Modeling the Effect of D4R Agonists on Gamma Power and Schizophrenic Symptoms

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Introduction

- **Schizophrenia** is a mental disorder characterized by episodes of psychosis, including hallucinations and delusions.
- Schizophrenic symptoms are associated with dysfunctions of the dopaminergic pathway.
- While most research focuses on the dopamine D2 receptor, recent studies show potential involvement of **D4 receptors (D4Rs)** in schizophrenia via interaction with **NMDA receptors (NMDARs),** which are involved in schizophrenia.
- We study the effects of **D4R agonists** on **low gamma power** (30-40 Hz). Resting gamma power tends to be higher in schizophrenic patients.

Our goal was to determine the efficacy of D4R antagonism as a potential schizophrenia treatment.

Methods

1. Modified a Python NEURON[4] model of the **hippocampal CA3 region** in a schizophrenic individual.
   - Simulates 1200 CA3 neurons including: *a*) 800 pyramidal cells, *b*) 200 PV basket cells, and *c*) 200 oriens-lacunosum moleculare cells.
2. **Scaled conductance** (and thus currents) of NMDARs on pyramidal (PYR) neurons.
   - Decreased conductance between 0.1x to 1x the control simulation to simulate D4R agonism.

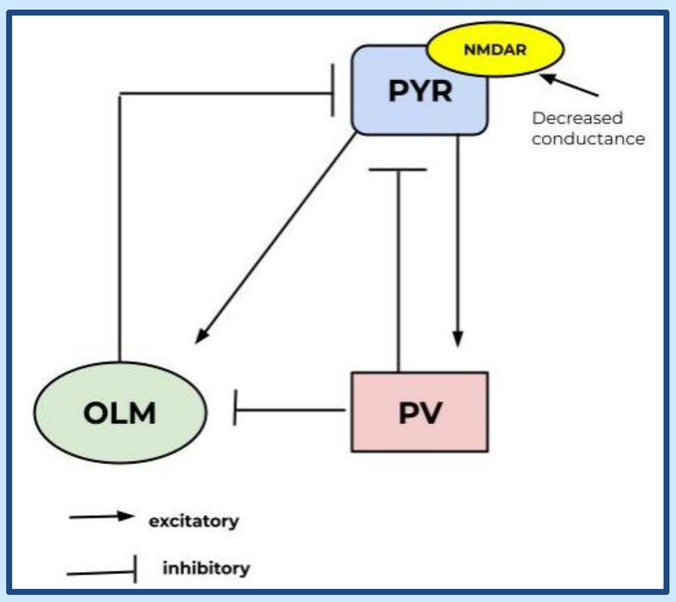

Figure 5. Schematic diagram showing targets for simulated D4R agonism.

1. Ran 1 trial for the model without the agonist and 5 trials with the agonist.
   - Measured **gamma power** for each trial.
     - low gamma: 30 to 40 Hz
     - medium gamma: 45 to 60 Hz
     - high gamma: 65 to 90 Hz

Results

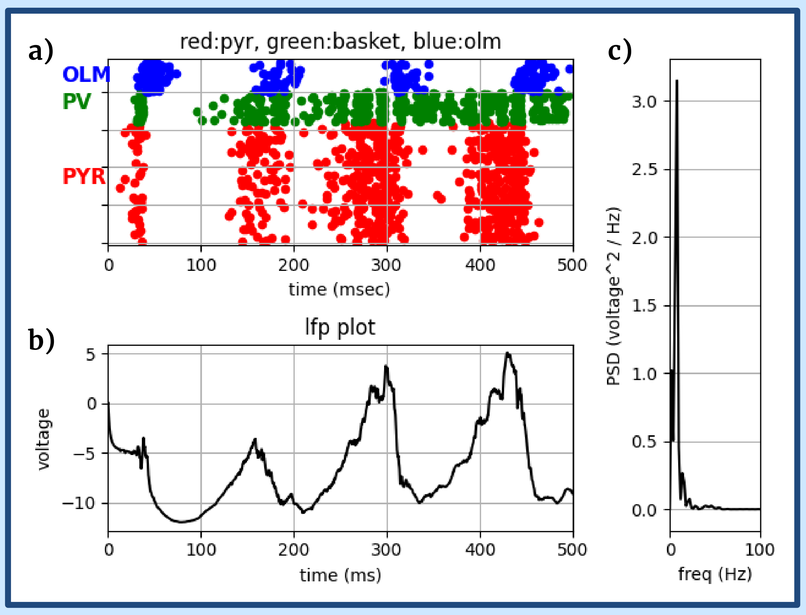

Figure 1. Baseline simulation rhythm. a) Raster plot where each row represents a neuron and each dot represents an action potential. b) Simulated local field potential (LFP). c) Power spectral density (PSD) of LFP.

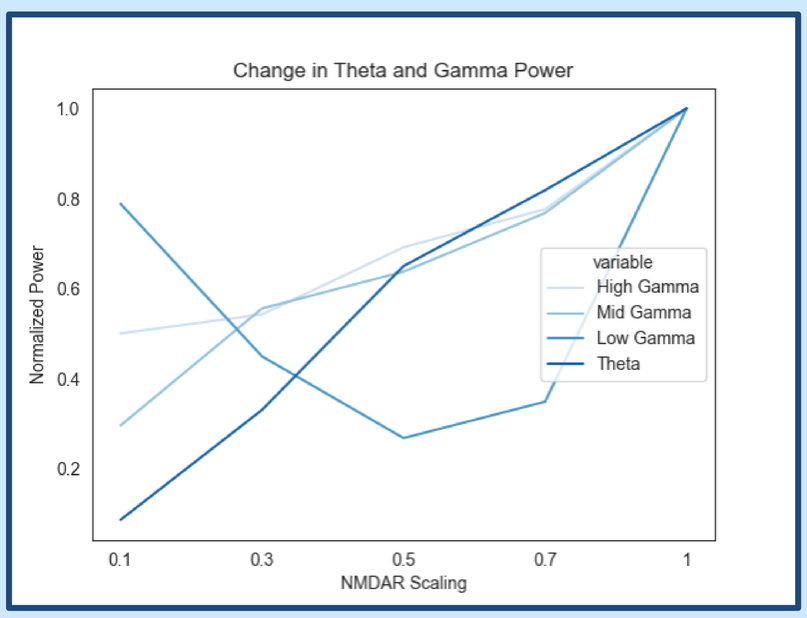

Figure 2. Change in theta and gamma power after scaling NMDAR conductance of Pyramidal cells in proportion to the control simulation.

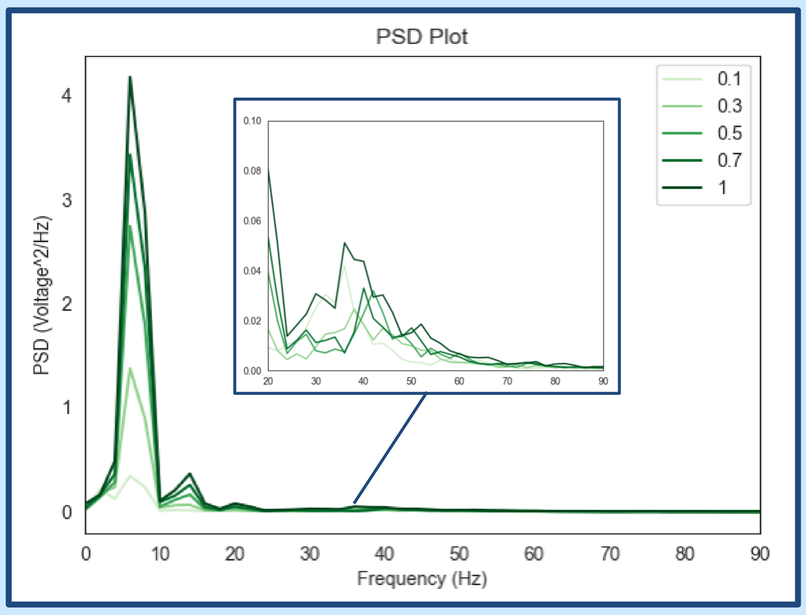

Figure 3. Power Spectral Density (PSD) graph.

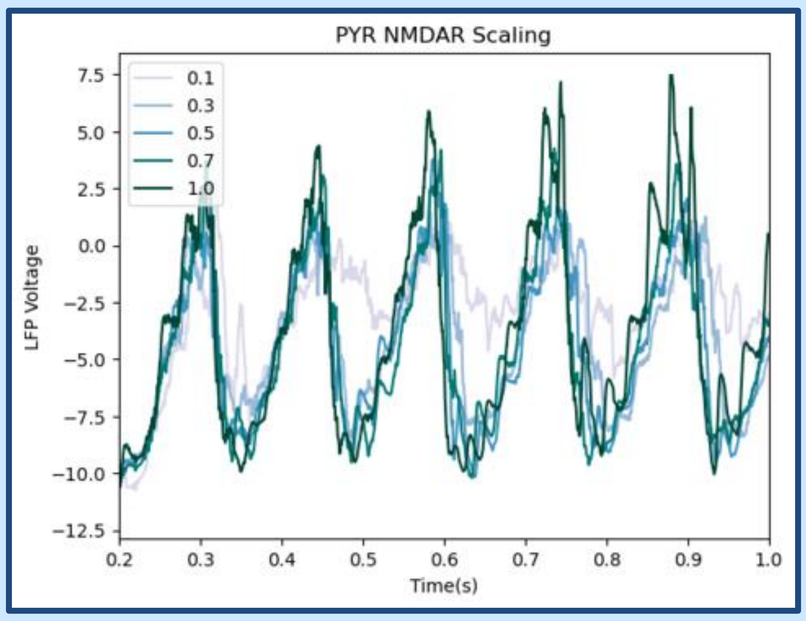

Figure 4. Change in Local Field Potential (LFP) voltage over time after scaling NMDAR conductance.

Discussion

- Clinical studies correlate D4R agonism with increased low gamma power, associated with increased schizophrenic symptoms.
- Our model indicates that **D4R agonism,** as simulated by a decrease in NMDAR scaling, **may increase or decrease low gamma power depending on the existent NMDAR current.**
- If the average schizophrenic patient lies between 0.1-0.5 on our NMDAR scaling, then **D4R agonism would cause a relative increase in low gamma power.**
- However, if the average schizophrenic patient is greater than 0.5 on our NMDAR scaling, **D4R agonism would decrease low gamma power**, contradicting previous studies.

Future Research:

- Better correlate the model with EEG data of schizophrenic patients to **increase clinical relevance and study schizophrenic symptoms.**
- Study the **direct impact** of adding a D4R on low gamma power.

Limitations:

- By indirectly simulating the addition of D4Rs through NMDAR modification, we ignore other possible D4R pathways.
- The model simulates neural activity of the average schizophrenic patient, which **excludes true variability amongst patients.**

References

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