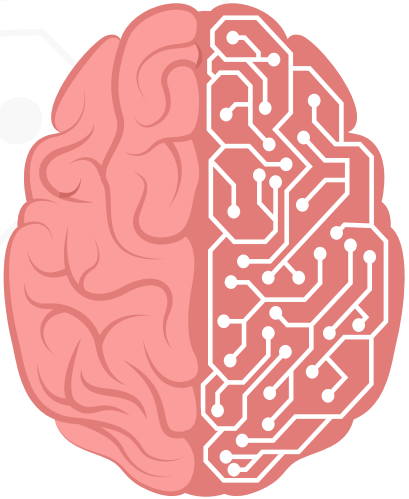


GABAergic Control of Network Activity in an *in vitro* Model of Alzheimer's Pathogenesis

Lucas Lu

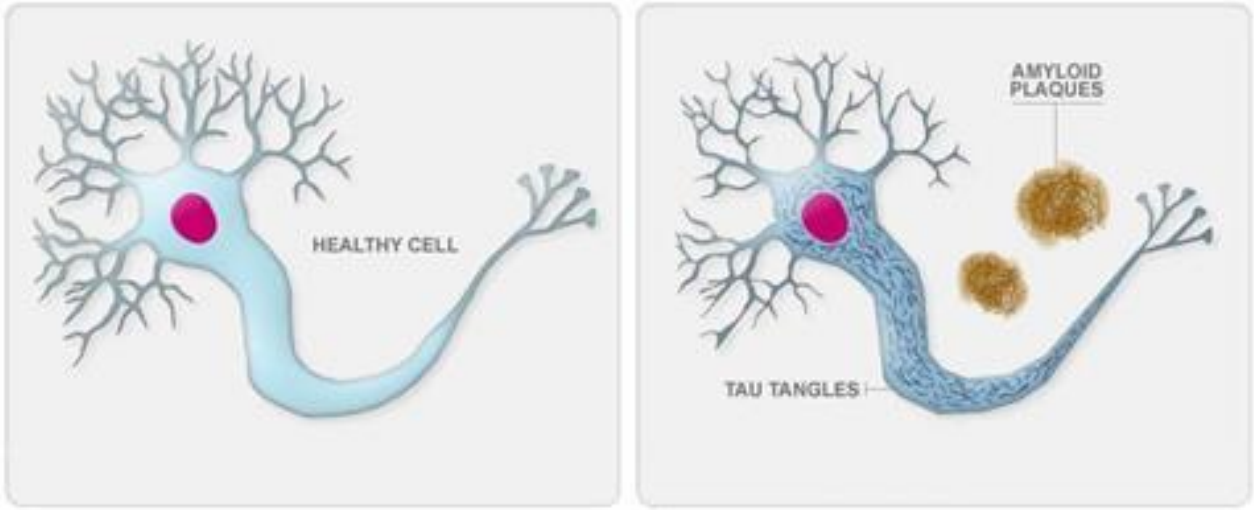
Table of Contents.

Alzheimer's Disease.

Irreversible neurodegenerative disease with no disease-modifying treatments.

Hallmarks: Tau Tangles and Amyloid Beta Plaques

Tau recently recognized as an early component of the pathogenesis.



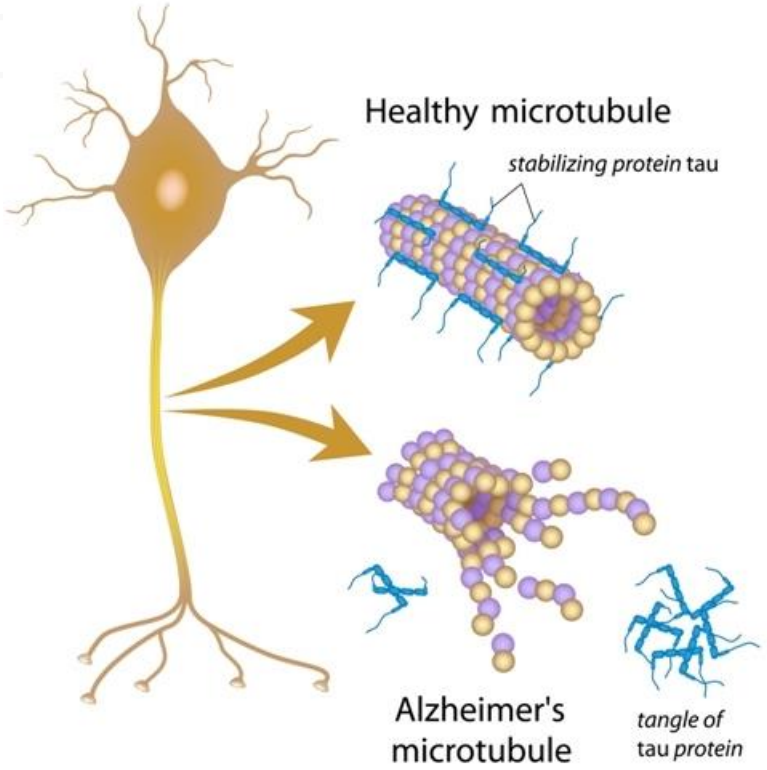
Pathological Tau.

Healthy tau

- Stabilizes microtubules.
- Cellular transport to axon and dendrites.

Pathological tau

- Destabilizes microtubules.
- Forms intracellular tangles.
- Cleaved tau or modified tau can accumulate at the synapse and hinder synaptic communication.

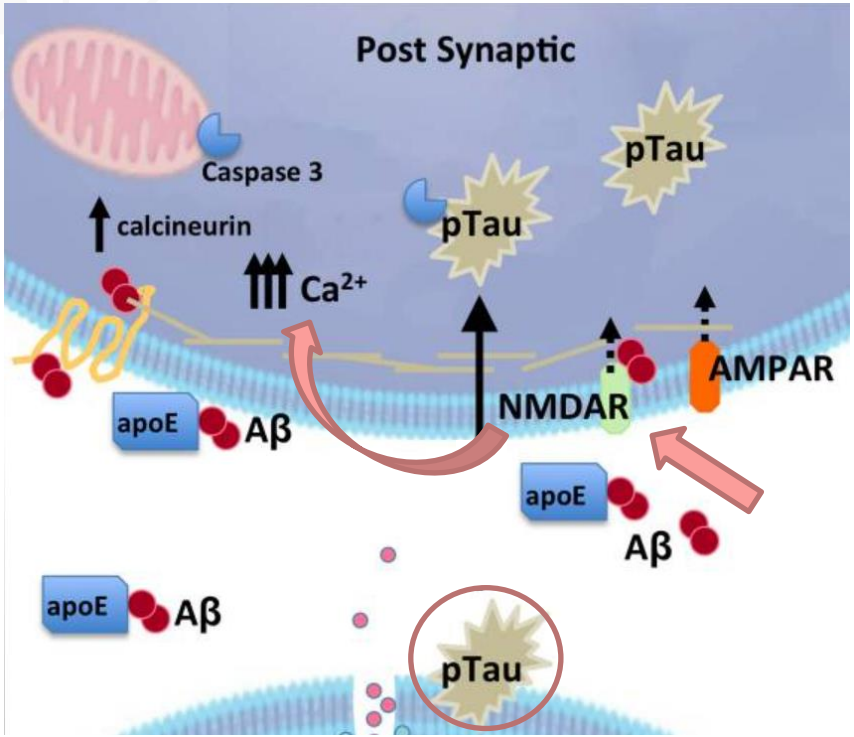


Tau Accumulation at the Synapse.

Modified tau accumulates in the synapse.

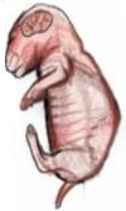
Accumulation of tau may enhance excitatory activity → **Hyperactivation Model.**

Inhibitory GABAergic interneurons are thought to be vulnerable to the effects of abnormal tau.



In Vitro Neural Cultures.

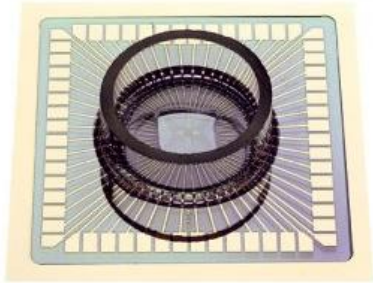
Harvest wild type (WT) mice brains

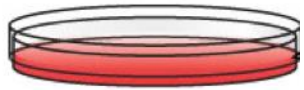


Micro-dissected brain sections

Single-cell suspension

Microelectrode Array

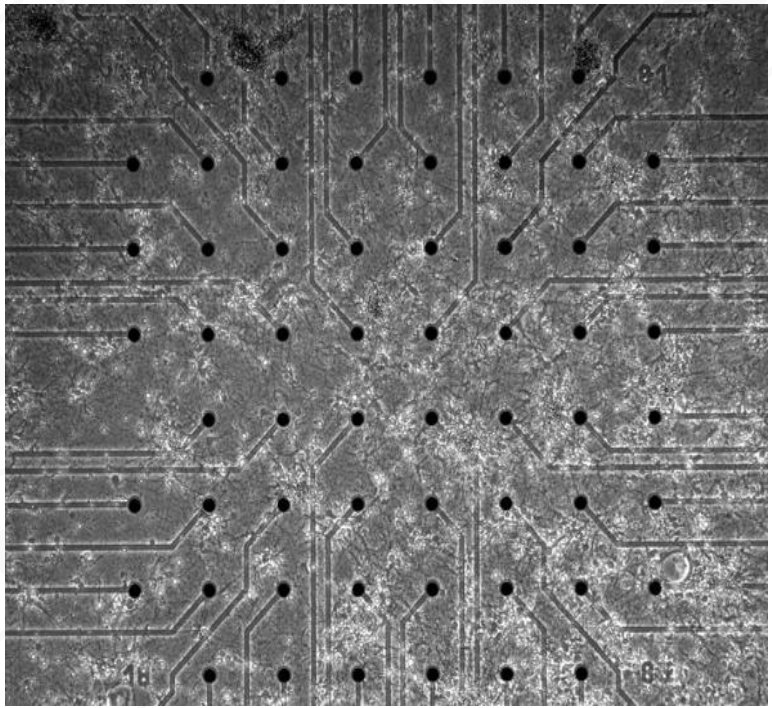




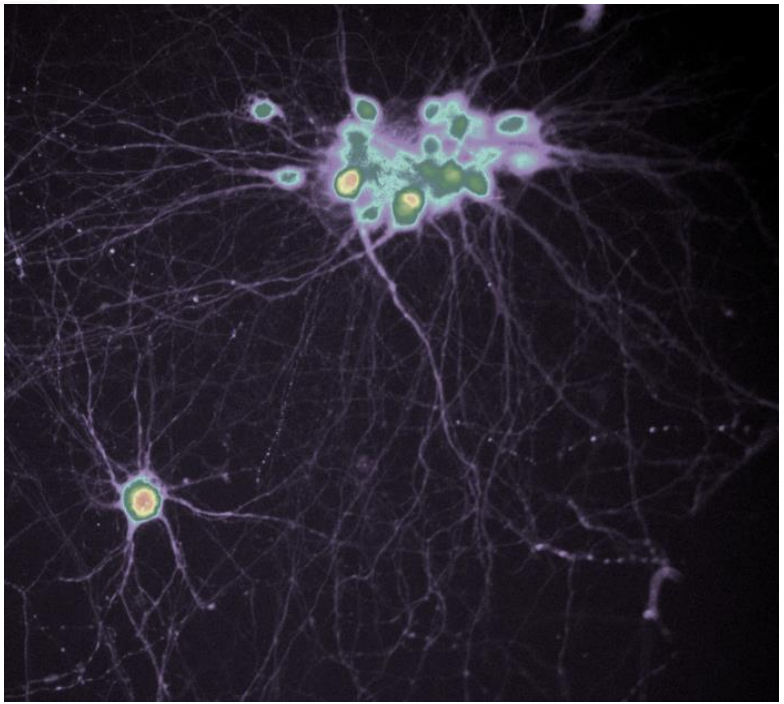
Coverslip cultures

In Vitro Neural Cultures.

MEA Electrode Grid



Fluorescence Imaging

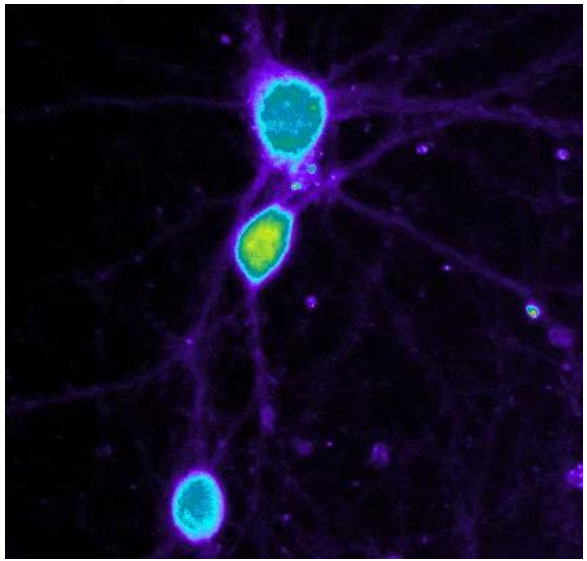


Fluorescent Calcium Imaging of Bicuculline.

Excitatory activity imaged with fluorescence intensity.

Bicuculline is a GABAergic antagonist.

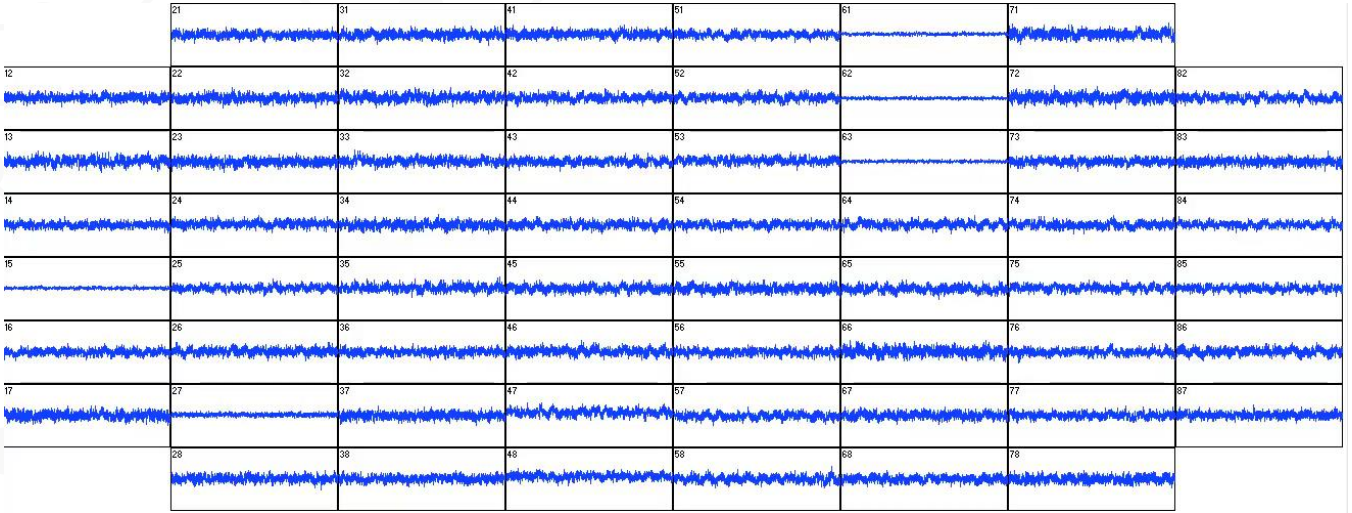
We challenge neurons with bicuculline to induce hyperexcitability.



Microelectrode Arrays (MEAs).

60 electrodes detect action potentials of neurons.

Action potentials are spike events, which form bursts in sequence.



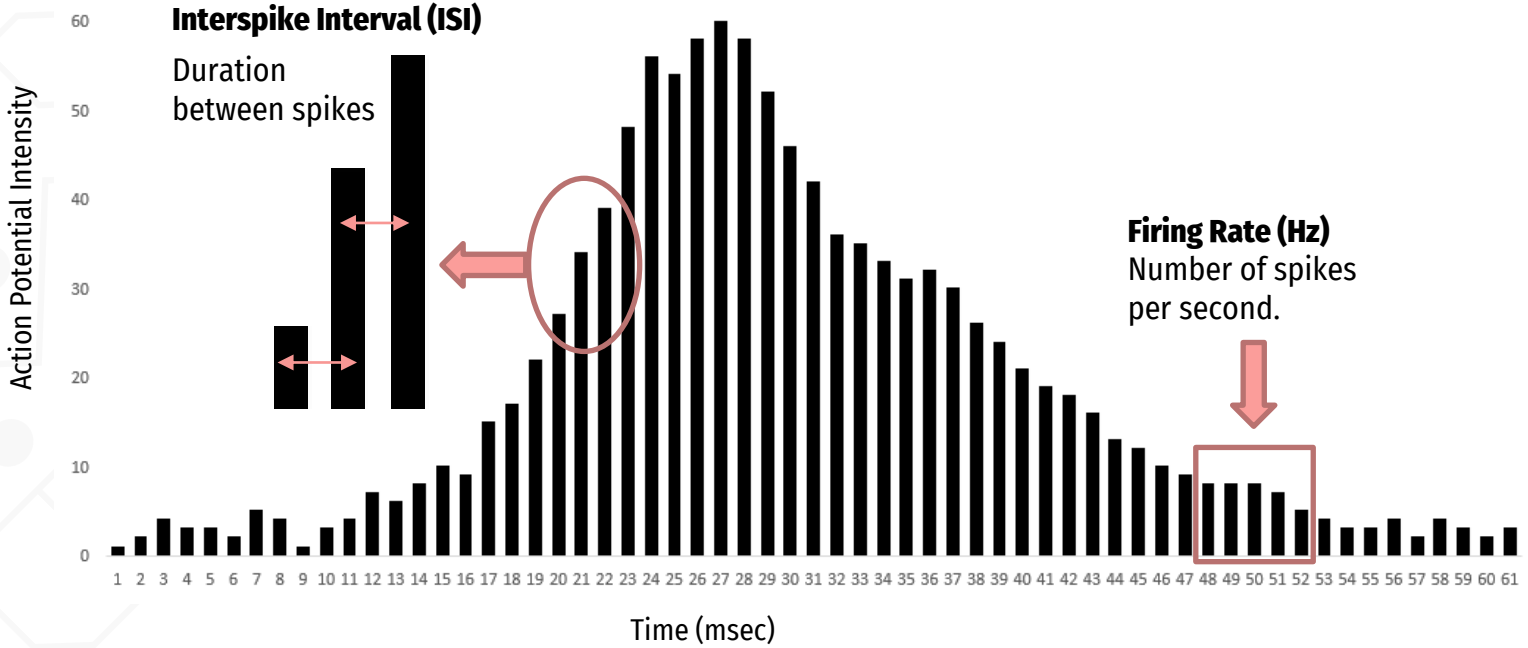
Electrophysiology Characterization.

Burst Duration

Duration of the burst

Interburst Interval (IBI)

Duration between bursts

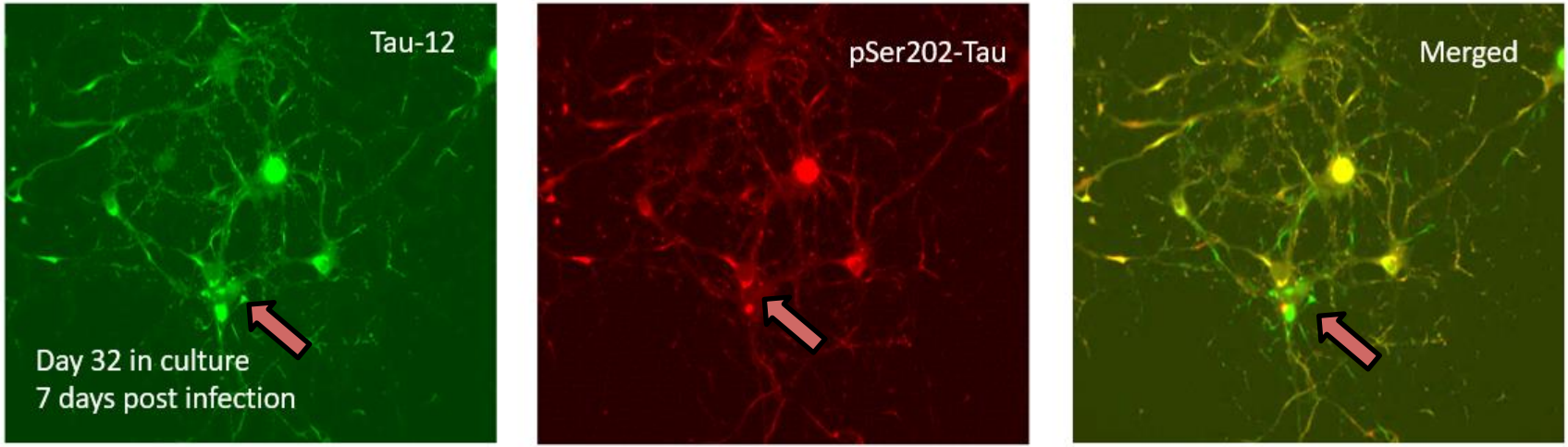


PLSF Lentiviral Construct.

Lentiviral construct containing the P301L and S320F mutations that creates tau aggregation.

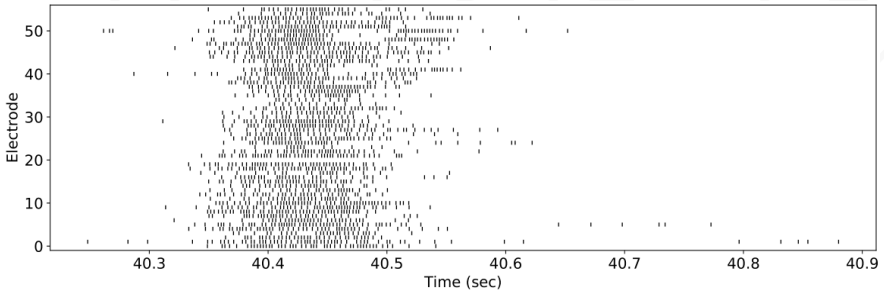
High infection rate (>95% within 5 days) quickly induces tau tangle-like aggregations.

Accumulation of tau aggregates at the synapse disrupts neuronal communication.

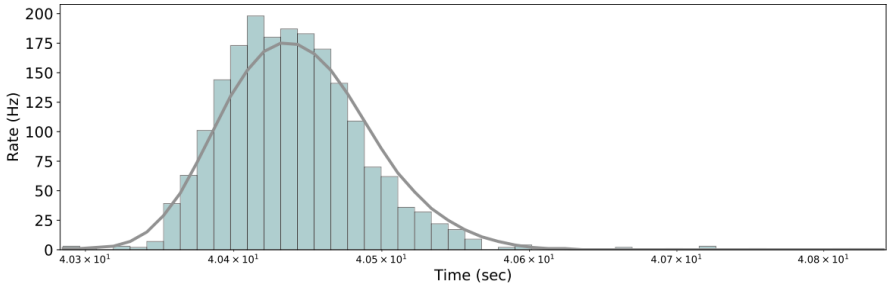


Healthy vs. Pathological Electrophysiology.

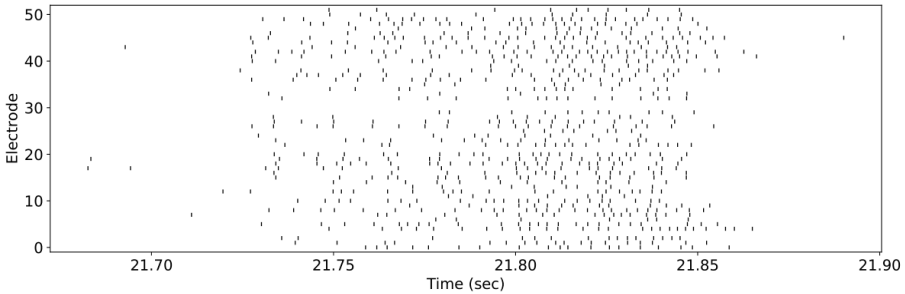
Normal burst



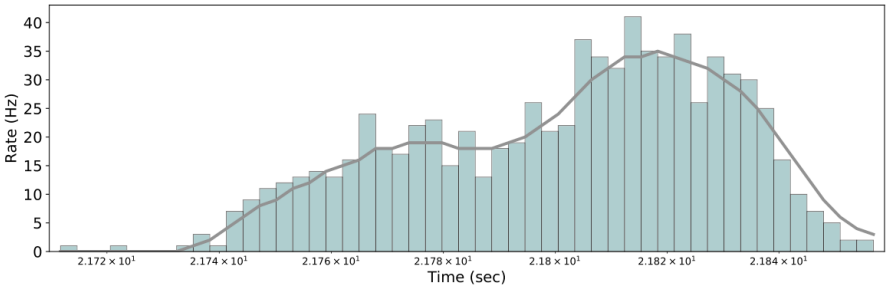
Tighter bursts, higher firing rates, low ISI and IBI.



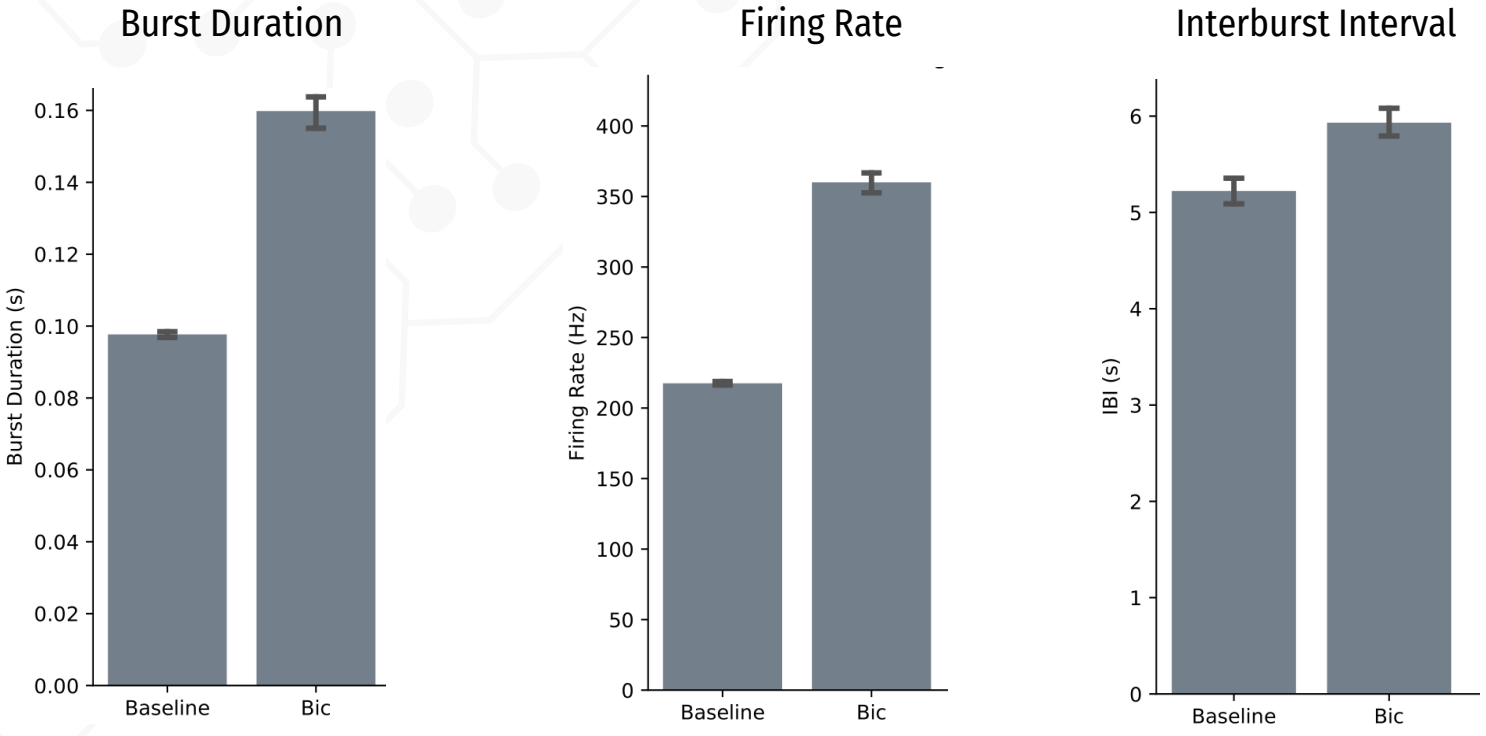
Abnormal tau



Disorganized bursts, reduced firing rates, higher ISI and IBI.



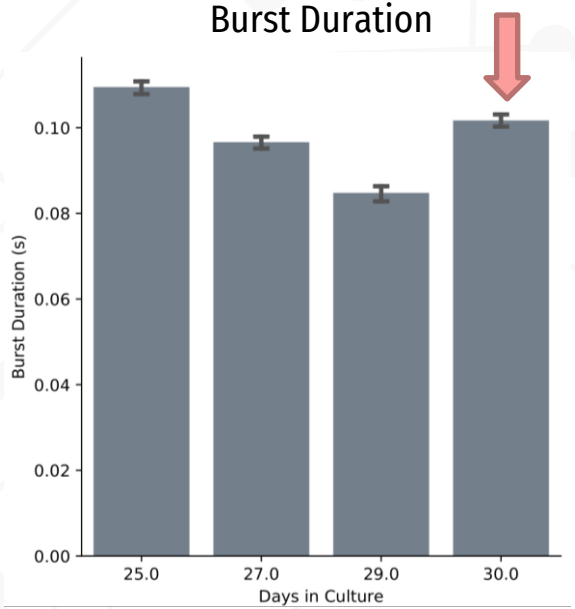
Neuronal Electrophysiology without Inhibition.



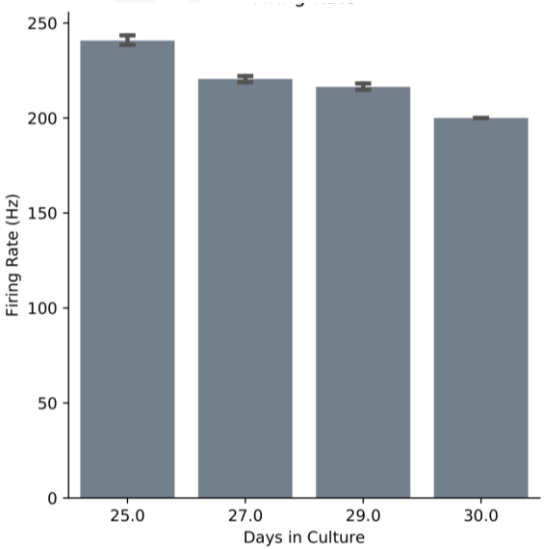
Neuronal Electrophysiology under Abnormal Tau.

Number of electrodes active on day: **25** (67.7%), **27** (74.8%), **29** (55.2%), and **30** (55.5%)

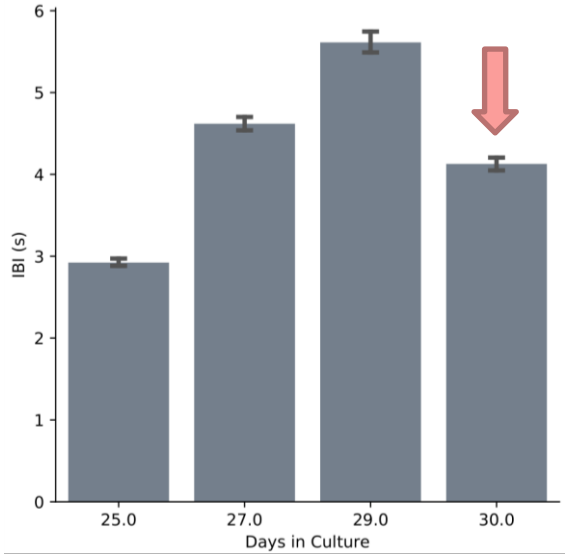
Burst Duration



Firing Rate



Interburst Interval

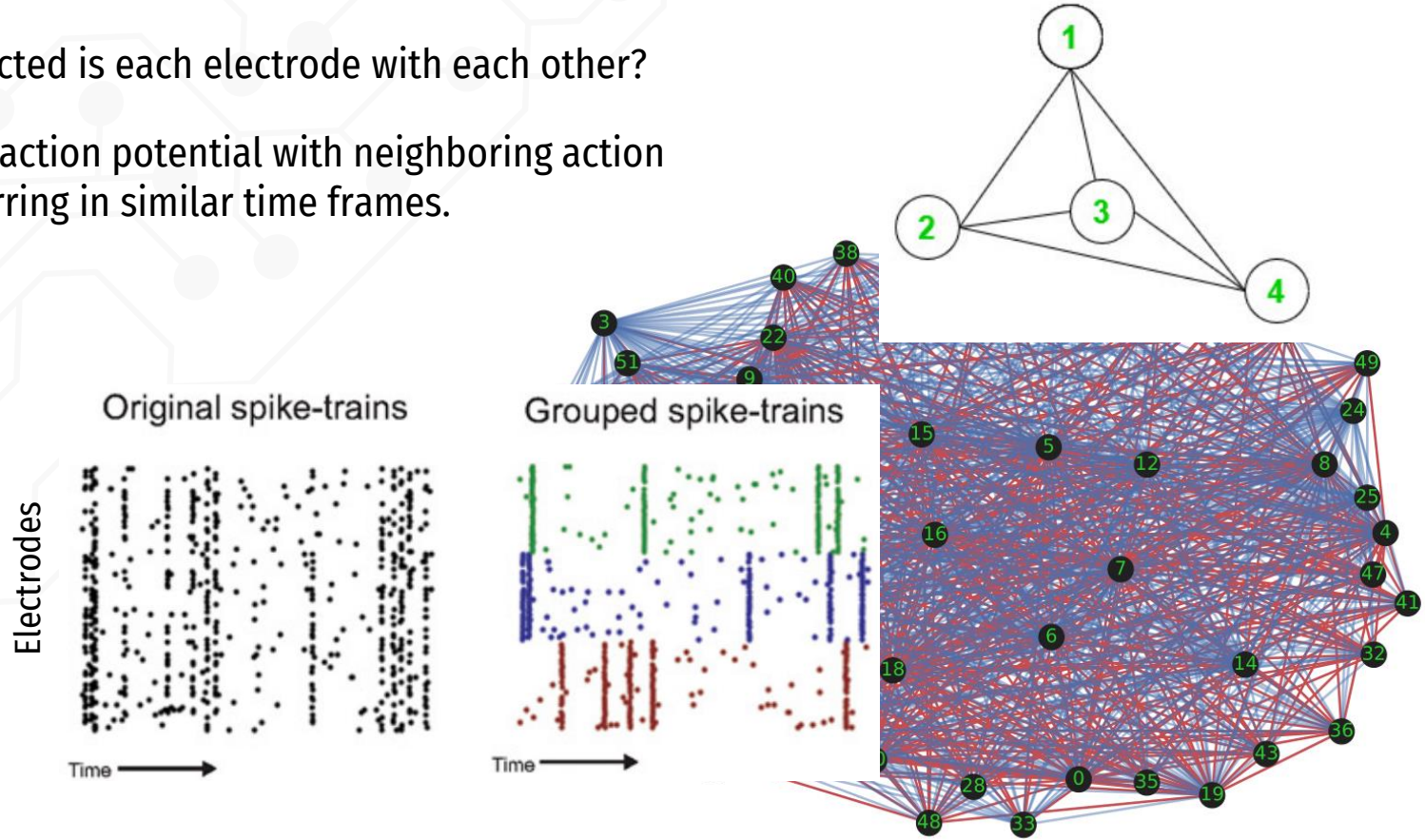


Abnormal tau pathology does not recapitulate GABAergic loss.

Network Communication: Node Degree.

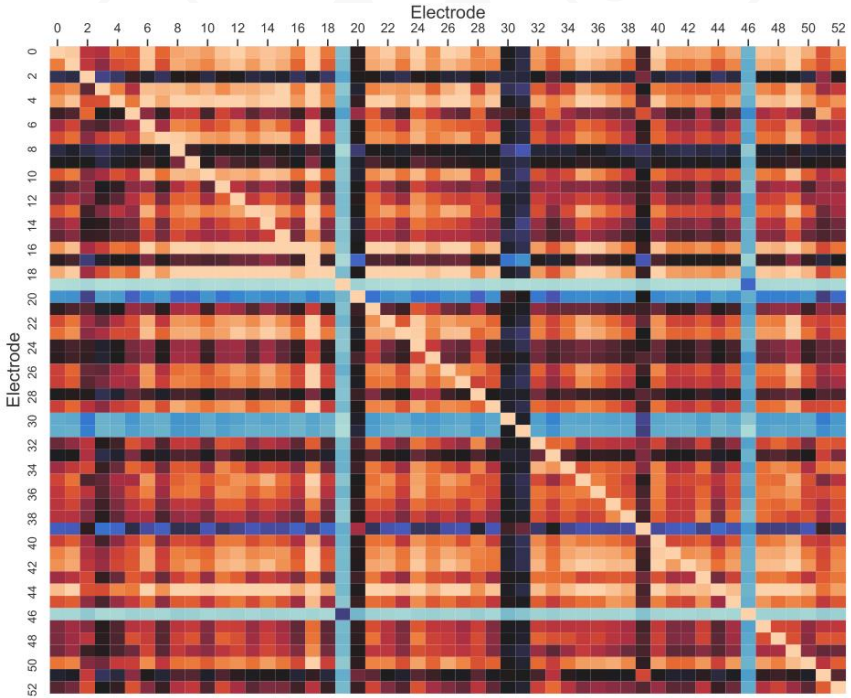
How well connected is each electrode with each other?

Compares each action potential with neighboring action potentials occurring in similar time frames.

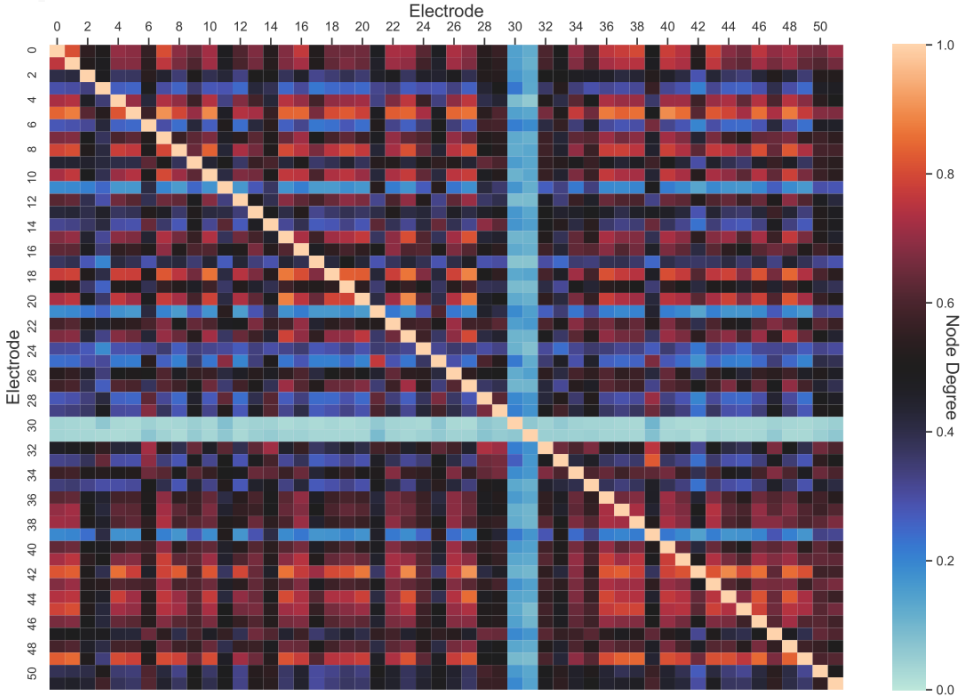


PLSF Node Degree.

3 days Post-Infection

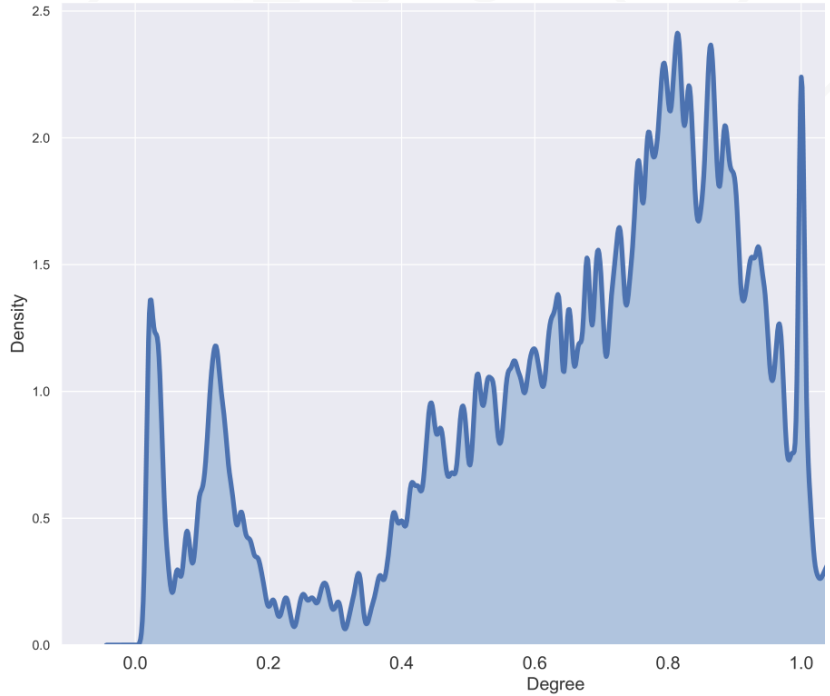


5 days Post-Infection

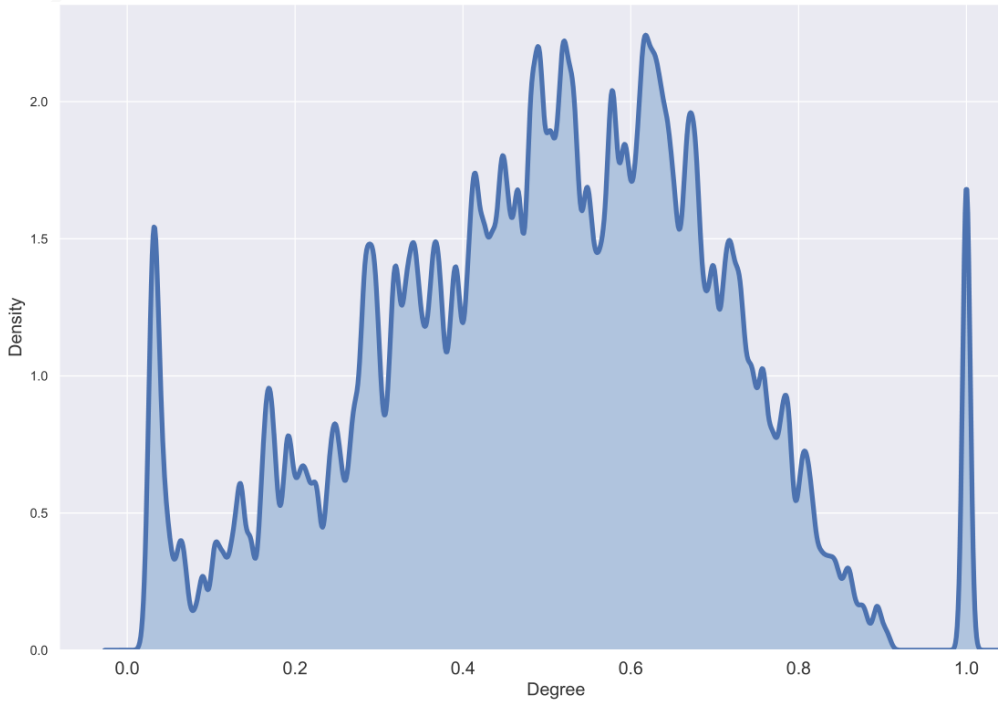


PLSF Node Degree.

3 days Post-Infection



5 days Post-Infection



Summary and Conclusion.

One of the first attempts to investigate AD pathogenesis on a network level.

Hyperexcitability of neurons may be caused by:

1. Excessive excitatory activity *or* 2. Absence of inhibitory activity

PLSF neurons did not exhibit enhanced excitatory activity, but showed deterioration of network communication.

Loss of excitatory activity rather than GABAergic neurons.

Activities of neurons under GABAergic inhibition do not recapitulate those of neurons under abnormal tau development.

Treatments designed to restore activity in AD patients will require more than correction of GABAergic activity.

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