Changes in Neural Activity during Deep Brain Stimulation in Patients with Parkinson's Disease: Correlation with Stimulation Parameters, Tremor, and Outcomes

Authors: Dakota Graham, Bradley Greger PhD

Acknowledgements: Francisco Ponce MD, Meg Lambert RN, Christopher Buneo PhD, Stephen Helms Tillery PhD

Abstract

Goal: Elucidate how DBS is interacting with neural physiology when applied to the STN
Deep brain stimulation (DBS) is a safe and effective treatment for various neurological disorders such as Parkinson's Disease (PD)
Mechanisms of DBS are still unclear
Recordings were gathered from the subthalamic nucleus (STN) of PD patients while stimulating STN at different frequencies

Modulation of action potential (AP) aligned local field potential (LFP) during stimulation within the therapeutic frequency range was observed
Applications: Understanding these mechanisms will help drive development of more specialized DBS → more effective/expand treatment to more pathologies

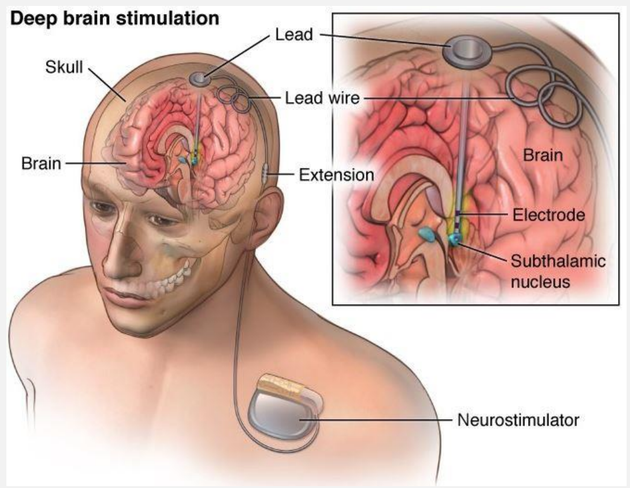
Introduction

Deep Brain Stimulation (DBS)

- Disorders treated with DBS: Parkinson's Disease, Essential Tremor, Dystonia, Epilepsy
- DBS prevalence: Over 150,000 devices implanted [5]
- Current hypothesis of mechanisms: DBS acts as a reversible lesion [3]
  - Still under debate

Parkinson's Disease (PD)

- Epidemiology: Affects 10 million people worldwide [6]
- Symptoms: Tremor, Rigidity, Slow Movements
- Medication side effects: Unwanted rhythmic movements, fluctuations in medication effectiveness
- Pathology: Decreased dopamine levels and neural degeneration



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Challenges

- Understanding the effect of DBS on neural tissue
- Linking the effect on neural tissue to symptom reduction of PD
- Efficiently optimizing treatment for each patient

Goal

- Investigate possible mechanisms of DBS
- Uncover changes in neural activity due to stimulation
  - Link these changes in activity to expected patient outcome given therapeutic ranges of DBS
- Develop a system for measuring tremor intraoperatively

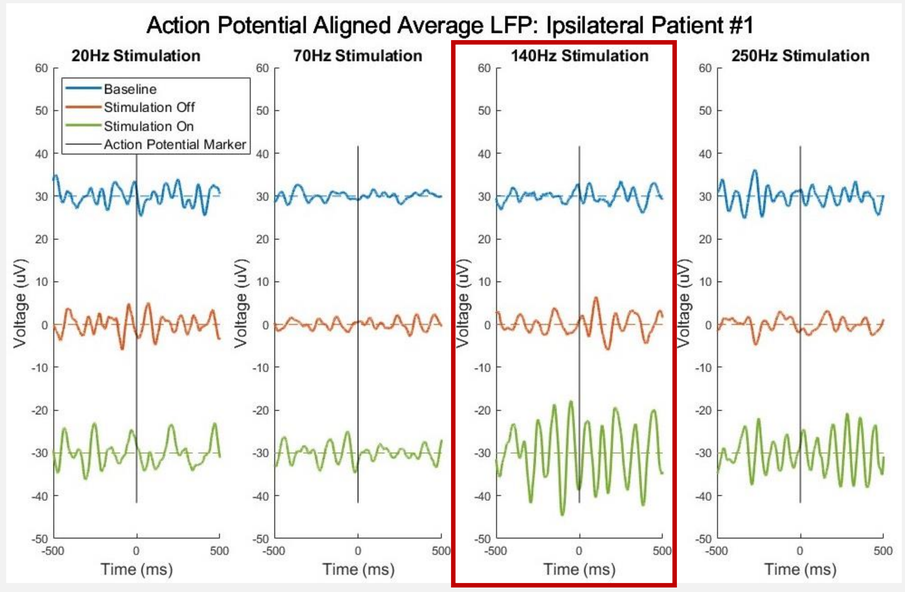
Learning Objectives

- Exposure to operating room protocol
- Neural analysis: Firing rate & action potential aligned LFP
- Hardware: Design of tremor measurement system

Specific Aims

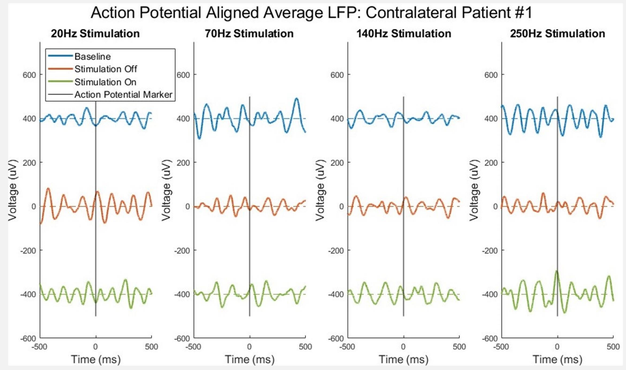
1. Intraoperative microelectrode recording from single neurons in the STN.
2. Analyze effect of DBS on action potentials (APs) and local field potentials (LFPs).
3. Correlate changes in APs and LFPs with reductions in tremor.

Results/Discussion



Ipsilateral action potential aligned averages (large image)

- Changes observed during stimulation at high frequencies
- Largest change during 140Hz stimulation
- Small changes during 250Hz stimulation
- Therapeutic frequency range of DBS for STN: 135 – 185Hz [1]
- No clear changes in cell firing rate were observed



Contralateral action potential aligned averages seen (small image)

- No apparent differences between baseline, stimulation on, and stimulation off

Conclusion/Future Work

Conclusion: Data supports an ipsilateral enhancement of LFP during high frequency stimulation

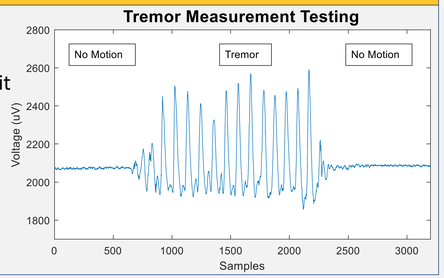
- Limitations: unable to link neural signals with patient benefit

Future Work: Stimulate/Record while the patient is "awake"

- Removes confounds of anesthesia
- Allows for observation of tremor

Quantify Patient Benefit: Measure reduction of tremor

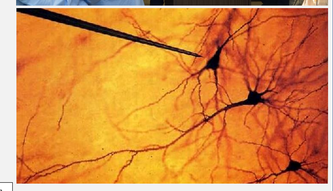
- Accelerometer attached to the patient's wrist
- Unified Parkinson's Disease Rating Scale part III (UPDRS III)



Methods: Neural Recording

Patient population

- Parkinson's Disease
- DBS in Subthalamic Nucleus
- Number of patients: 4



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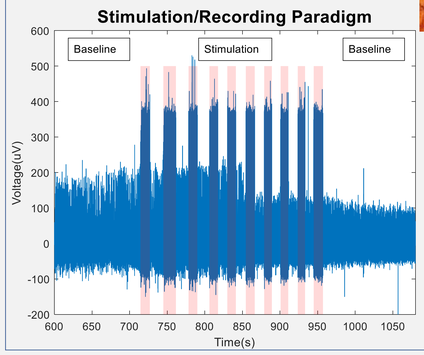
Microelectrode recording

- Placement: Ipsilateral & contralateral STN
- Neural activity: Action potentials & local field potentials
- Sampling rate: 24kHz



DBS Stimulation

- Amplitude: 3 Volts
- Pulse width: 90 µSeconds
- Frequencies:
  - 20, 70, 140, and 250Hz
- Duration: 10 intervals
  - 10sec ON/10sec OFF

Methods: Analysis

Stimulation Artifact Removal

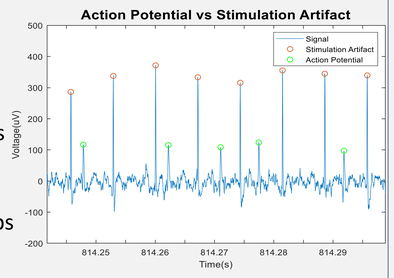
- Amplitude thresholding
- Peak width (max/min)

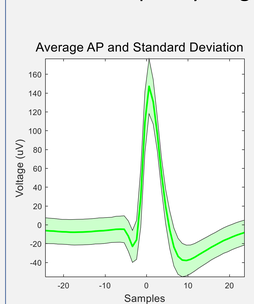
Spike Sorting

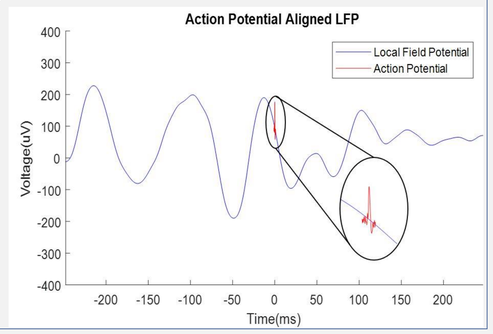
- Principle Component Analysis
- Visualizing wave shape

Action Potential Aligned LFP

- Determine phase relationships between APs and LFP
- LFP frequency range: 3-55Hz







References

[1] R. Ramasubbu, S. Lang, and Z. H. T. Kiss, "Dosing of Electrical Parameters in Deep Brain Stimulation (DBS) for Intractable Depression: A Review of Clinical Studies," *Front Psychiatry*, vol. 9, Jul. 2018.
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