Investigating the Neural Consequences of Gut Microbiome Dysbiosis in Huntington's Disease

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Introduction

- **Huntington's Disease (HD):** A progressive, hereditary neurodegenerative disorder often characterized by abnormal neural firing and burst activity.
- **Gut Microbiome Dysbiosis:** An imbalance in the composition of the different microorganisms present in the human gut (HD is often associated with gut dysbiosis despite being studied primarily as a brain disease).
- **Gut-Brain Axis (GBA):** A bidirectional communication network between the gastrointestinal tract and the central nervous system (CNS).
  - The specific mechanisms through which gut dysbiosis in HD patients affect cognitive symptoms remain unknown and understudied.
- This project aims to quantify the effects of HD gut dysbiosis and determine which of four proposed mechanisms are most impactful in HD neuron firing rate and time.
  - The mechanisms studied are inflammation, BDNF-induced plasticity loss, metabolic stress, and neurotransmitter loss.
- Understanding gut dysbiosis in HD could reveal new therapeutic targets to alleviate symptoms or slow disease progression.

Methods

- Modified a mean-field rate model to simulate healthy and HD conditions. (Gambazzi et. al, 2010)
  - Incorporated the four aforementioned gut dysbiosis mechanisms.
- Stimulated mechanisms by adjusting synaptic noise and efficacy, connectivity, and time constants (e.g., depression, adaptation).

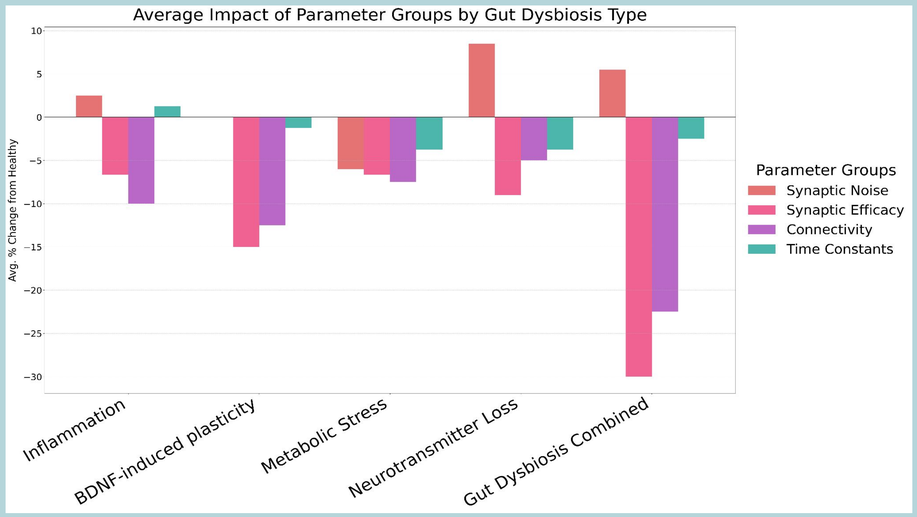

Fig. 1 Summary of Gut Dysbiosis Changes

- The model simulated the **mean firing rate** and **inter-burst intervals (IBIs)** over 100,000 ms (10 seconds), which were compared across all conditions using **two-tailed t-tests** *(Fig. 2 and 3)*.
- A **variance-based Sobol sensitivity analysis** was performed for each condition.
  - **Total-order Sobol indices** (ranging from 0 to 1) quantified how much each parameter group contributed to the variance in firing rate.

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Results

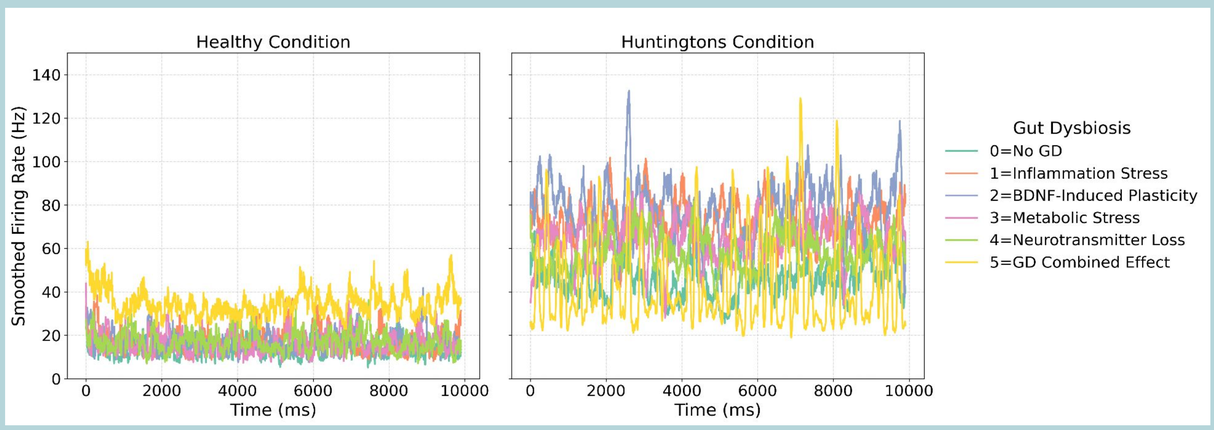

Fig. 2 Mean Neuron Firing Rate over time in Healthy and HD Models

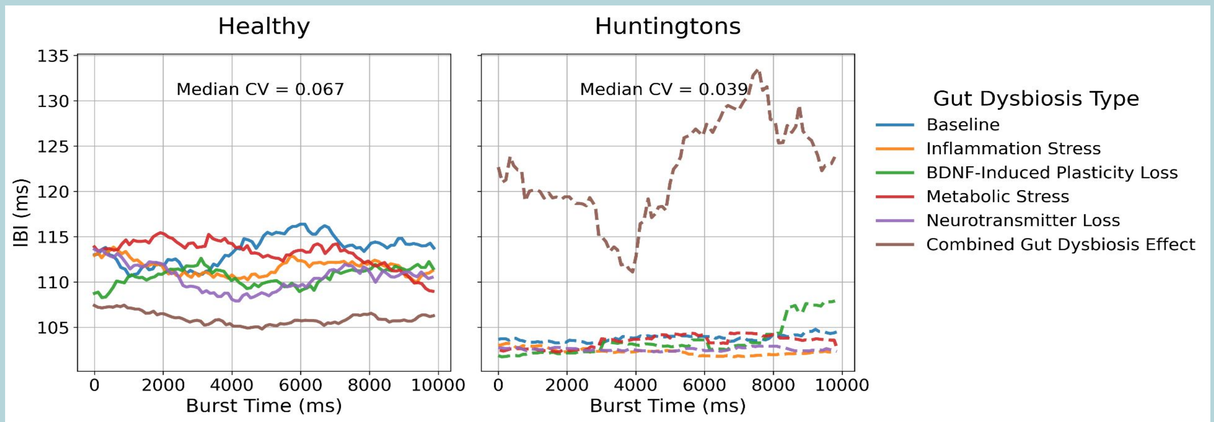

Fig. 3 Interburst Interval over time in Healthy and HD Models

Fig. 4 Total-order Sobol Indices in Healthy and HD Models

Discussion and Conclusion

- Under **combined gut dysbiosis**, firing rates significantly decreased in healthy models and significantly increased in HD models ($p < 0.05$).
- HD models exhibited **more stable IBIs** on average ($CV = 0.22$), excluding the outlier effect from combined gut dysbiosis.
- **BDNF-induced plasticity loss** and **inflammation** caused the largest changes in firing rate and inter-burst intervals, while **neurotransmitter loss** had the least impact in both healthy and HD models.
- Across all conditions, **synaptic noise** had the highest total-order Sobol index, indicating it contributed most to firing rate variance.

Limitations

- The model does not capture single-neuron or spatial network dynamics.
- Gut dysbiosis effects were abstracted through parameter changes without direct biological validation.
- Findings are model-dependent and require experimental validation for clinical relevance.

Future Work

- Investigate additional gut dysbiosis mechanisms beyond those modeled in this study.
- Explore interactions between multiple dysbiosis mechanisms and their combined effects on neural dynamics.
- Develop therapeutic strategies targeting **BDNF-induced plasticity loss** and **inflammation**, key contributors to altered firing and bursting in HD.