

Modulations in Pallidal Local Field Potentials in the Systemic 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Nonhuman Primate Model of Parkinson's Disease During a Voluntary Reaching Task*

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Abstract— This case-study characterizes the changes in neuronal activity that occur within the globus pallidus (GP) in the behaving systemic 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) nonhuman primate model of Parkinson's disease (PD) while on and off dopaminergic therapy. Local field potentials (LFP) were recorded from a scaled 8-contact deep brain stimulation (DBS) lead during a center-out reaching task. Spectral LFP activity and reach behavior were correlated with parkinsonian motor signs and changes in behavior during dopaminergic treatment. Dopamine therapy i) increased reaction time and decreased reach time, ii) shortened the onset-times of LFP synchronization and desynchronization during reaction time, and iii) eliminated desynchronization of the high beta band. These findings suggest that dopamine-induced improvement in bradykinesia is related to a change in the pattern of synchronized oscillatory activity in GP.

I. INTRODUCTION

Understanding the mechanisms of action of dopamine-replacement therapy and deep DBS will be critical for improving upon and discovering new therapies for PD. Dopaminergic medication has been shown to reduce firing rates in the internal globus pallidus (GPi) and subthalamic nucleus (STN) in PD patients [1] and animal models [2]. Early hypotheses suggested that DBS suppresses output from the stimulated site, creating a lesion-like effect [3-5], while later studies suggested that DBS increases output from the stimulated site, regularizing discharge patterns and blocking the flow of pathologic information [6, 7].

Characterization of the physiological changes that underlie the development of PD and mechanisms of therapy have more recently shifted from a focus on changes in mean discharge rate to changes in patterns of activity throughout the basal ganglia-thalamo-cortical network. This includes the development of synchronized oscillations, which can be recorded as spectral peaks in bipolar LFPs [8-13]. Current hypotheses based on these and other studies have proposed that abnormal patterns and synchronization of neuronal activity, not changes in mean firing rate, underlie the motor signs associated with PD; and furthermore, that DBS and dopaminergic medication improve motor signs by modifying these abnormal patterns, thereby allowing cortical motor areas to function without interference from altered activity

arising from subcortical structures [14]. At present, it remains unclear how the behavioral manifestation of PD and dopaminergic therapy correlates with the underlying neuronal activity. This case-study examines this relationship by recording LFPs from the GP during a cued-reaching task in the MPTP primate model of PD both off and on dopaminergic medication.

II. METHODS

A. Task and Surgical Procedure

Data were collected from one nonhuman primate ('L', female, *Macaca mulatta*, 6.0 kg, 18 y.o.). All procedures were approved by the Institutional Animal Care and Use Committee of the University of Minnesota and complied with United States Public Health Service policy on the humane care and use of laboratory animals. Animal L was trained to perform a rapid and over-trained, center-out unilateral reach task. Trials were initiated when the animal placed its hand on a start pad. After a variable delay (1-1.5 sec) a colored circle (15 cm) appeared on the touch screen in one of eight locations (randomized), providing the animal with both target direction and go-cue (Figure 1A). A trial was considered complete if the reaction (max 0.5 sec) and reach time (max 0.8 sec) were within specified limits. A successful trial (animal touched

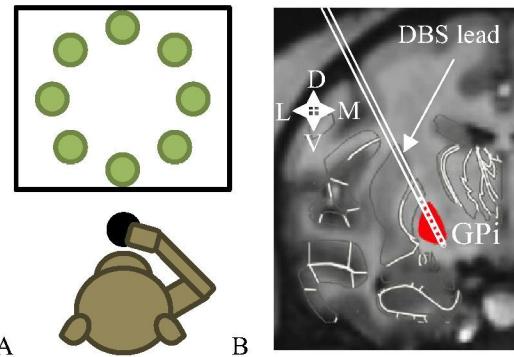


Figure 1: A) Primate was required to hold its hand on a startpad and then reach to touch one of eight possible cues presented on a touchscreen. B) Location of 8-contact DBS lead implanted within the posterolateral segment of the GPi (red). Post-DBS implant CT scans were co-registered with pre-operative MRI and overlaid with a linearly morphed coronal atlas slice. The white boxes on the DBS lead indicate estimated positions of most ventral (C0) to most dorsal (C7) contacts. Orientation denoted as dorsal (D), ventral (V), medial (M), and lateral (L).

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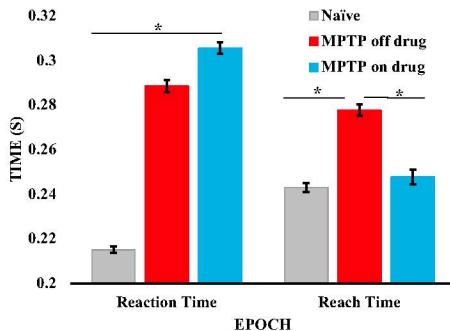


Figure 2: Behavior in the naïve (grey), MPTP off levodopa (red), and MPTP on levodopa (blue) conditions. Significant differences reported in the results section are denoted with **. Error bars denote standard error of the mean (SEM) in this and subsequent figures with Naïve ($n=1151$), off-drug ($n=3526$), and on-drug ($n=1276$) observations.

within the target boundary) resulted in an immediate juice reward.

All surgical procedures have been described previously [15]. Briefly, the animal was implanted with an 8-contact scaled version of a human DBS lead (Numed, Hopkinton, NY) through a cephalic recording chamber targeting GP. Mapping of the external globus pallidus (GPe) and GPi was completed using microelectrode recordings (MER), neuronal somatosensory and somatomotor responses and micro-stimulation responses. Co-registration of a post-implant CT scan and pre-operative MRI, along with MER mapping, were used to confirm electrode placement. The animal was treated with a single right intracarotid injection of MPTP to induce a moderate hemi-parkinsonian state (0.5 mg/kg) [16]. A therapeutic levodopa dose (16 mg/kg) was considered effective when significant behavioral differences were observed relative to the MPTP off-drug state (Figure 2).

This case-study included 8 recording sessions (6 MPTP off-drug, 2 MPTP on-drug) in which the animal completed at least 300 trials/session. LFPs were collected from all eight DBS contacts, bandpass filtered at 1-500 Hz and sampled at 3 kHz. Inspection of impedances showed contacts C6 and C7 were unstable and were excluded from further analysis.

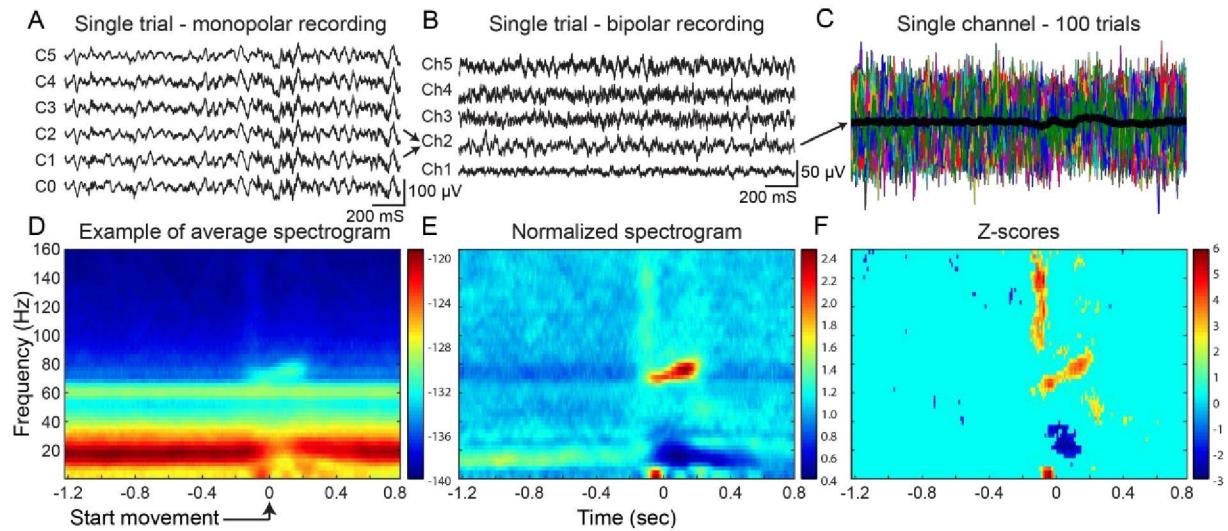


Figure 3: Method for analyzing spectral content of LFPs. A) Example of monopolar LFP recordings from DBS contacts C0-C5 during a single reaching trial in the MPTP off- drug state. B) Bipolar montage of channels 1-5 created from the monopolar LFPs in A. C) Overlay of 100 trials of bipolar channel 2, with the mean shown in black. D) Spectrograms of each individual trial were triggered to the time of movement onset (arrow) and averaged across a session to create the population averaged spectrogram. E) The population averaged spectrogram was normalized by the bootstrapped population. F) Z-scores were calculated by subtracting off the mean from the normalized spectrogram and thresholded at a 95% confidence level.

B. Time-Frequency Analysis

Spectral analysis of the LFP recordings was performed offline in Matlab (v2010b, Mathworks, Natick, MA) with custom scripts and the Chronux toolbox [17]. All monopolar recordings were passed through a moving window line noise subtraction algorithm to remove continuous noise artifacts. Bipolar LFP recordings were computed for each pair of adjacent DBS lead LFPs to remove common far-field signal from the chamber return electrode (Figure 3). The use of the term ‘LFP’ throughout the remaining analysis and discussion relates to the bipolar LFP. Trials whose signal exceeded mean ± 6 standard deviations of the bipolar LFP on any channel were identified as artifacts and removed from further analysis.

Each trial was triggered to the time of presentation of the go cue (-1000 ms to 1000 ms) or to the start of reach movement (-1220 ms to 780 ms). Cue-triggered and movement-triggered spectrograms were calculated for each trial using the multi-taper method with a 100 ms wide, 10 ms step moving window, 2.5 Hz frequency resolution, and 1 taper, and were averaged over all trials for a given session. Z-scores were calculated by averaging the spectrograms over trials and normalizing by a bootstrapped population. Time windows of the average spectrogram were randomly selected to generate a bootstrap population of 1000 random spectrograms with the same frequency content of the recorded average spectrogram but without the temporal dynamics time locked to cue presentation or reaction times. To identify task-related changes, the baseline (-1,000 to 0 ms) period was made to have zero mean for each frequency bin and task related z-scores were computed by subtracting baseline frequency over the entire z-score matrix.

C. Statistics

For visualization, Z-scores were thresholded at ± 1.96 to reveal significant movement-related modulations with $\alpha=0.05$. Frequency bands of interest were visually identified (1-6 Hz, low beta 10-20 Hz, high beta 20-35 Hz, low gamma 70-85 Hz, high gamma 90-160 Hz), and time-series were

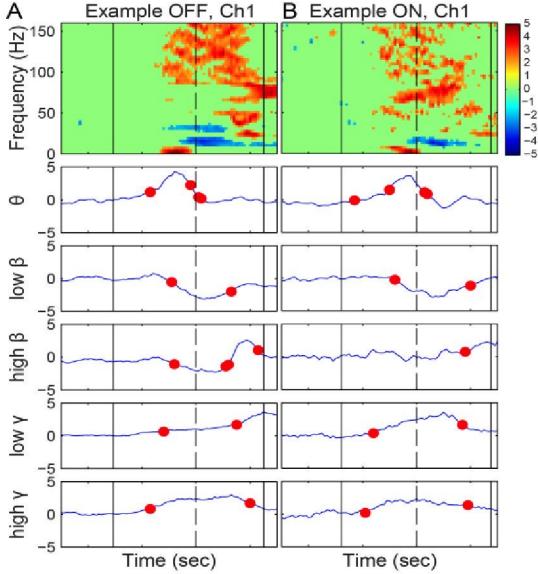


Figure 4: Change-point analysis of spectral content during cued reach task. Comparison of MPTP drug-OFF (A) and MPTP drug-ON (B) conditions for bipolar channel 1 for individual recording sessions. Z-score spectrograms (top color plots) and corresponding change-point analysis in the lowest band (1-6 Hz), low β (10-20 Hz), high β (20-35 Hz), low γ (70-85 Hz), and high γ (90-160 Hz) bands. Blue traces show the time-series of the frequency band, solid black lines show the average time of cue onset and time of target touch, dashed black lines show time of movement onset, red dots show times of significant change.

produced by averaging the spectrogram z-scores over the frequency bins within a band. Change-point analysis [18] was applied recursively to the frequency band time-series to identify the onset and offset times of modulations within each band.

The experimental design was a repeated measure design with the independent variable on/off drug condition nested within recording session (block). Performance measures included reaction time, reach time, and binary measure of success/error (touch within target boundary or not). In addition, a multivariate analysis of reaction time and reach behavior was examined for differences in co-variation across drug on/off conditions. The same analysis was performed on the change-point time values. Unless otherwise specified, means and standard deviations are reported in the text.

III. RESULTS

The lead was implanted in the posterolateral segment of the GPi (Figure 1B), with C0 located on the ventral GPi border just dorsal to the optic tract. Contacts C1-C5 were in the GPi and C6/C7 were in the GPi/GPe border and GPe, respectively. Impedances for C6 and C7 were unstable and were excluded from further analysis. As a result, the analysis only included contacts within GPi.

A. Behavioral Differences

Behavioral measures of performance in the naïve animal indicated that the animal had reached a consistent performance across days with little variability (reaction time 215 ± 96 ms and reach time 243 ± 90 ms). Post-MPTP performance was significantly altered, indicating that the single MPTP dose was effective in rendering the animal parkinsonian (reaction time 288 ± 87 ms and reach time 278 ± 116 ms).

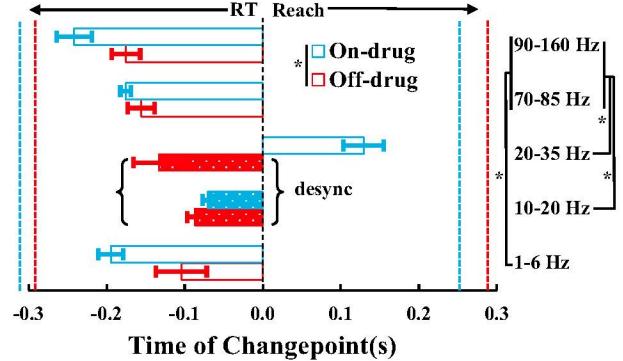


Figure 5: Population statistics on change-point analysis. Significant differences reported in results are denoted by *. Vertical dashed lines represent the average reaction (negative) and reach (positive) times relative to reach onset ($t=0$) for on (blue) and off (red) drug condition. Solid fill represents onset of desynchronization, open fill represents onset of synchronization.

Reaction times, reach times, and the covariation of these measures differed considerably across on /off drug conditions (Figure 2). Overall, levodopa given in the MPTP state resulted in longer reaction times ($F=35$, $p<0.0001$) but faster reach times ($F=34$, $p<0.0001$). A multivariate analysis of reaction time and reach time indicated that in both on- and off-drug conditions, these covariates were negatively correlated (off-drug $r=-0.08$, 95% CI -0.16 and -0.05 , and on- drug $r=-0.12$, 95%, CI -0.18 and -0.07). While overlapping correlation CIs failed to show differences between on/off drug conditions ($F=106$, $p<0.001$), the ratio of reaction time to reach time was significantly different across drug conditions ($F=106$, $p<0.001$), with higher ratios on-drug (1.57 ± 0.04) compared to off-drug (1.19 ± 0.02).

B. Event Triggered Spectrograms

The LFP is hypothesized to reflect a summation of global or network wide activity [19]. The spectral content of the LFP during a single trial could contain additional information that is not time-locked to the task. Therefore, identifying movement-related activity requires averaging over hundreds of trials (Figure 3C-F) in order to isolate the spectral content of interest.

Time-locked, averaged pallidal LFPs in the MPTP off-drug state demonstrated i) synchronization in the lowest band (1-6 Hz) that began 104 ± 32 ms prior to movement onset, ii) desynchronization in the low (10-20 Hz) and high (20-35 Hz) beta bands that began 87 ± 10 ms and 130 ± 33 ms before movement onset, respectively, iii) synchronization in the low gamma band (70-85 Hz) 156 ± 17 ms before movement onset, and iv) synchronization in the high gamma band (90-160 Hz) 175 ± 18 ms before movement onset, as detected by change-point analysis (Figure 4A and Figure 5 (red)).

After administration of dopaminergic therapy (Figure 4B and Figure 5, blue), change-points occurred earlier than in the off-drug condition in the lowest band (1-6 Hz, 195 ± 16 ms) and in the high gamma band (90-160 Hz, 241 ± 22 ms), while low beta (10-20 Hz, 71 ± 6 ms) and gamma (70-85 Hz, 175 ± 7 ms) bands did not change. Interestingly, high beta (20-35 Hz) desynchronization was no longer present during the reaction time in the drug-on condition. The onset of the first change-point occurred 129 ± 26 ms after reach onset. Across the two drug-on recording sessions and across all LFP channels, beta

desynchronization was detected in only one observation (outlier). As such, the dopaminergic therapy eliminated high beta band desynchronization.

IV. DISCUSSION

In this case-study, externally cued movement was preceded by GPi LFP activity in the parkinsonian state across all frequency bands (<160 Hz). Synchronization across the gamma bands preceded desynchronization in the beta bands. Similar patterns were noted in the GPi during dopaminergic therapy, however they occurred earlier relative to movement and desynchronization in the high beta band was absent. The treatment-induced early onset of GP activity could have been related to longer reaction times (~20 ms longer). However, shorter onset latency relative to the go-cue was also observed (Figure 5). Thus the early onset of activity was not solely related to increases in the duration of the reaction time epoch.

No known dopaminergic drug studies exist examining GPi LFPs during externally cued movement in PD. The observed correlation between beta desynchronization and gamma synchronization in this study is consistent with previous reports from others recording in the sensorimotor cortex [20]. Furthermore, although studies of STN LFPs in PD patients have shown an inverse relationship between the latency of beta desynchronization and motor impairment [21, 22], this was not observed in this study. And, while reach times improved towards pre-MPTP (naive) levels, reaction times were longer post-MPTP in the on drug state. This is consistent with an influence of dopaminergic medication on preparatory activity leading to prolonged reaction times. Dependence of motor-preparative processes on dopaminergic activity has been shown in STN beta band desynchronization in self-paced movements [21]; one possible explanation for the increased reaction time is the lack of high beta desynchronization. Alternatively the effect of dopamine on nonmotor circuits could also play a role. The combination of earlier synchronization of gamma and delta/low theta together with desynchronization of low beta band activity could be argued to contribute to the improvement in movement time.

While beta band synchronization/desynchronization has been argued to play a key role in the development of bradykinesia and its improvement with dopaminergic medication, it is more likely that these events occur as the result of a combination of changes across multiple power spectrums. An extension of the current study, including LFP and behavioral responses to therapeutic levels of DBS and replication across animals, will help elucidate key mechanisms involved in the amelioration of motor planning and performance.

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