Beta activity in the STN has also been used as a feedback signal in closed-loop DBS, where stimulation is delivered when beta amplitude exceeds a certain threshold. This BCI-controlled adaptive DBS proved to be superior to conventional continuous DBS in the treatment of PD [4]. Beta oscillations have also been used as target for neurofeedback training for PD. Khanna et al. showed that patients with PD can achieve above-chance level control of the one-dimensional height of a cursor using beta band oscillations (13-30 Hz) detected in local field potentials (LFPs) recorded from an ECoG grid placed on the sensorimotor cortex [5]. However, cortical beta power may not be the best biomarker for the disease, since its amplitude is similar in PD and non-PD patients [6], [7] and in PD patients on DBS or levodopa therapy compared to PD patients off therapy [8]. In this study, we sought to investigate whether it is possible to use a basal ganglia LFP-based BCI as a neurofeedback tool to train patients with PD to downregulate their beta oscillations in the STN. Our study was also informed by recent evidence indicating that beta activity consists of short-lived phasic bursts in basal ganglia-cortical motor network, and that the incidence of prolonged beta bursts over a certain threshold is more closely related to motor impairments in PD [9]. Therefore, our paradigm was designed to reduce the incidence of phasic increases in beta oscillations localized in STN. Preliminary results suggest that, despite some cross- and within-subject variations, it is possible to use neurofeedback to train PD patients to downregulate pathological beta oscillations in STN LFPs, and that this can lead to reduction of beta synchrony in the cortical-STN motor network.

II. Methods

A. Graphic User Interface (GUI) Design

Fig. 1 shows the GUI used in the current study. A basketball appears in the top-left corner of the screen at the beginning of each trial (Fig. 1a) and moves toward the right of the screen at a constant speed throughout the trial. The vertical movement of the ball depends on the beta power in a selected channel estimated in real-time. If the estimated beta power (shown as the height of the red bar) is larger than the predefined threshold *T* (shown as the green line on the right side of the screen), the ball will drop down by a fixed distance, as shown in Fig. 1(b).

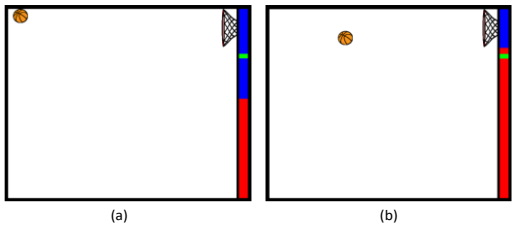

Fig. 1. GUI of the neurofeedback paradigm.

Thus, the final vertical position of the basketball at the end of each trial indicates the total number of incidences when beta power was above the threshold during the trial. The duration of each trial, i.e. the time for the ball to move from the left to right side ranged between 5 and 8 s. The beta threshold and the size of each drop were set so that, if the patient was at rest without doing anything, the basketball would drop to the bottom of the screen within 5 seconds due to the natural temporal variation in the power of beta oscillations.

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B. Recordings

We recorded three PD patients (aged 40-60 years, one female) who had undergone bilateral implantation of DBS electrodes in the STN. The recordings were undertaken 3-6 days after the first surgery for electrode implantation and prior to the second operation to connect the electrode to the subcutaneous pulse generator. The study was approved by the local ethics committee and all patients gave informed written consent before the experiment. Bilateral STN LFPs and EEG signals covering "Fz", "FCz", "Cz", "Oz", "C3", "C4", "CP3", and "CP4" in the standard 10-20 system were recorded using a TMSi Porti amplifier (TMS International, Netherlands) at a sampling rate of 2048 Hz with common average reference. In addition, electromyography (EMG) was recorded from Flexor Carpi Radialis of both arms and the masticatory muscle in each patient to check whether they made any movements during the neurofeedback training. 3D accelerometers were placed on both hands to monitor the presence of tremor.

C. Calibration Procedure

Prior to the online experiment, a calibration was performed for each participant in order to: 1) select the target bipolar LFP channel, 2) select the individual specific frequency-band for the online experiment, and 3) determine the threshold which triggered the vertical movement of the basketball during the online neurofeedback training. First, each patient performed 30 trials of cued finger pinch movements with each hand similar to the paradigm used in [10]. Data recorded during these overt movements were processed offline using a continuous wavelet transform. The bipolar LFP channel contralateral to the performing hand with maximal movement-related power reduction and the peak frequency (f) in the beta band (13-30 Hz) was identified. Then a 5 Hz frequency-band centered around f ([f-2, f+2] Hz) was used as the individual specific beta frequency-band. Second, we collected 60 s of LFP data for each patient during rest just before the online neurofeedback training. Beta power was estimated in real-time with a 250 ms update rate, resulting in 239 beta power values. Then we removed all values located beyond 3 standard deviations from the mean. Next, we selected the 75th percentile of the remaining values as the threshold T. This means with the patient at rest, 25% of the time beta power would exceed the threshold.

D. Estimating beta power online

During the online experiment, the beta power of an individually selected frequency band was calculated every 250 ms using a segment of 500-ms data recorded from the selected bipolar LFP channel. This led to an overlap of 50% of the data for each update. In each update, we first subtracted the mean value of the current window from the raw data. Next, the mean-subtracted data was band-pass filtered between 5 and 85 Hz. A Fast Fourier Transformation (FFT) was applied to the filtered data and the average power of the selected frequency band was regarded as the beta power of the current update. Each trial contained 20-32 updates as the time for the basketball to move from left to right was set to 5-8 s.

E. Experimental design

During the recording, patients were seated in a chair in front of a laptop on which the neurofeedback GUI was presented. After finishing the abovementioned calibration procedure, each patient completed online neurofeedback training using the selected bipolar LFP channel from both STNs separately. The experimental procedure consisted of 5 sessions with each containing 10 continuous 'training' trials and another 10 continuous 'no-training' trials for comparison (Fig 2). During neurofeedback training, subjects were instructed to try to keep the basketball at the top of the screen. They were explicitly told that imagining hand movements may help to improve performance and encouraged to do so but were also reminded not to make any real movements. During the 'no training' trials, subjects were instructed to just pay attention to the moving basketball without having to control its position. The order of the 'training' and 'no training' blocks was randomized for each session. Each block started with a 10 s introduction about the requirement of the current block. Each trial consisted of a 2 s period where patients were instructed to get ready followed by 5-8 s of 'training' or 'no training'. Breaks were given between sessions and the recording for each STN lasted for around 30 minutes.

Fig. 2. Experimental procedure for neurofeedback training.

F. Offline data analysis

Data streams including LFP, EEG, EMG, triggers, positions of the basketball, and beta power of each update, were all recorded for further analysis. To evaluate the effect of the proposed neurofeedback training, the trajectories and the final positions of the basketball were averaged across trials for the training and no-training conditions and compared. To further evaluate whether the neurofeedback training-induced power modulation was limited to the selected beta frequency band and the selected STN LFP channel only, time-frequency decomposition was applied offline to the selected bipolar LFP recordings from both STNs, and EEG measurements from both motor cortices (C3 and C4). This was achieved by continuous Morlet wavelet transformation with a linear frequency scale ranging from 1 Hz to 95 Hz and a constant number (= 6) of cycles across all calculated frequencies. The resultant power of each time point at each frequency was normalized and decibel converted against the average of the 'ready' period of each trial.

G. System architecture

Fig. 3 shows the architecture of the neurofeedback system. We used Microsoft Visual Studio 2010 to develop the graphical user interface (GUI) for feedback presentation; Matlab 2018a for online data processing; an open source tool, Lab Streaming Layer (LSL) [11] to center and synchronize different data streams including recordings from the amplifier, the trigger stream produced by the GUI, and the results of the data processing procedure from Matlab. Parallel to the online processing loop, all the data streams were also stored on a local hard drive for further offline analysis.

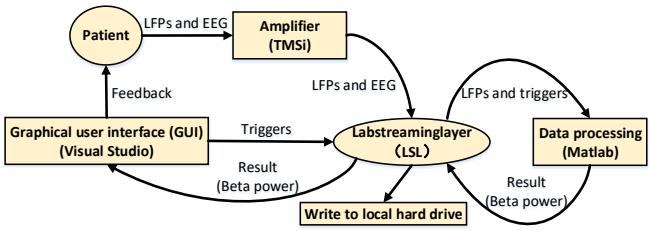

Fig. 3. Architecture of the neurofeedback training system.

III. Experiments and Results

A. Experiments

Six data sets were collected from 6 STNs (3 patients with bilateral DBS electrodes implanted). Since tremor tends to introduce power change in beta power [12] and interfere with the performance in the task, we excluded 2 data sets (P1 right side and P2 left side) where the contralateral hand was strongly affected by tremor. During the experiments, all patients used the first session to familiarize themselves with the task and to practice different strategies. As a result, we had 3 data sets (P1 left sides, P2 right side, and P3 right side) with 4 experimental sessions, and another data set (P3 left side) with 5 experimental sessions for further analysis.

B. Results

1) Basketball movement control: To evaluate the effect of the neurofeedback training, we first compared the recorded basketball positions throughout the trial between training and no-training conditions.

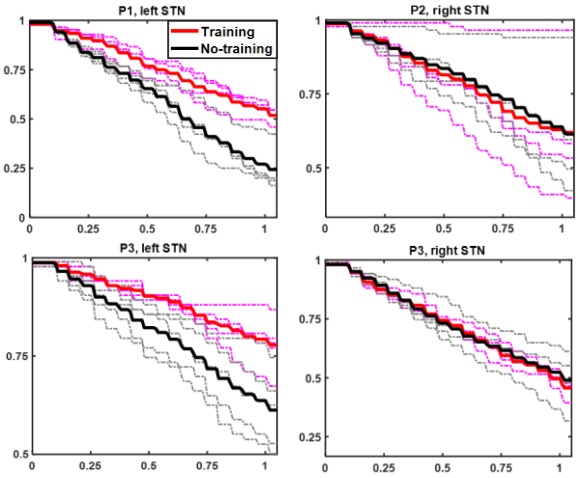

Fig. 4. Basketball movements during training (red or pink) and no-training (black or gray). The dotted and solid bold lines correspond to the average trajectories of each session and the overall average of all sessions, respectively. X and Y axes indicate the normalized horizontal and vertical positions of the basketball on the screen.

As mentioned in the *GUI* subsection, the vertical movement of the basketball was controlled by the incidence of beta bursts. Fig. 4 shows the basketball movement trajectories averaged across trials during the two conditions. Two data sets (P1 left STN and P3 left STN) showed significant differences in the final basketball position between the training and no-training conditions ($p=7.23\times10^{-6}$ for P1 left STN, $p=5.20\times10^{-4}$ for P3 left STN, two-sample t-test). This suggested that these two patients managed to down-regulate their left STN beta oscillations during neurofeedback training compared to the no-training condition. Inspection of EMG activity indicates that the difference was not caused by any overt movements made during the training condition. Accelerometer measurements revealed that P1 had frequent tremor in the left hand, which may explain the lack of volitional modulation in beta activity from the right STN.

2) Beta modulation in LFP and EEG: Fig. 5 and Fig. 6 show the baseline-normalized time-frequency plots of the targeted STN and EEG channels from the ipsilateral motor cortex (Fig. 5) and the non-targeted STN and corresponding motor cortex EEG (Fig. 6), for the two data sets where the effect of neurofeeback training was statistically significant.

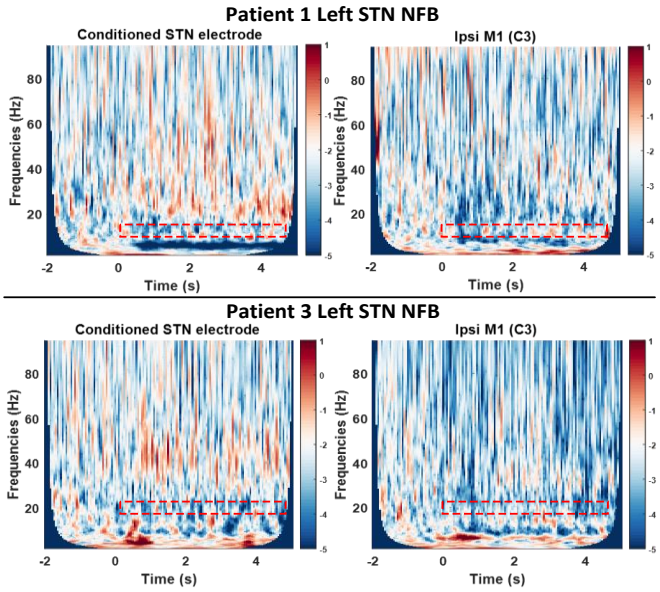

Fig. 5. Time-frequency plots of P1 left STN (upper panel) and P3 left STN (lower panel). The left and right columns indicate the plots of targeted STN LFP and ipsilateral cortical EEG signals, respectively. Bars indicate decibel (dB) changes relative to baseline. Dash blocks indicate the targeted beta bands.

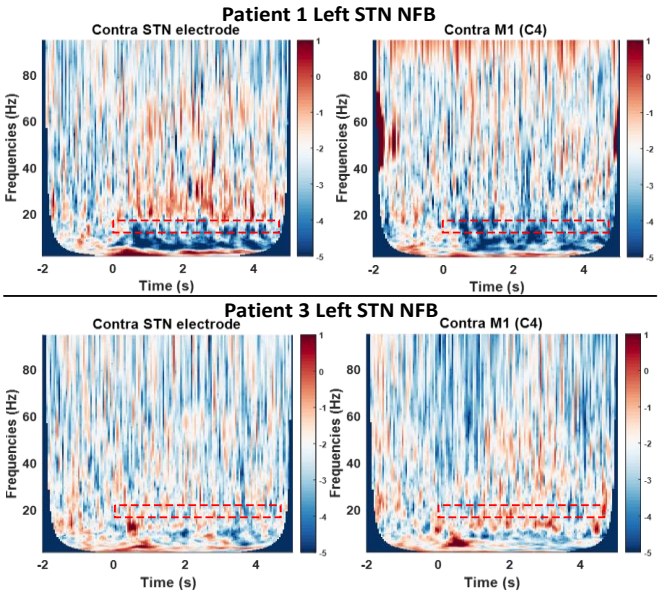

Fig. 6. Time-frequency plots of P1 right STN (upper panel) and P3 right STN (lower panel). The left and right columns indicate the plots of contralateral STN LFP and cortical EEG signals, respectively. Bars indicate dB changes relative to baseline. Dash blocks indicate the targeted beta bands.

The targeted beta frequency band was 13-17 Hz and 18-22 Hz for Patient 1 Left STN and Patient 3 Left STN, respectively. Time point zero indicated the onset time of the basketball movement after which the patients were supposed to perform neurofeedback training. Fig. 5 shows that there is reduction in the targeted frequency bands during the NFB training trials comparative to the pre-cue in both the targeted STN and the ipsilateral motor cortex. In addition, we also observed increase in the higher frequency gamma band, and lower frequency theta/alpha band. This pattern was consistent with previously reported frequency-specific modulations in STN LFPs observed both during actual and imaginary movements [10]. We also observed a similar pattern of modulation in both the beta and gamma frequency bands in the contralateral STN and motor cortex in Patient 1. However, in Patient 3, no obvious beta reduction was found in the contralateral STN or contralateral motor cortex during the NFB training (Fig 6).

IV. Discussions

This is the first study, as far as we are aware of, which aims to use neurofeedback (NFB) training to facilitate the modulation of pathological beta oscillations in the STN in Parkinson's disease. Our paradigm providing visual feedback that was only sensitive to beta synchrony exceeding a certain threshold allowed some patients to gain a sense of agency and to reduce beta oscillations in the cortical-basal ganglia motor network within a short period of training time, which was around 30 minutes only for each side. A few points are worth further discussion. ***1.) Within and cross subject variations in the NFB training performance.*** For Patient 2, the NFB training did not induce any beta modulation in either the STN LFPs or EEGs, no matter which STN (left or right) was used as the neuorofeedback target. This was despite the fact that a significant beta reduction was observed with overt movements. In this case, it was likely that the patient was not able to acquire the proper strategy required for the task given the short time for the training. For both Patient 1 and Patient 3, NFB training was effective when targeting the left STN contralateral to the right (dominant) hand, indicating that the patients did find a successful strategy to perform the task. For Patient 1, tremor in the left hand might have affected the performance of NFB targeting the right STN, even though beta in the right STN was co-modulated when the NFB was targeting the left STN. In contrast, for Patient 3, no significant co-modulation of beta activity was found in the contralateral right STN or right motor cortex. Accordingly, neurofeedback training targeting the right STN didn't induce any beta change in this patient. This may be due to differences in precise electrode location, but it also suggests that the reactivity of the two STNs in the same patient can differ strongly in terms of how easily beta oscillations can be modulated with NFB training. Further studies are required to see if training targeting the STN contralateral to the non-dominant hand, or if the presence of involuntary tremor make neurofeedback training more difficult. It also remains to be tested whether increasing the number of training sessions over multiple days would increase the performance of patients in the task. **2.) Potential baseline change in ongoing beta oscillations.** In the current study, the 75 percentile of beta power recorded over a 60s resting period before the training started was used as threshold, and the threshold was kept constant throughout the experiment for each STN. Since baseline beta oscillations may change over time, updating the threshold for each session may compensate for this and facilitate neurofeedback training. **3.) The effect of endogenous beta modulation on motor performance**. Neurofeedback training targeting STN beta oscillations is potentially a safe and alternative approach to induce modulation in brain oscillations. However, whether this can have any therapeutic effect for improving motor symptoms in PD depends on whether effective neurofeedback training is associated with improvement in motor performance, and whether the effect persists beyond the time when the visual feedback is provided.

V. Conclusion

In this preliminary study, we designed a neurofeedback training paradigm targeting beta oscillations in the STN with the aim to enable patients with Parkinson's disease to modulate this pathological signal associated with motor impairments. Three PD patients participated in the experiment, among whom two patients achieved significant beta down-regulation during neurofeedback training compared with a no-training condition. This suggests that it is possible to train PD patients to reduce beta synchronization in the cortico-basal ganglia network within a short training session. As a next step, we will start to investigate the impact of STN LFP neurofeedback training on the performance of real movements and evaluate possible benefits of carry-over effects in PD patients. This could benefit patients with lasting improvements following a NFB training sessions.

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