Identifying Characteristics of Neural Network Dysfunction in Parkinsonian Mice

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Abstract

Keywords:

Summary of Comments on ADAreportTaylor.pdf

This page contains no comments

1 Introduction

Parkinson's disease (PD) is a disorder of the nervous system characterized by tremors, rigidity, movement dysfunction, and cognitive impairment.

One mechanism of interest in the progression of PD is dopamine loss. In PD patients there is a gradual dying off of dopamine-producing (dopaminergic) cells which leads to a decrease in dopamine levels in the brain. As a neurotransmitter, dopamine is essential to the regulation of brain activity and its loss leads to dysfunctional neuronal activity particularly in the *external globus pallidus* (GPe) of the *basal ganglia*. This region is associated with motor function and it is believed that the motor symptoms of PD originate from this region as normal activity patterns are disrupted by dysfunctional activity. [6]

Previous work has identified some of the characteristics of the network dysfunction caused by low dopamine. These include

β-oscillations in LFP Studies in humans such as [3] and [2] have found evidence of increased power in the β-frequency (15-30 Hz) band of the LFP spectrum. The LFP signal is believed to represent the sum of the electrical activity of all neurons in the vicinity of the probe. Thus an increase in a particular frequency band corresponds to an increase in synchronized oscillation at the corresponding frequency.

Decreased firing rates Initially it was believed that changes in the firing rate of neurons was a cause of PD, however recent studies have failed to detect such changes [8].

Synchronous inhomogenous patterns of firing between neurons An alternative model has been proposed by [10] that a pattern of burst firing may be responsible. These patterns manifest as "on-off" patterns of periods of high firing followed by periods of low firing.

Small time-scale synchrony between neurons In addition to synchrony in firing rates, we also expect short-scale synchrony in which neurons cofire in small time windows [7].

Taken as a whole, these symptoms can be characterized as increased oscillatory activity as waves of activity that dominate the natural patterns present in healthy brains. This rhythmic behavior interferes with the spatial and temporal encoding of network activity

Page: 2

Number: 1 Author: loaner Subject: Highlight Date: 2/20/2016 10:43:30 AM

I would start a new paragraph here. There seems to be two ideas here: 1. PD and progrssion of PD through dopamine loss. 2: Role of dopamine itself...

Number: 2 Author: loaner Subject: Highlight Date: 2/20/2016 10:46:00 AM

Try to break this sentence into smaller one each with a single idea.

Number: 3 Author: loaner Subject: Highlight Date: 2/20/2016 10:49:42 AM

These 'characteristics' include?

Number: 4 Author: loaner Subject: Highlight Date: 2/20/2016 10:47:52 AM

Am I supposed to know what LFP is? Is this an acronym or something well known in the literature?

Number: 5 Author: loaner Subject: Sticky Note Date: 2/20/2016 10:52:41 AM

So what is a take away from this point? It is not clear to me what if decreased firing rates is a characteristic identified by previous work or not.

Number: 6 Author: loaner Subject: Highlight Date: 2/20/2016 10:50:14 AM

alternative to what?

Number: 7 Author: loaner Subject: Highlight Date: 2/20/2016 10:56:49 AM

Multiple usage of as. Also I am kind of lost by the past part of the sentence.

Number: 8 Author: loaner Subject: Highlight Date: 2/20/2016 10:57:26 AM

which rhythmic behavior?

and contributes to the motor dysfunction symptoms. Currently, disrupting this rhythmicity through interventions such as deep brain stimulation have proven effective, however we still lack an understanding of the mechanisms behind this rhythmicity and how it develops as the disease progresses.

Thus for this work we are investigating how previously studied indicators of network dysfunction develop over the course of PD progression. ~~To this end~~ we introduce a novel experimental design in which we gradually deplete dopamine through multiple low-doses of 6-OHDA. In this way we spread the dopamine loss over a span of weeks which more accurately mirrors the course of disease in human patients. Similarly to human patients, motor symptoms do not develop in mice until dopamine levels have been reduced by approximately 80%.

This design allows for the study of the progression of network dysfunction as a function of dopamine loss. We can obtain measurements from mice at various stages of dopamine depletion, ranging from healthy to completely depleted.

However, at the time of this writing we only have data collected from healthy and completely depleted mice with no data from partially depleted mice. As a first step in studying the progression of the disease, we set out to find differenes between the endpoints of healthy and completely depleted subjects.

2 Data

2.1 Experimental Design

Previous experiments studied dopamine depletion with an experimental design in which dopamine is depleted by 80-90% over a short time period through the administration of a single high dose of the toxin 6-OHDA. This toxin selectively kills dopaminergic cells in a process which mimics PD.

However, this short timeline of depletion does not accurately reflect the progression of PD in a clinical setting; dopamine levels of patients can decrease over a period of years before the first motor symptoms appear. Typically dopamine levels have dropped by 60-80% before motor-symptoms present [5]. The period of time before symptoms present is called the *prodromal* phase and the ability to diagnose during this stage could allow for more effective treatment.

Page: 3

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be more specific when defining the rhythmic behavior.

Number: 2 Author: loaner Subject: Highlight Date: 2/20/2016 11:00:57 AM

make this a separate sentence? this is a good place to use it as a stress of the paragraph.

Number: 3 Author: loaner Subject: Cross-Out Date: 2/20/2016 11:01:53 AM

Number: 4 Author: loaner Subject: Highlight Date: 2/20/2016 11:04:00 AM

are you not experimenting on humans? was the experiment explicitly design for mice to mirror human behavior? I don't get to know this until the end of the paragraph.

2.2 Data Collection

The data we collect is extracellular electro-physiological recordings from awake mice. The area from which we record is the *external globus pallidus* (GPe) of the *basal ganglia*. As mentioned before, this region is associated with motor function and it is believed that the motor symptoms of PD originate from this region.

To obtain the electro-physiological recordings the mice are placed on a free-spinning wheel. The mice are then placed into a stereotaxic frame and a craniotomy is performed in which the piece of skull over the recording site is carefully removed. Then a 16-channel probe is carefully inserted into the target area.

Once inserted, the probe records neuronal activity for a session of approximately 15 minutes. Each channel can record either spike activity or the *local field potential* (LFP) channel.

A channel recording spike activity measures the electrical activity of nearby neurons. When a neuron fires the electrical potential of the cell rapidly rises and then falls. These events can be detected by the characteristic spike in voltage at the recording site. This signal is collected at a 40 kHz sampling rate. For purposes of minimizing data storage, only channels with firing neurons are selected; thus we typically have three or four channels per recording.

A channel recording the LFP measures the sum of action potentials of nearby neurons. Instead of individual spikes, the LFP reflects broader oscillatory patterns in neuronal activity. This signal is collected at a 1 kHz sampling rate.

2.3 Pre-Processing of spike channels

A necessary preprocessing step is to transform the raw channel signal into a *spike-train*, the times of the spikes. This process consists of two main stages: spike detection and spike sorting.

2.3.1 Spike Detection

Spike detection is the process of identifying the spikes occurring in the recording.

A common approach is to use a sub-threshold: if the signal drops below a certain voltage value we record a spike. This value should be low enough to avoid classifying noise as a

Page: 4

Number: 1 Author: loaner Subject: Sticky Note Date: 2/20/2016 11:17:13 AM

Nice! I like this reminder.

Number: 2 Author: loaner Subject: Highlight Date: 2/20/2016 11:19:15 AM

You used LFP earlier without telling us what it means!

Number: 3 Author: loaner Subject: Highlight Date: 2/20/2016 11:22:29 AM

Is there a reason for this sentence to be a separate paragraph?

spike (false positive) while still high enough to avoid missing low amplitude spikes (false negatives). The difficulty is in deciding which value to set this threshold.

To obviate the need to select a threshold we develop a new method for automatically selecting thresholds that adapts the to noise characteristics of the signal.

For this approach we scan through the data collecting signal segments which pass the following criteria:

- Aligned on a local minimum (to avoid duplication)
- Local minimum below threshold
- Local maximum above threshold
- Local minimum is before local maximum

On this pass through the data we collect spikes along with segements of noise which happen to fit the criteria.

Then we run the procedure on the signal in reverse. Because spikes have their minimum before their maximum, on this pass we don't collect spikes, only noise. This allows us to fit a null distribution for the amplitudes of noise which passes our criteria. We model this distribution as a multivariate normal.

Once we have fit the null distribution the problem reduces to hypothesis testing: for the segments collected in the first pass we test against coming from the null distribution. We select spikes using a FDR of 0.01.

2.3.2 Spike Sorting

Because the activity of several neurons might be recorded at a single site, we need to attribute spikes to individual neurons. To achieve this we apply a technique called *spike sorting*. The spikes of a neuron have a characteristic shape determined by the specific morphology of the neuron's dendrites. We use this characteristic shape to sort spikes into clusters of similar shape which are generated by the same neuron.

Thus we take a short window of time ($\approx$ 2 ms) around each spike, aligned on the minimal voltage of the spike. This represents the entire waveform of the spike. Using these curves we apply a state-of-the-art Bayesian clustering technique for our spike-sorting developed by [4].

Page: 5

Number: 1 Author: loaner Subject: Highlight Date: 2/20/2016 11:24:06 AM
Same paragraph?

Number: 2 Author: loaner Subject: Highlight Date: 2/20/2016 11:29:26 AM
Noise

Number: 3 Author: loaner Subject: Highlight Date: 2/20/2016 11:32:50 AM
Move 'developed by' right after Bayesian clustering technique.