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Robustness of Beta Desynchronization from Chronically Implanted Cortical Electrodes on Multiple Time Scales*

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***Abstract*— Adaptive deep brain stimulation (aDBS) promises a significant improvement in patient outcomes, compared to existing deep brain stimulation devices. Fully implanted systems represent the next step to the clinical adoption of aDBS. We take advantage of a unique longitudinal data set formed as part of an effort to investigate aDBS for essential tremor to verify the long term reliability of electrocorticography strips over the motor cortex as a source of bio-markers for control of adaptive stimulation. We show that beta band event related de-synchronization, a promising bio-marker for movement, is robust even when used to trigger aDBS. Over the course of several months we show a minor increase in beta band event related de-synchronization in patients with active deep brain stimulation confirming that it could be used in chronically implanted systems.**

***Clinical relevance* — We show the promise and practicality of cortical electrocorticography strips for use in fully implanted, clinically translatable, aDBS systems.**

I. INTRODUCTION

Deep Brain Stimulation (DBS) is a common clinical treatment for severe neurological movement disorders such as essential tremor (ET) or Parkinson's disease (PD). In current clinical practice, stimulation is applied in an open loop configuration, where stimulation parameters are set manually by a clinician through trial and error [1]. Stimulation then remains on at the set frequency and voltage. Particularly in the case of diseases like ET, where patients often experience tremor symptoms only during movement, this open-loop stimulation approach may be inefficient[2]. Patients may experience side effects even when at rest, and excessive stimulation may waste battery power leading to more frequent battery replacement surgeries [3]. To solve this problem, much recent research in DBS has focused on the development of adaptive DBS (aDBS) algorithms which would automatically adjust the stimulation to the patient's needs [1], [4], [5]. In some cases, aDBS may reduce tremor more effectively than regular open-loop stimulation [2], [6]. aDBS, therefore, is an improvement over conventional DBS that promises to reduce side effects, improve clinical outcomes, and even improve our understanding of the disease.

For adaptive algorithms to be successful, a robust bio-marker must be found that can control stimulation [1]. Past work has shown the success of aDBS algorithms triggered by changes in cortical band power, as detected with a strip of electrocorticography (ECoG) electrodes [2], [6]. Specifically, these studies used the well documented phenomenon of beta band (12-30Hz) event related de-synchronization (ERD) in the motor cortex during movement [7]. For these sort of systems to be feasible in real world applications these bio-markers must be robust; there can be no significant short-term change in the characteristics of cortical rhythms as a result of DBS that could obscure beta ERD signals. Additionally, the control signal must not be obscured by long-term decay of the signal-to-noise ratio (SNR) of the electrodes or changed by drift in the underlying neural dynamics. The slower the long-term changes, the less often the algorithm will have to be adjusted while remaining effective.

Fully implanted systems have many advantages that would facilitate adoption, primarily focused on the complete lack of external hardware. Many experimental systems rely on distributed setups, built around a connection between the implanted device and a computer, which make them impractical in real world situations. Wearable technologies such as smartwatches are more practical, but come with their own problems. They introduce an additional external point of failure, and can significantly increase latencies in the control system [3]. With all system components implanted, patients would need not carry around additional hardware or undergo extra surgeries. Moreover, cortical local field potentials are known to present many characteristics that can be correlated to patient activity and have already been demonstrated as control of aDBS [4], [6]. Fully implanted systems based on ECoG strips, are therefore a good solution.

This leaves concerns about the long term stability of these signals. Previous work has shown potential interactions between stimulation sites in the deep brain and cortical regions that could lead to change over time [8]. There have also been promising results from investigation into the long-term decay of SNR as a result of scarring around the electrodes [9]. To the best of our knowledge, the stability of beta ERD as an aDBS control signal has not been investigated. In this study, we take advantage of an existing dataset to determine beta ERD is robust against both short term interference from

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aDBS and long-term drift as a result of chronic stimulation.

II. METHODS

This study takes advantage of longitudinal data collected at the University of Washington over the course of the development of aDBS algorithms for ET using ECoG strips. As a result, it provides a unique opportunity to evaluate the long term effectiveness of this approach to DBS. The data available for our analysis consists of a cumulative 32 hours collected from 3 patients during a series of full-day visits spread out over many months. Of this data, only the experiments that contained a recorded ground truth for patient movement were amenable to all of the analysis described below. As a result, special care is taken to avoid errors due to comparisons across inconsistent sample sizes

TABLE I
SUMMARY OF PATIENT DEMOGRAPHICS.

ID	Age	FTM Score[1]	Stimulation Parameters		# Prompts
			Voltage (V)	Frequency (Hz)	
1	58	15 – 23	2.0 – 3.0	140 – 150	81
2	82	15 – 26	2.5 – 3.8	130 – 140	164
3	79	13 – 18	2.5 – 3.2	90	48

A. Data Collected

Data was collected from 3 patients with Activa PC+S stimulation platforms implanted unilaterally into the ventral intermediate nucleus of the thalamus (VIM) as treatment for advanced ET [3]. Patient demographics are shown in Table I. All experiments were approved by the Institutional Review Board at University of Washington Medical Center, and use of the Activa PC+S and Nexus D system was approved by the FDA through an Investigational Device Exemption. The experiments were performed in accordance with all relevant guidelines and regulations. The subjects provided informed consent according to direction from the Institutional Review Board prior to enrollment in our study.

After an early proof-of-concept which demonstrated the Activa PC+S platform's potential [3], work focused on the development of cortically-driven aDBS. The bulk of the data was collected during trials that tested the use of classifiers to control aDBS stimulation based on changes in cortical band power. Specifically, these classifiers took advantage of the beta ERD phenomenon to deliver stimulation only when movement was detected [2]. To test these classifiers, patients were instructed to hold their hand out in front of themselves whenever the prompt 'Hand' was shown on screen, and to return to rest whenever the prompt 'Rest' was shown. This particular posture holding task was chosen as it was found to reliably elicit tremor in our patients, was therefore a reliable way to test the efficacy of the aDBS algorithms during development. Most importantly, this method was used repeatedly even as the cortical aDBS algorithms increased in sophistication [2], [6].

[1]Range of evaluations using the Fahn-Tolosa-Marin tremor rating scale

B. Data Analysis

1) Frequency Band Selection: Selection of the frequency band used in this analysis is a critical step. Based on the literature, beta ERD usually occurs in the 12-30Hz range [7]. This band is therefore of great interest as a potential control signal. The aDBS algorithms used during the generation of the data were sensitive primarily to changes in the 4-30Hz band [2]. The short term analysis to detect potential entrainment as a result of aDBS focuses on the 4-30Hz band and the long term analysis to detect slow drift as a result of stimulation itself focuses on the 12-30Hz (beta) band. The converse is also checked. Since the original data was acquired at either 200 Hz or 422Hz, we are well below the Nyquist frequency.

2) Interval Selection: Although our patients were engaged and participated actively in experiments, movement prompt display times are not as close to the true movement times as might be desired. Since patients demonstrated a reaction delay, beta ERD would likely not be observed in a comparison directly around the prompt [3]. To calculate beta ERD, we use Welch's method as implemented by the `scipy` package in python to calculate the power spectrum for an interval of length t_a just before the onset of the movement prompt. Power in the desired band is then calculated by integration with Simpson's rule using the `scipy` package. A time period equivalent to the estimated max reaction time t_r is then discarded, and a second sample of beta band power is calculated from another interval of length t_a. Beta ERD magnitude ($\Delta Power$) is then calculated as the difference in band power between the pre- and post-movement interval. Optimal duration of both t_a and t_r are estimated to maximize the number of beta ERD events observed.

3) Statistical tools: Due to the low number of patients in this and much other experimental human work, we must be careful to avoid introducing error through our statistical analysis. In particular, we focus on the Kruskal-Wallis test, the non-parametric equivalent of one-way ANOVA [10]. Since it is non-parametric, it operates on the median rather than the mean, and can safely be applied to the non-normal distributions observed in our data set. Additionally, this test is robust against differences in the number of samples in the groups being compared.

Showing these distributions in a meaningful way is also difficult for the same reason. Therefore, when possible we elect to use the boxen plot: a more detailed variant of the well known box-and-whisker plot. The central bar represents the median, and each narrowing represents a 10% quantile away from that median. The triangular flags at either end of the boxen plot represent the minimum and maximum values.

III. RESULTS

293 movement prompts from three patients were included in the analysis. A grid search was performed to find the pair of t_a and t_r that gave the maximum proportion of observed ERD events in the 12-30Hz band, to correct for reaction delays. Options between 1 and 10 seconds were considered for t_a and between 0 and 10 seconds for t_r. Of

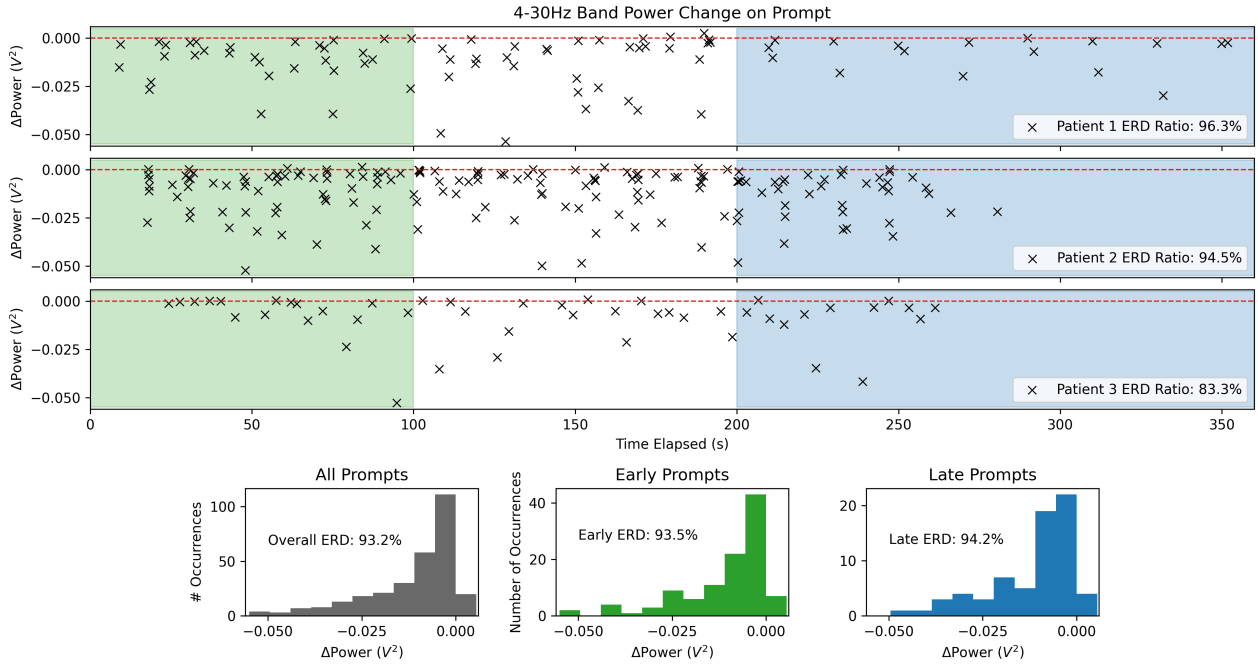

Fig. 1. Short-term change in cortical band power over the course of individual experiments for each of the three patients (top plots). Each point represents the change in cortical 4-30Hz band power as a result of prompted movement onset, during experiments where this same band was used to trigger aDBS. Individual patient ERD ratios are shown in figure legends. Multiple experiments were carried out over several clinical visits, and all plotted points are time aligned to the starts of each individual experiment. Collapsed distributions of power changes from early (green region) and late (blue region) prompts show no difference (bottom plots). ERD values shown suggest that beta ERD is a robust phenomenon.

these combinations, two pairs gave similarly good results. A $t_a = 4s$ with $t_r = 3s$ performed the best, with 95.0% of events showing beta ERD. This was closely followed by $t_a = 2s$ with $t_r = 3s$ at 94.5% of events showing beta ERD. This difference is small enough to likely be insignificant (0.04 times the standard deviation). Since any resulting control algorithms benefit from shorter response times, we chose to carry out our analysis using $t_a = 2s$ with $t_r = 3s$.

Results for the short term analysis are shown in Fig. 1. The top three plots show 4-30Hz band ERD for each of the three patients with relevant data. All recording sessions from all experimental visits were overlaid and aligned at the start time of each individual experiment. The $t_a = 2s$ and $t_r = 3s$ interval configuration was used to calculate the power change, plotted at the time the movement prompt was shown. The red dashed line is a visual reference for the level where no ERD would have been observed. Visual inspection reveals no obvious trend over time, and this is verified by statistical comparison of prompts that occurred early and prompts that occurred late in individual experiments. The distribution of powers for prompts in the first 100 seconds of each experiment (green region and histogram) and after the 200 second point (blue) show qualitatively similar distributions. This is supported by a Kruskal-Wallis test between these two, which fails to reject the null hypothesis that the early and late samples came from a distribution with the same median ($p = 0.493$) [10]. Repeating this process with the 12-30Hz band yields similar results ($p = 0.267$). These results would indicate that the beta ERD are robust to interference from DBS on time scales of a few hundred seconds.

Longitudinal analysis of the same data over the course of months since implantation is shown in Fig. 2. Data from all movement prompts in a single session is gathered together into a single boxen plot. All sessions from all patients are shown in the plot. Since sessions were limited by patient availability, intervals between visits are not necessarily uniform. Visual inspection shows that there may be a slight increase in beta band ERD, meaning that the band power change becomes more negative, over the course of 6-10 months. This is supported by a Kruskal-Wallis test comparing the first and last sessions for patients 1 and 2 ($p = 0.001$ and $p < 0.001$ respectively). Patient 3 does not show any significant change ($p = 0.143$), though this may be due to the fact that there are only two sessions, separated by only two months. This result strongly suggests that ERD in the beta band is a viable control signal and robust over long periods of time. Additionally, it shows that cortical surface electrodes are capable of providing informative signals as much as 16 months after implantation.

IV. DISCUSSION

The results of this paper are in clear support of ECoG strips as a practical element of future developments of aDBS algorithms. We have shown that beta ERD is robust over short time scales of several hundred seconds despite the potential interference of aDBS triggered off this same band. We have also shown that beta ERD sensed from cortical strips do not decay over the time course of multiple months.

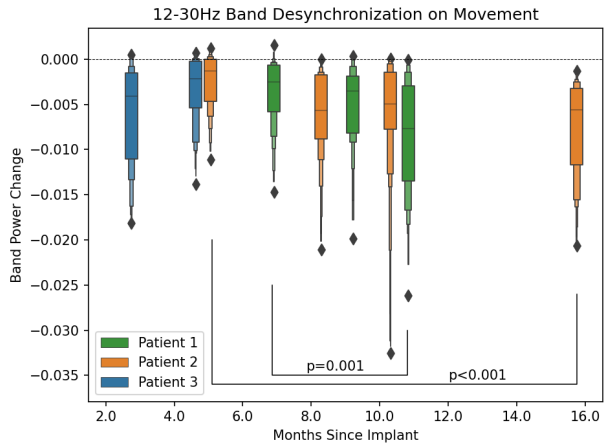

Fig. 2. Longitudinal changes in the beta band (12-30Hz) for three patients over the course of multiple experimental sessions. All beta ERDs from individual prompted movements during each session are grouped into boxen plots placed along the x-axis according to the number of months since the DBS system was implanted. The distributions for patients 1 and 2 show a tendency towards increased beta ERD, while patient 3 shows no trend.

These results are in agreement with similar research previously conducted with PD patients, and long term evaluation of ECoG as an option for long-term BCI systems [9], [11]. Cortical strips are therefore shown to be a reliable source of bio-markers for a fully implanted aDBS systems.

Implanted cortical strips also seem to be a safe extension to the regular DBS implantation process. Despite the additional surgical complexity involved with the implantation of cortical strips, which carries inherent risks, the clinical team involved with these patients has not observed any adverse events directly attributable to the implantation or presence of cortical sensing strips implanted for the PC+S project.

Although the Activa PC+S was an powerful platform for investigating these questions, this study does have limitations. The secondary analysis nature of this study, and small number of subjects may limit how well these results generalize. New implantable DBS systems promise to solve some of these problems by being rechargeable and sampling at much higher rates. This will allow long-term chronic recordings and analysis of a wider range of frequency bands. Future studies are needed to validate these results and investigate the precise nature of the long term increase in beta ERD. A detailed understanding of this trend would allow aDBS algorithms to slowly adapt to any changes and remain in an optimally functioning state. Since this would decrease the frequency at which the aDBS stimulator would need to be manually updated, it would reduce the number of expensive clinical visits.

Taken together, these results emphasize ECoG strips as a part of future aDBS systems. The availability of on-label cortical strips is therefore a crucial step towards widespread adoption of such systems. Once this occurs, patients with severe ET could begin to benefit from the advantages of fully-implanted aDBS systems.

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