

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).

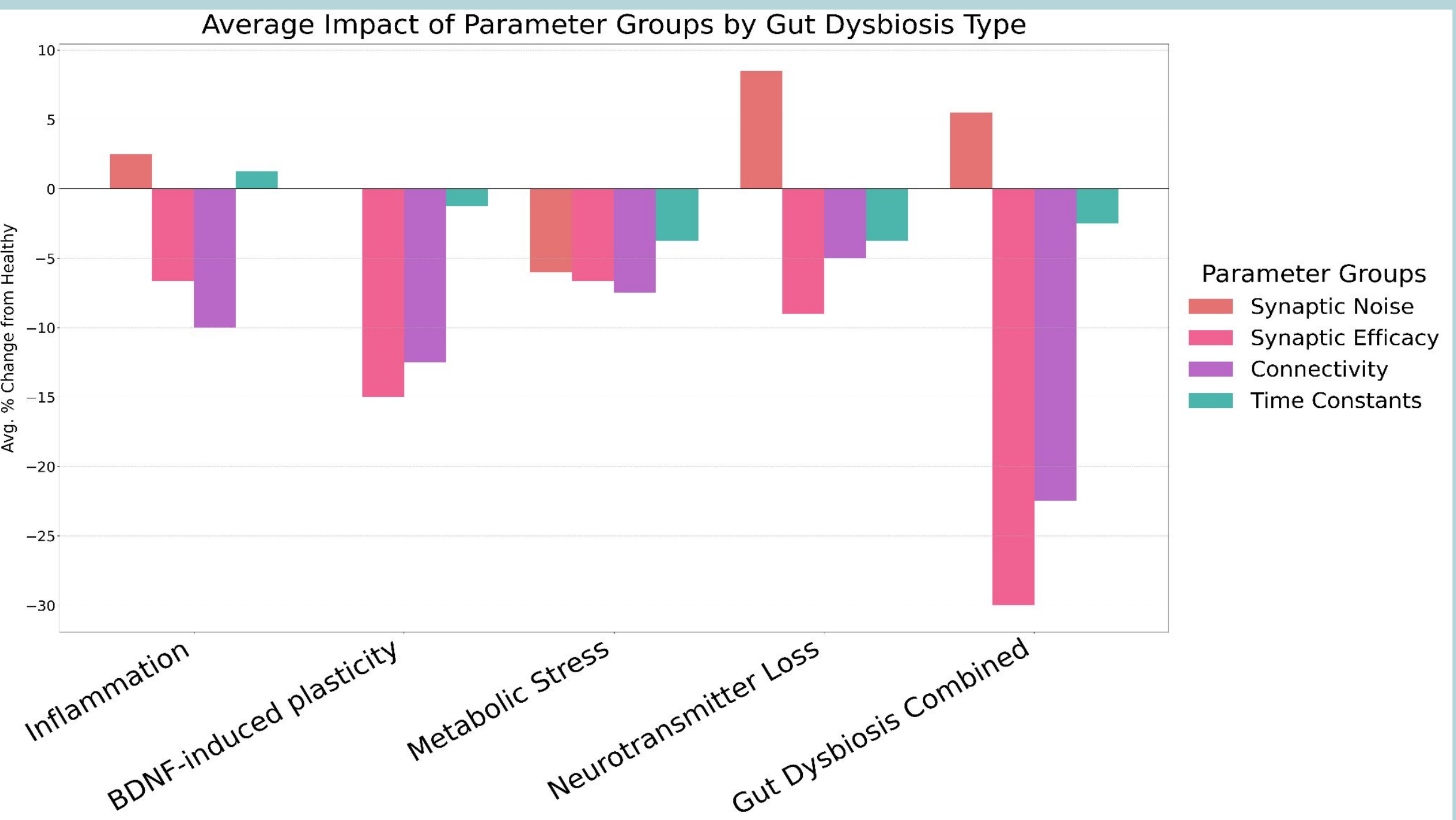


Fig. 1 Summary of Gut Dysbiosis Changes

- 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.

References

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Acknowledgements

We would like to thank Karla Montejó and the teaching fellows for their continued guidance, instruction, and support throughout our project. We are also grateful for the resources the RISE program and Boston University have offered, as well as our families who made it possible for us to attend this program.

Results

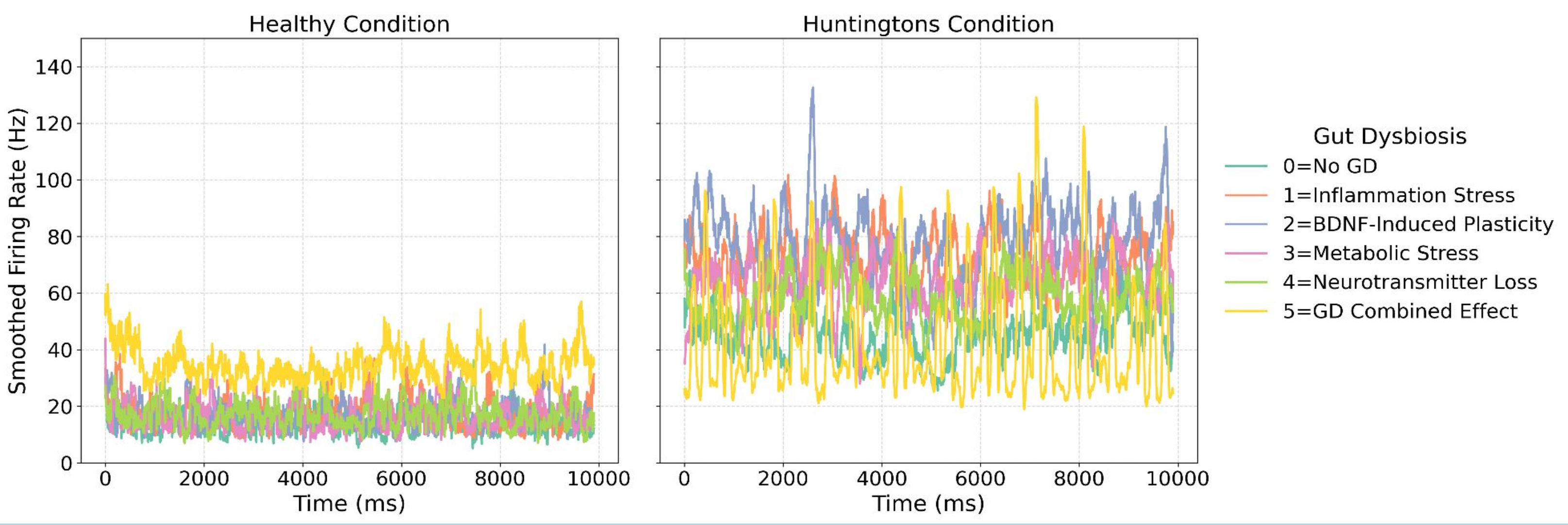


Fig. 2 Mean Neuron Firing Rate over time in Healthy and HD Models

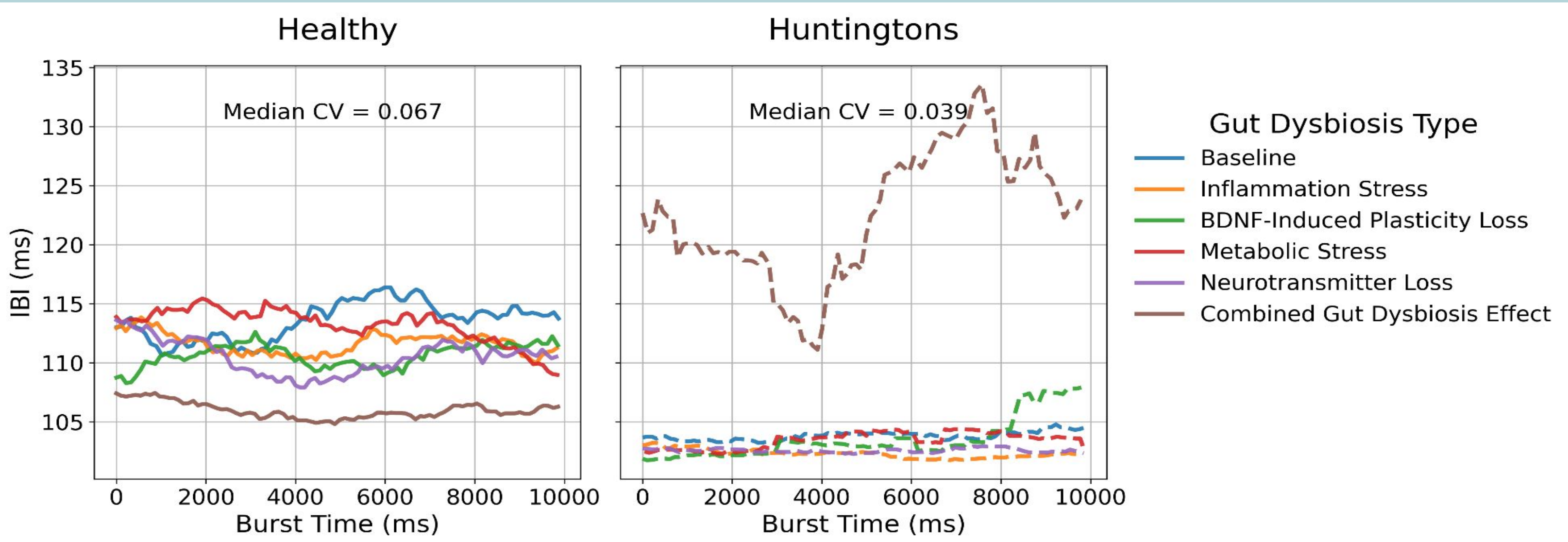


Fig. 3 Interburst Interval over time in Healthy and HD Models



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.