Computational Studies of Hippocampal CA3 in Autism

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Contents

What Is Autism Spectrum Disorder?

1. Neurodevelopmental disorder, difficulties in socializing, repetitive behaviour.[1]
2. Spatial reasoning and episodic memory are commonly impaired in ASD.[2]
3. 1 in 44 US children has been identified with ASD
4. No standard treatments exist yet.

Goal of Research

To explore the role of hippocampal CA3 in ASD with an emphasis on ions channels and gamma oscillations using computational approaches

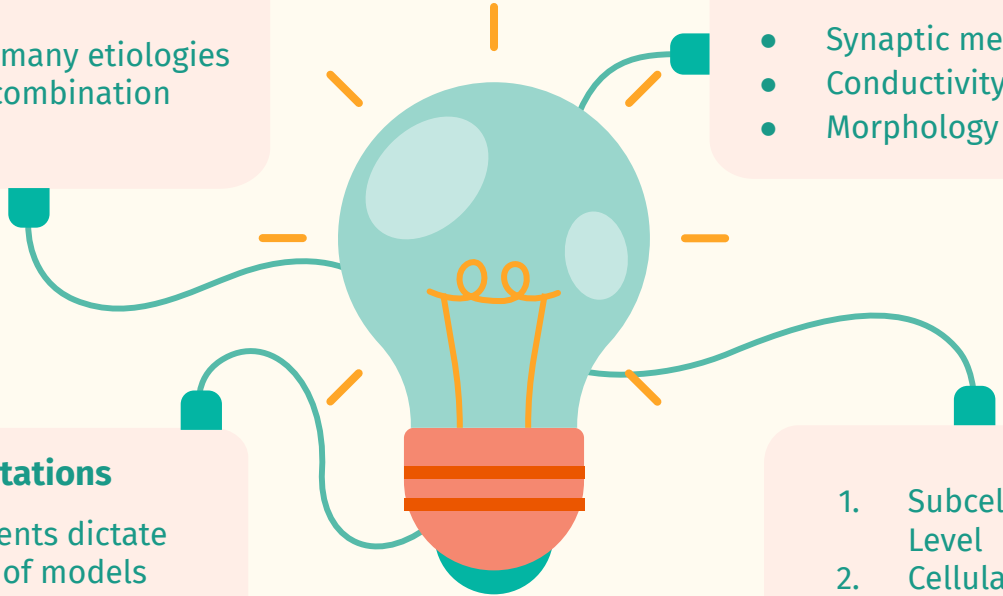
Crash Course Computer Modeling

Why use a computer model?

Able to evaluate ASD's many etiologies separately and in combination

Capable of Altering:

- Synaptic mechanisms
- Conductivity
- Morphology



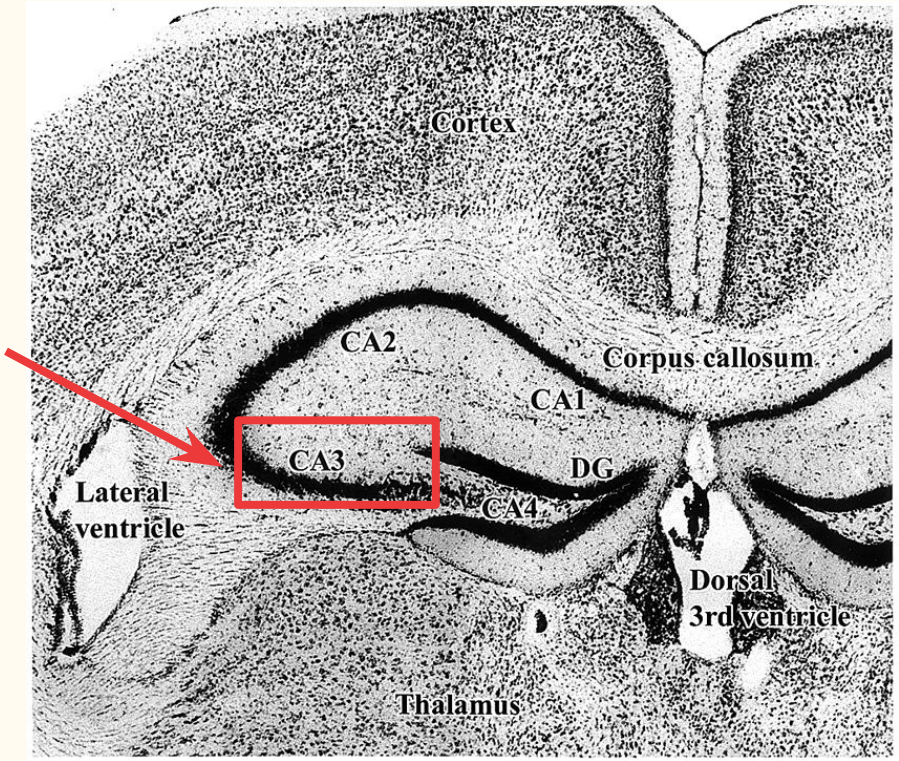
Limitations

Experiments dictate design of models

1. Subcellular Level
2. Cellular Level
3. Network Level

Hippocampal CA3

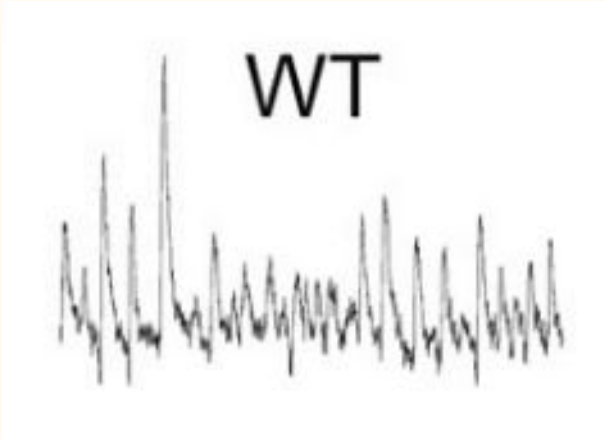
- Heavily studied in neurodegenerative disorders
- Cell excitability determined by ion channels
- Pyramidal cells project locally and across the hippocampal commissure.
- CA3 system is synchronously activated by recurrent, collateral connections



Wild type mouse Hippocampal CA3

Introducing Gamma

- Occurs in LFP throughout the brain, highly associated with hippocampus
- High frequency, rhythmic oscillations ranging from 30-90 Hz
- Hippocampal gamma is associated with consciousness, cognition, memory, and attentional processes



Hippocampal gamma oscillations

Knowns

Expression of ion channels determines cell excitability

Other animal models of ASD show disrupted gamma oscillations in hippocampus

Prevalence of epilepsy in ASD compared is much higher compared to general population.

Unknowns

What changes to the CA3 anatomy and physiology result in disrupted gamma oscillations and the emergence of epileptic seizures in ASD?

What do gamma oscillations look like in the CA3 region of BTBR mice?

Hypotheses

01

In line with previous research in other ASD mouse models, we expect reduced gamma oscillations would be observed in the hippocampal CA3 of the BTBR mouse model.

02

Manipulating HCN channels will lead to a pathophysiological CA3 function.

Specific Aims

SA 1: Replicate pathological changes to HCN channels in single pyramidal cells using experimental data from *Fmr1* KO mice

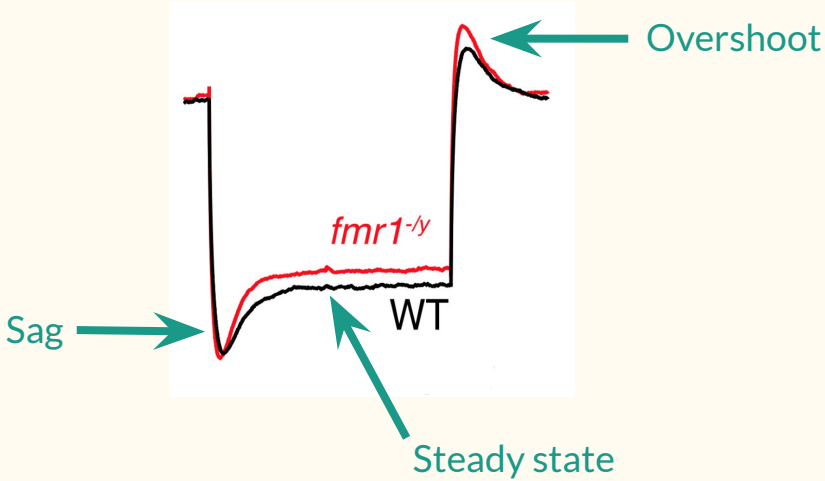
SA 2: Investigate the effects of pathological changes to HCN channels on the CA3 network

SA 3: Record and analyze gamma oscillations in the CA3 of BTBR mice vs. Wild Type control

SA1: Manipulating channels in a single pyramidal cell

Cell Excitability

- Ion channels like HCN determine intrinsic excitability
- HCN are non-selective ion channels
- In mouse model of Fragile X, HCN channels are elevated
- Atypical concentration of HCN has been linked to cognitive impairment, and incidences of epilepsy

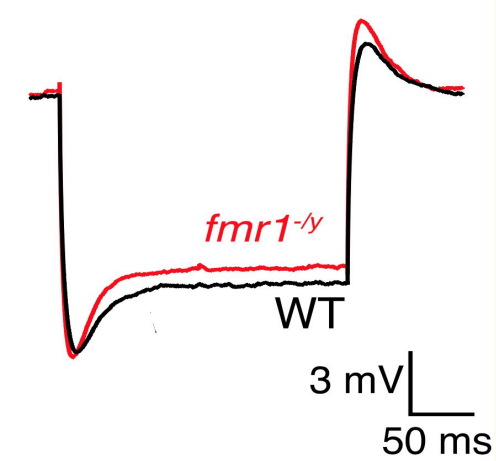


Methods

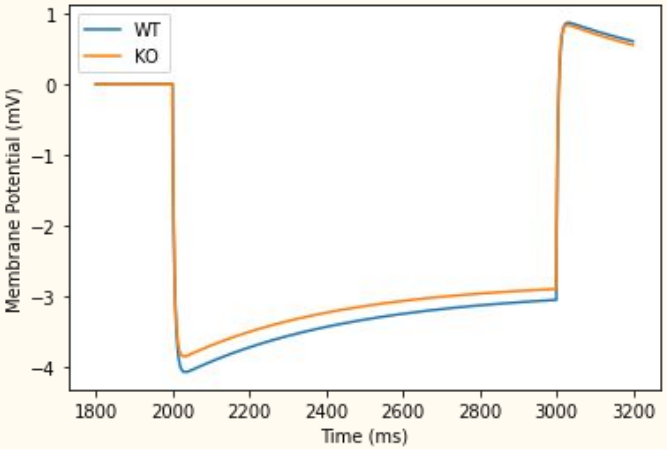
1. Adjusted concentration and subtype of HCN in model pyramidal cell
2. Stimulate single cell using hyperpolarizing and depolarizing step currents
3. Recorded voltage of single cell at both the soma and apical dendrites after applying currents
4. Compared with experimental data

Changing Cell Excitability

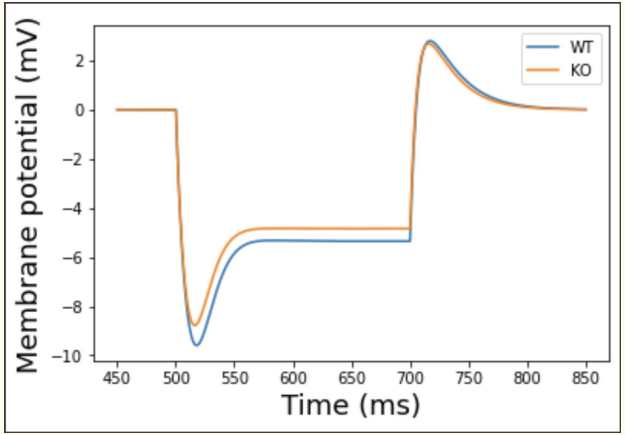
Mouse Model



Comp. Model Simulations



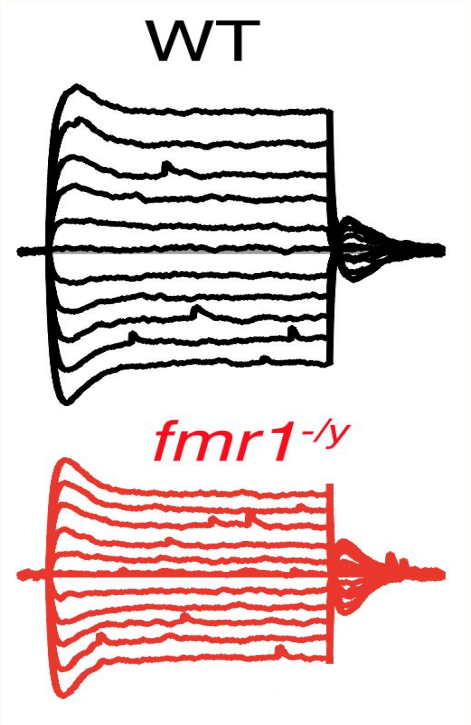
Increased concentration of **HCN2** in Apical Dendrites



Reduced concentration of **HCN1** in Apical Dendrites

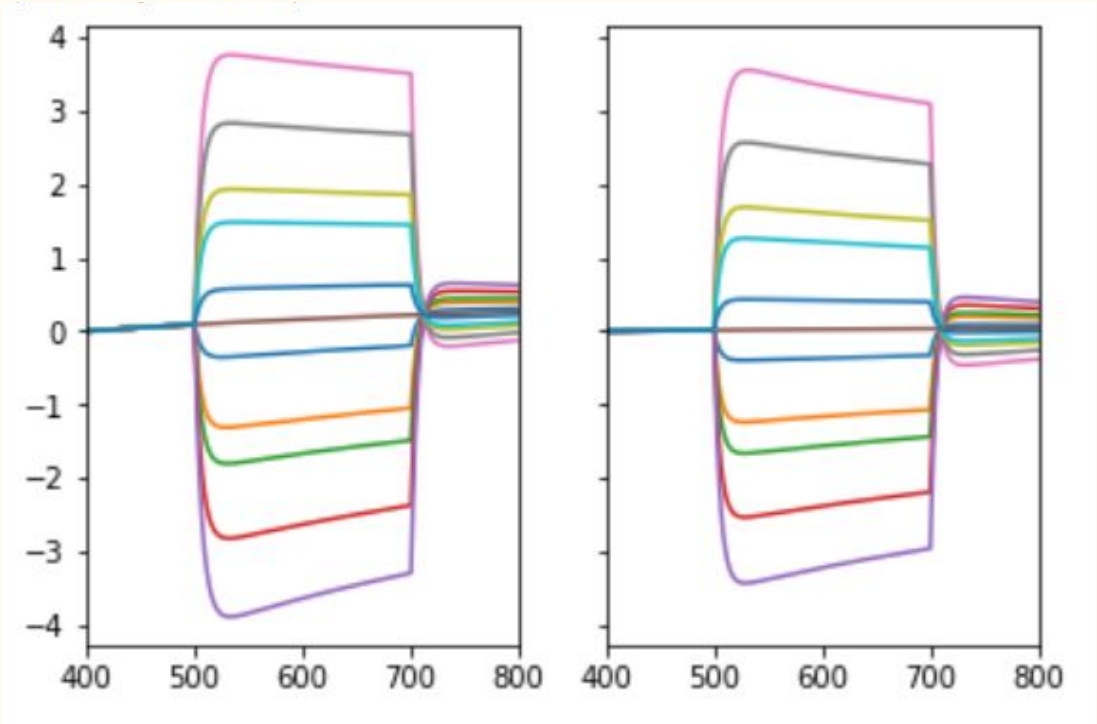
Changing Cell Excitability

Experiment



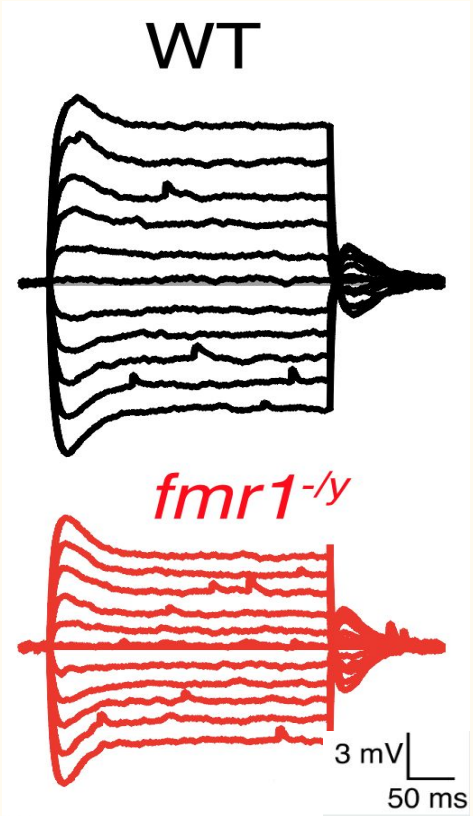
Simulations

WT **ASD**

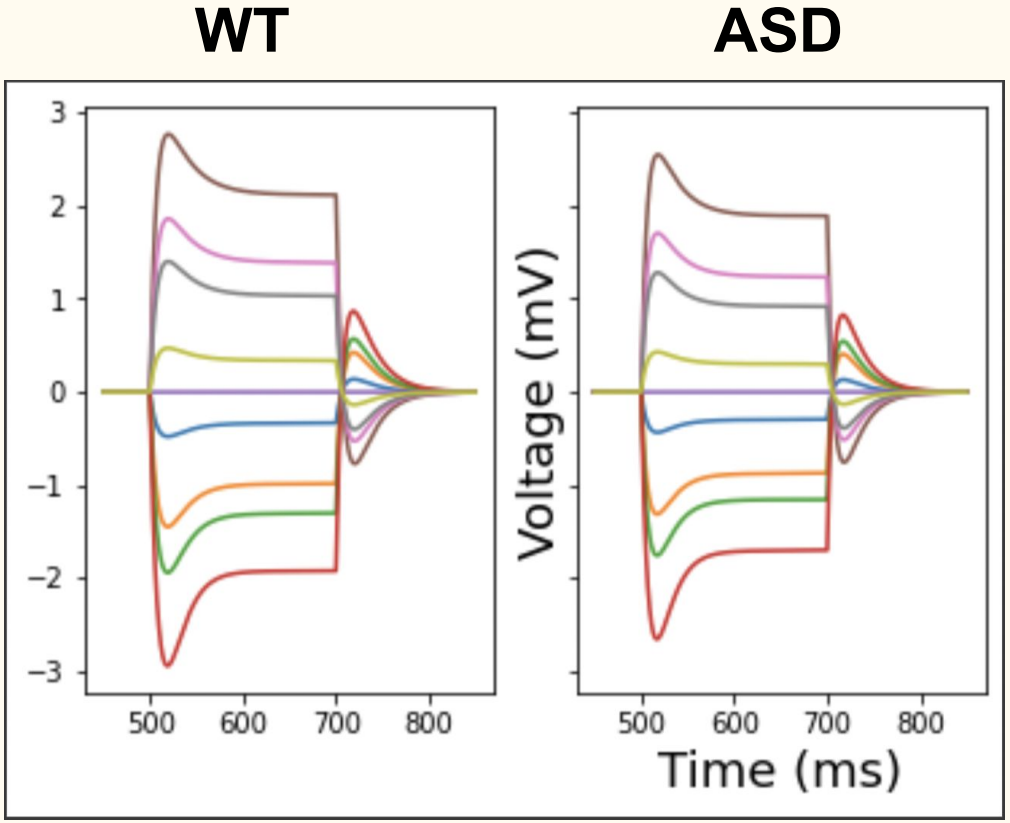


Changing Cell Excitability

Experiment

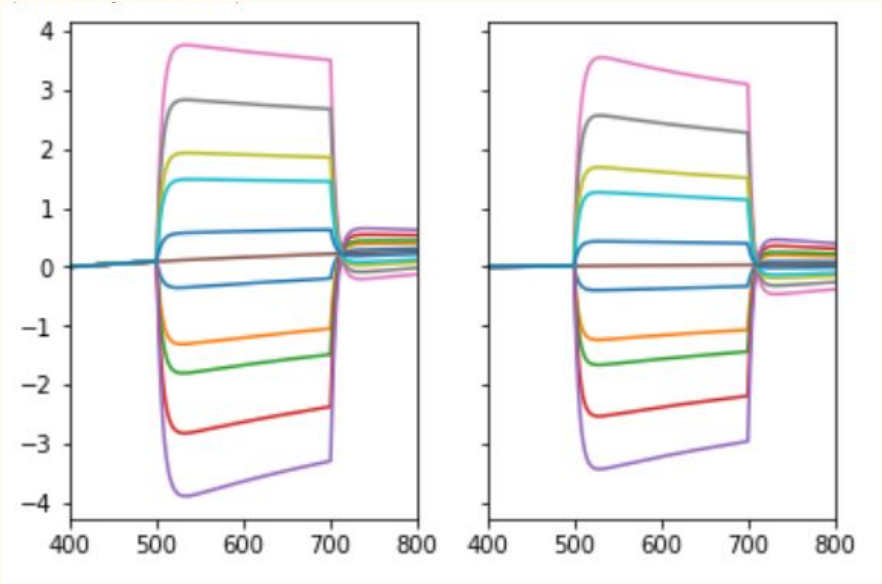


Simulations



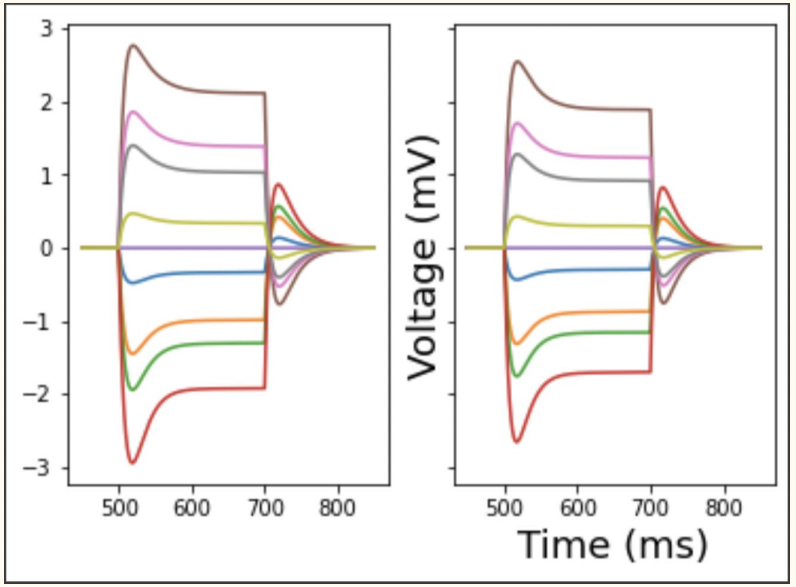
Changing Cell Excitability

WT ASD



HCN2

WT ASD



HCN1

SA2: Determine how changes in HCN affect activity throughout CA3 network

- Concentration and subtype of HCN channels affects firing rate of local cells

- Using synaptic mechanisms from previous studies, and changes to HCN from previous model, CA3 network model produced physiological results

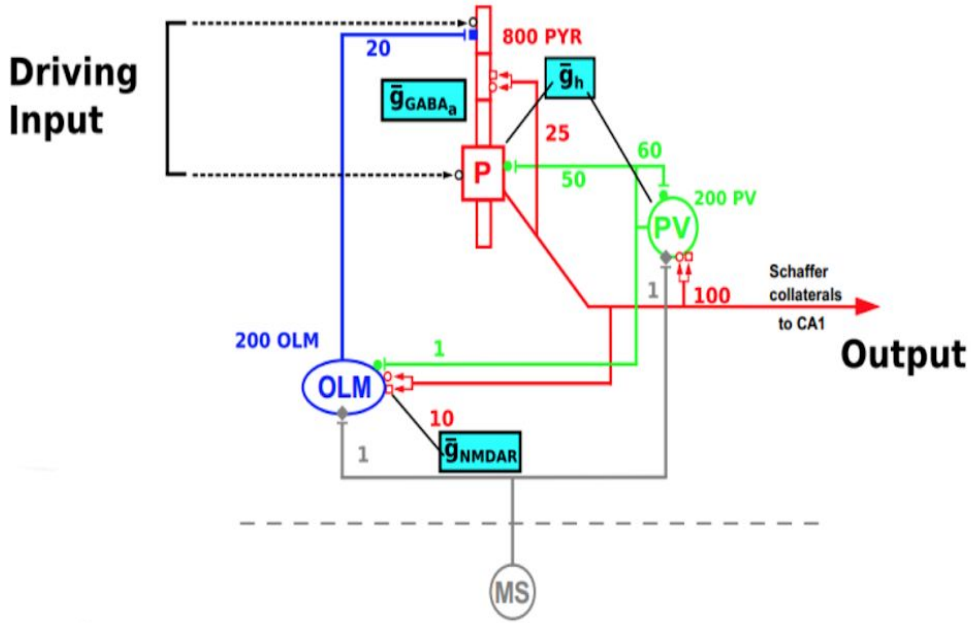
CA3 Circuit Schematic

Receptors
(activation, inactivation time constants)

$GABA_{a_{fast}}$	●	0.07, 9.1 ms
$GABA_{a_{slow}}$	■	0.2, 20 ms
$GABA_{a_{veryslow}}$	◆	20, 40 ms
AMPA	○	0.05, 5.3 ms
NMDA	□	15, 150 ms

→ Excitatory input

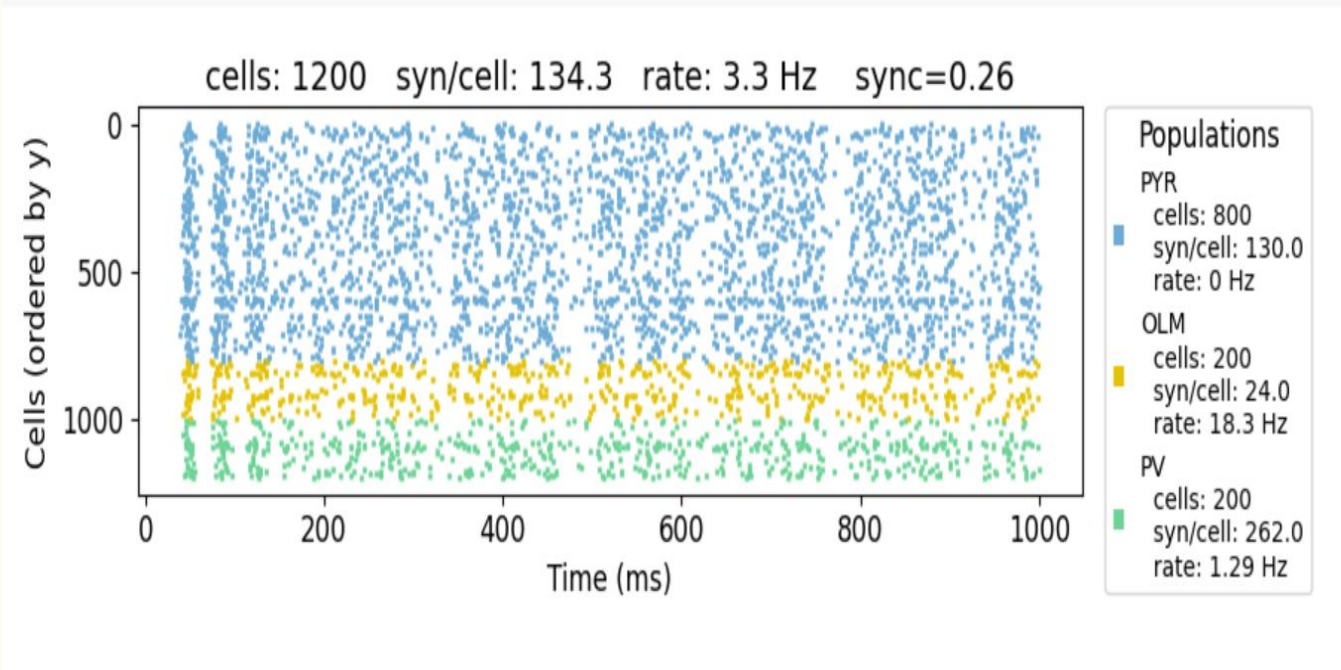
⊣ Inhibitory input



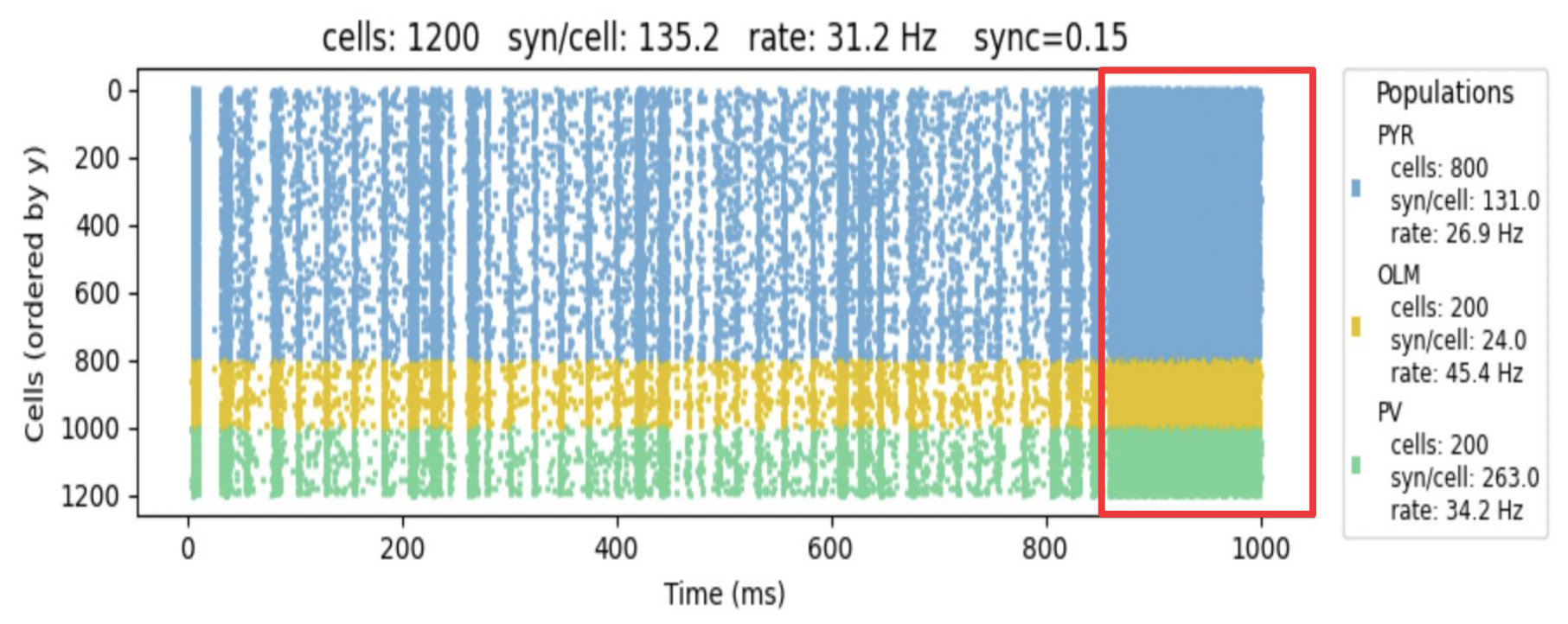
Methods

1. Ported existing model from NEURON to NetPyNE
2. Applied same changes made to HCN from previous model
3. Switched built-in synaptic mechanisms to custom mechanisms from the original model
4. Ran simulation and observe neuronal activity

Physiological Network Activity After Applying Background Stim Sources, switch to HCN1 Model



Seizure Activity by manipulating HCN1 based on FMR1 KO



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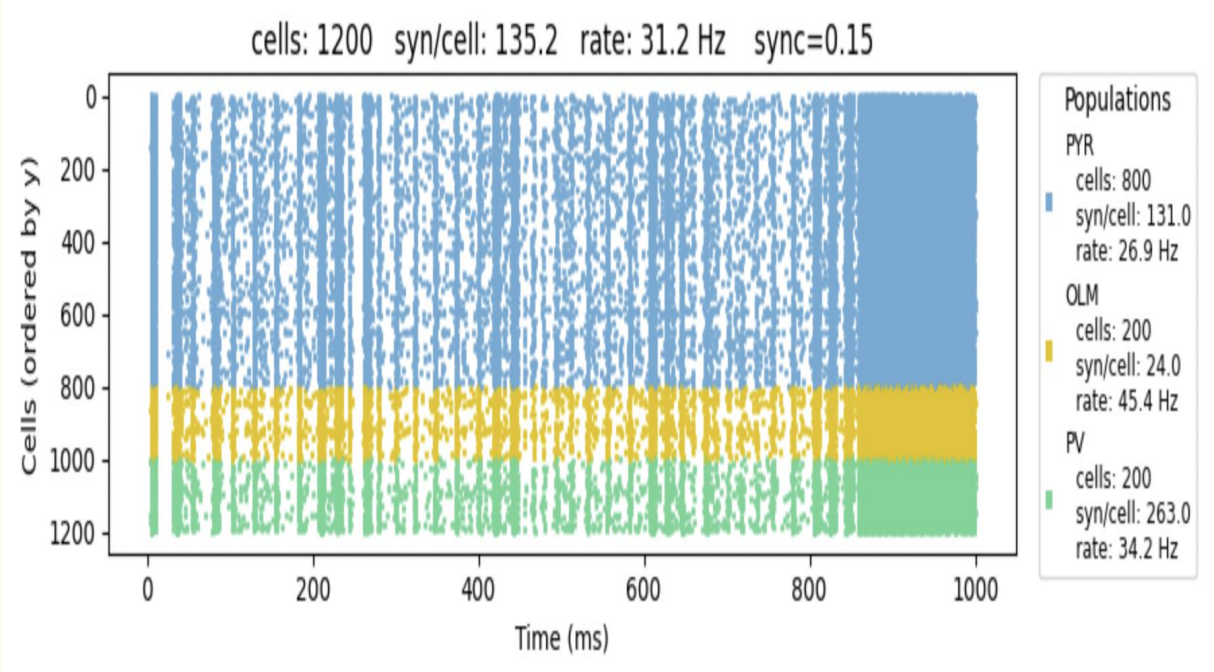
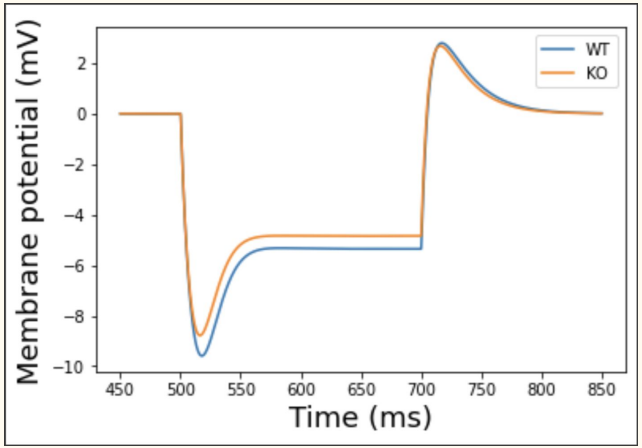
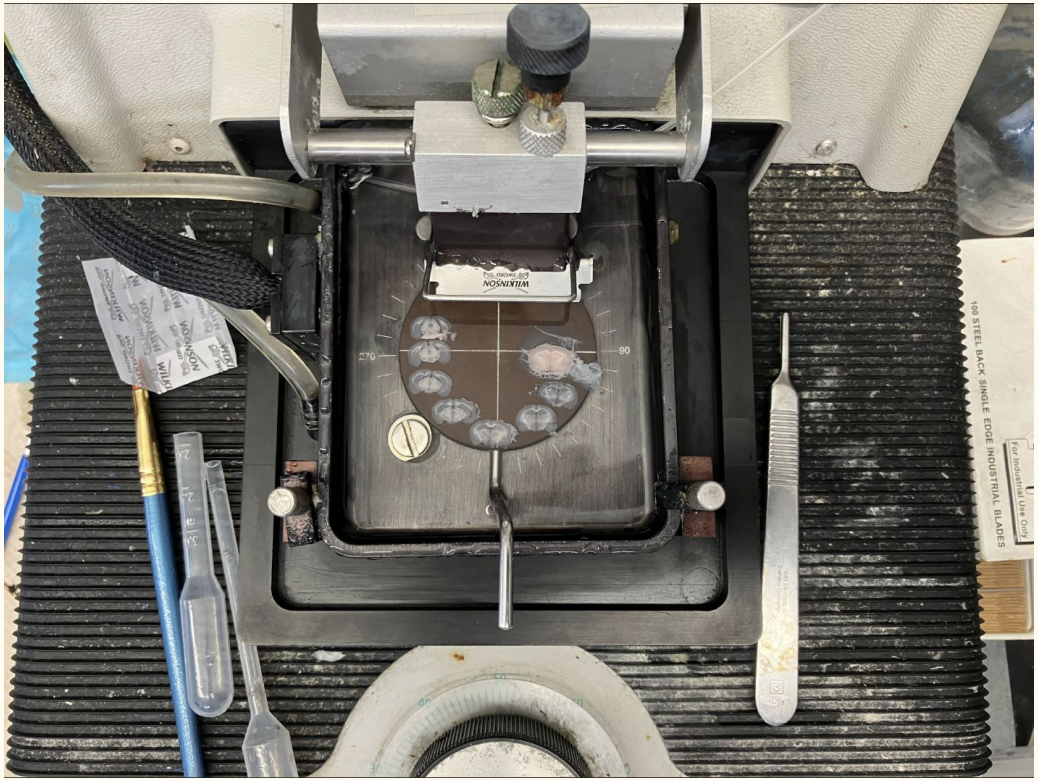
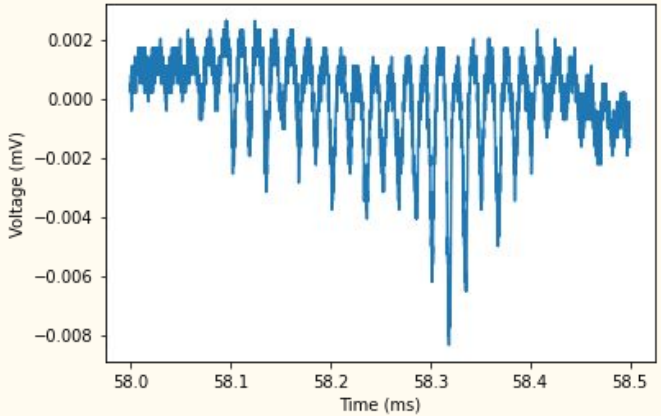




SA3: Record and compare gamma oscillations from BTBR and Wild Type mice

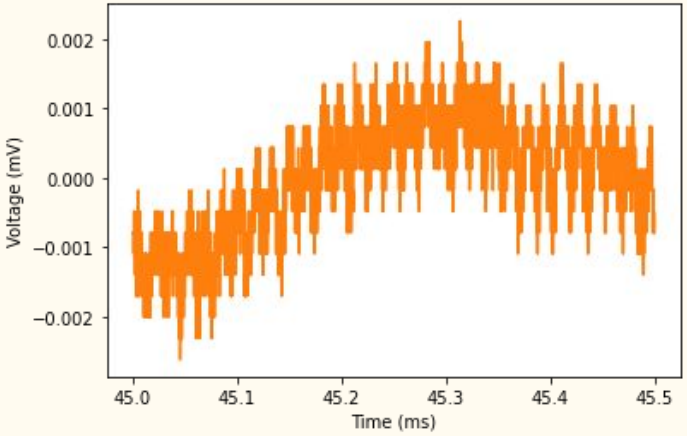


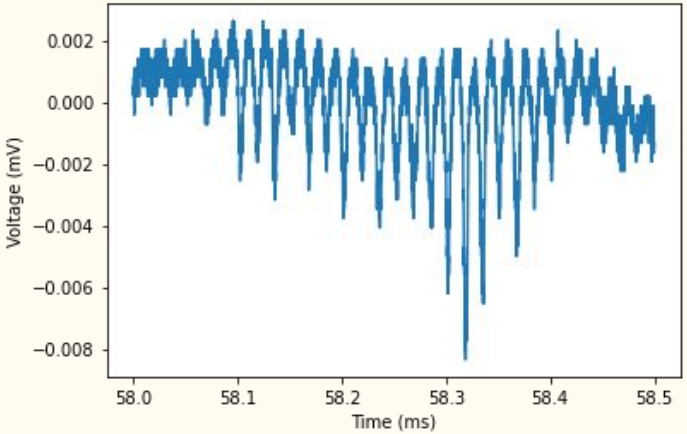


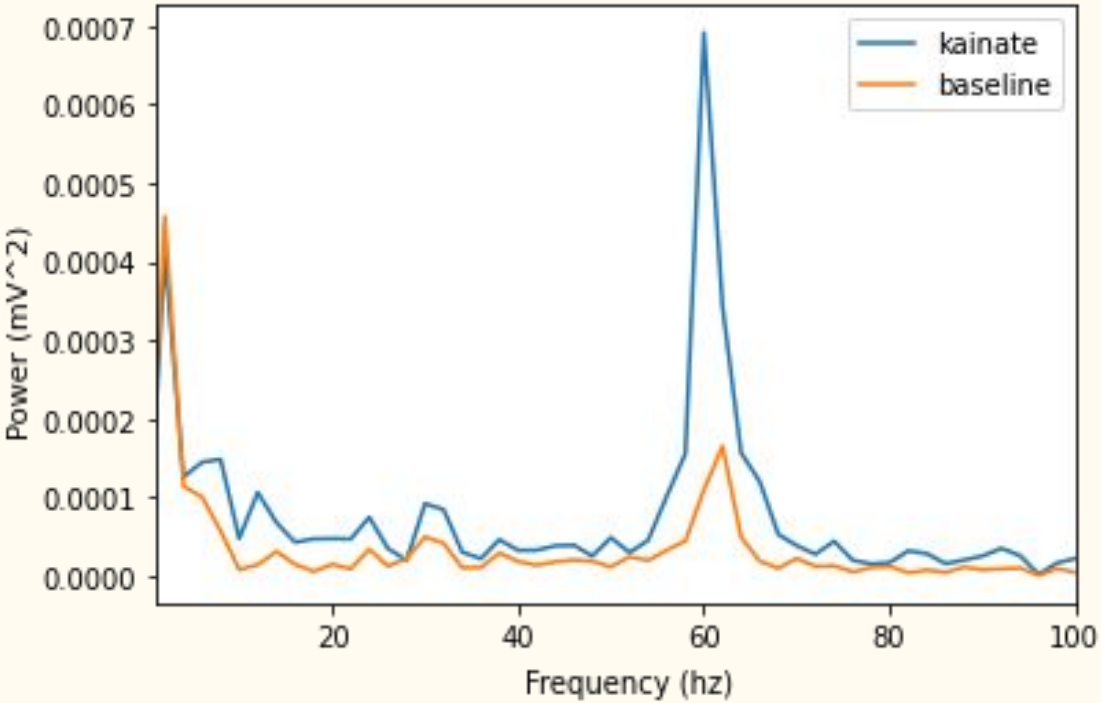
Methods

1. Obtained brain slices of both BTBR and WT control mice
2. Placed slices into the electrophysiology rig
3. Recorded activity in LFP of CA3 region of each slice and establish baseline
4. Applied 1 μM of kainic acid
5. Recorded activity in CA3 and observe findings for any occurrences of kainate induced high-frequency activity within LFP
6. Used gathered traces to compare gamma oscillations between BTBR and WT mice

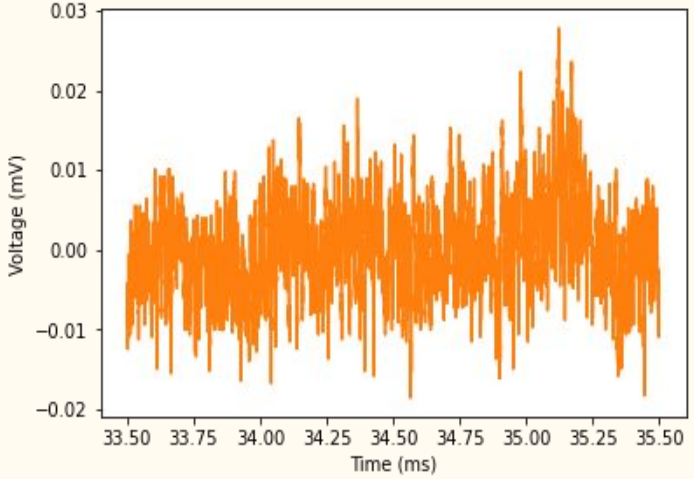
Baseline and Kainate Induced Activity in C57BL WT Mice

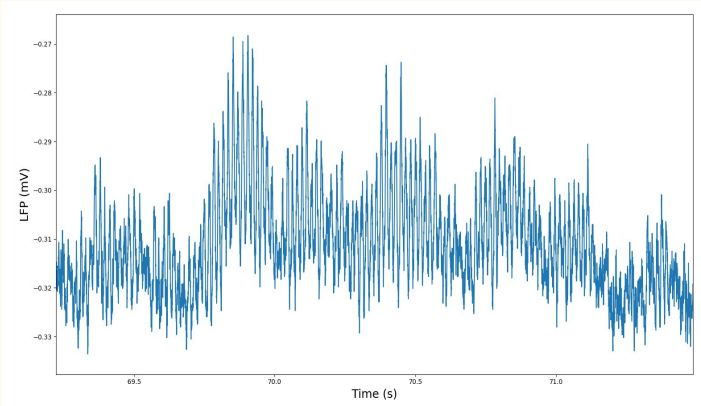


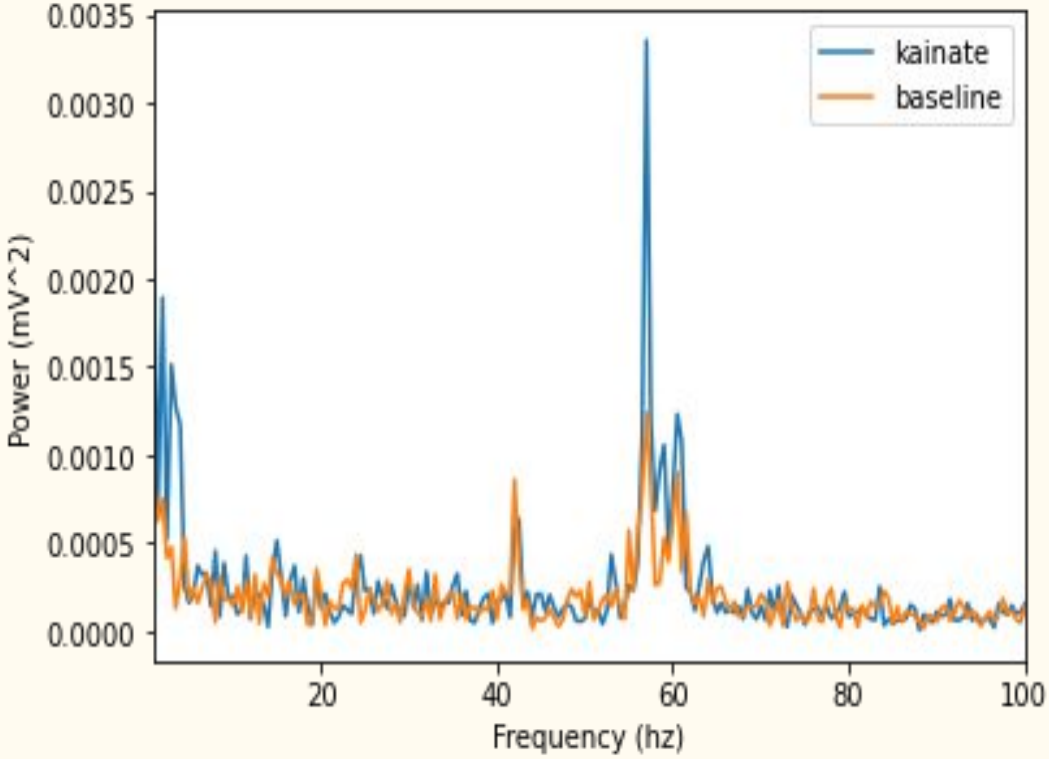




Baseline and Kainate Induced Activity in BTBR Mice



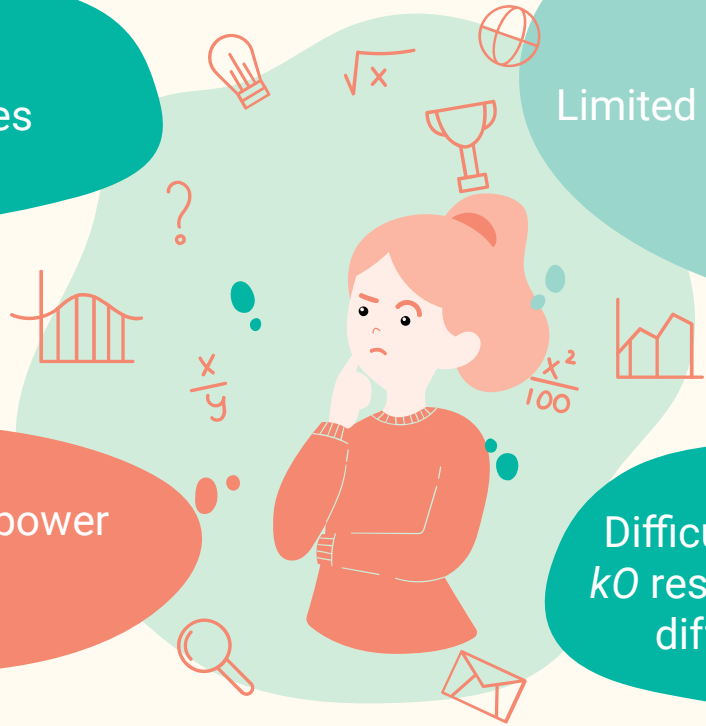




Roadblocks

Cross platform compatibility issues

Limited number of brain slices

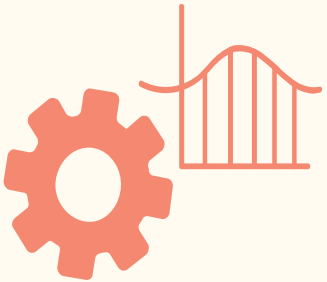


Computational power issues

Difficulty reproducing *fmr-1 kO* results due to interplay of different ion channels

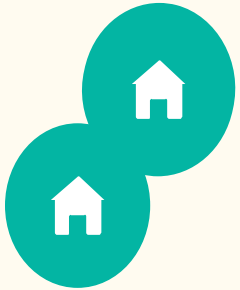
Significance

Computer



Bench

Bedside



Understanding the mechanisms of ASD symptoms beyond behavioral deficits can allow scientists to identify new pharmacological targets for ASD.

Future Steps

1. Manipulate synaptic strengths in CA3 model
2. Double CA3 Network and investigate effects of subcellular manipulations on left-right coupling model
3. Take recordings from more brain slices
4. Record LFP CA3 of left and right hippocampus simultaneously because of asymmetry in both humans and BTBR mouse (reduced hippocampal commissure)
5. Develop tools to determine the frequency and likelihood for gamma oscillations to occur

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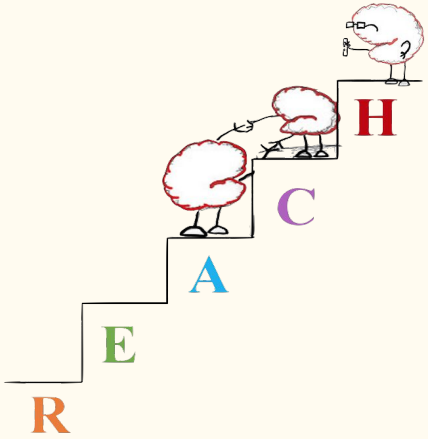

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