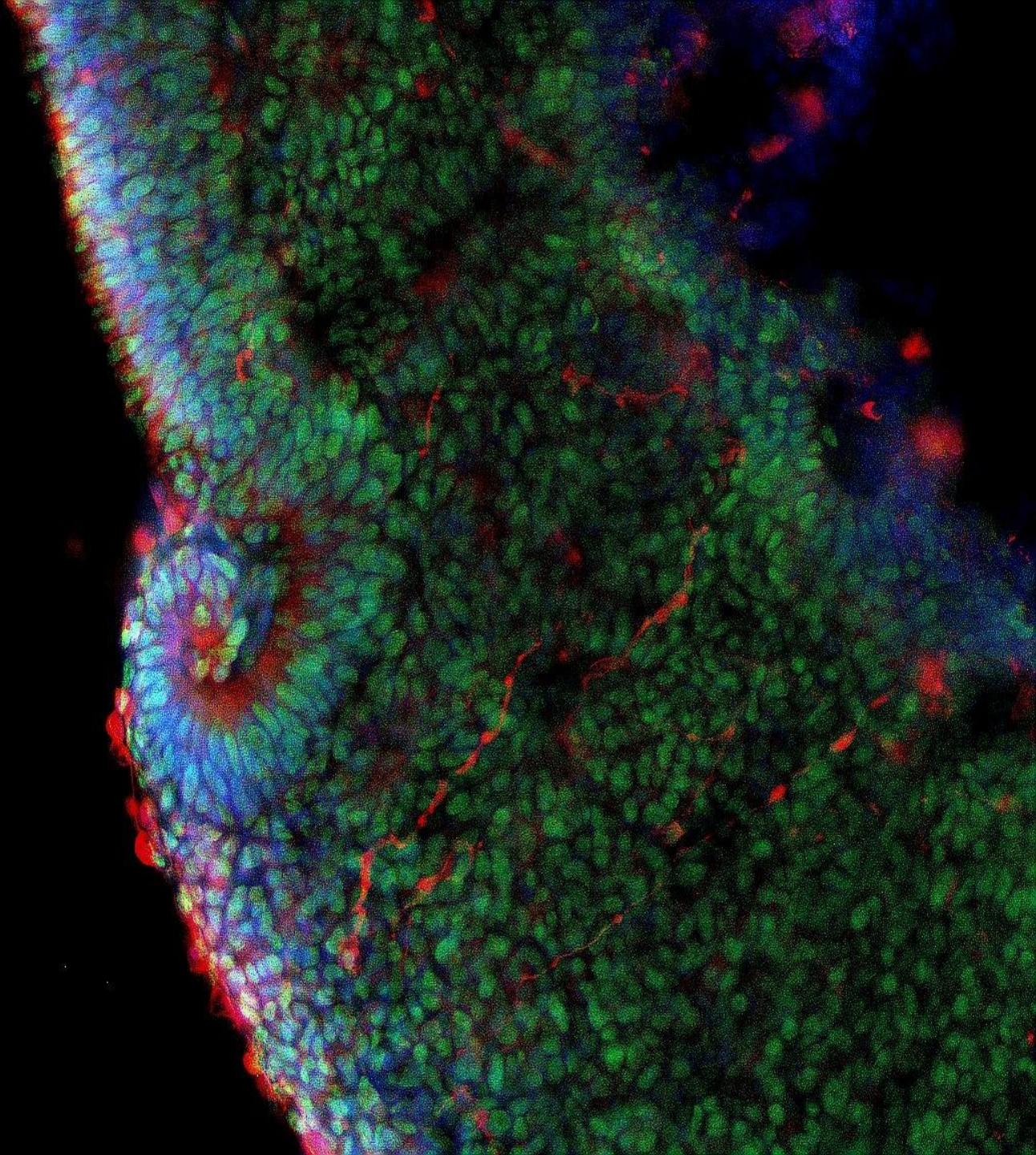


Studying the Effects of Dopamine Signaling in Parkinson's Disease with Human-Relevant *in vitro* Models

Greg Kaurala & James LaFemina
Sharf Lab
Dept of Biomolecular Engineering
UC, Santa Cruz

Contributors: Tal Sharf, Tjitse van der Molen, Cole Duncan, Anton Zatserklyaniy, Mia Niswonger, and Sawyer McKenna

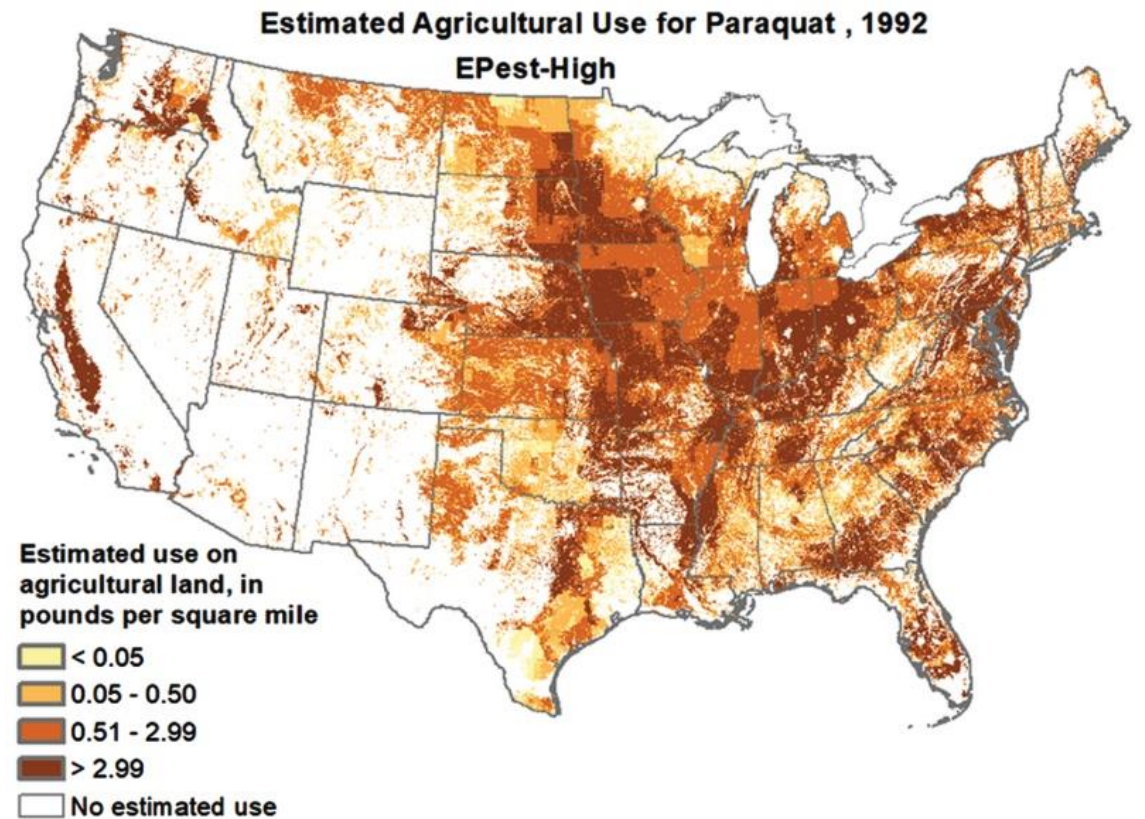
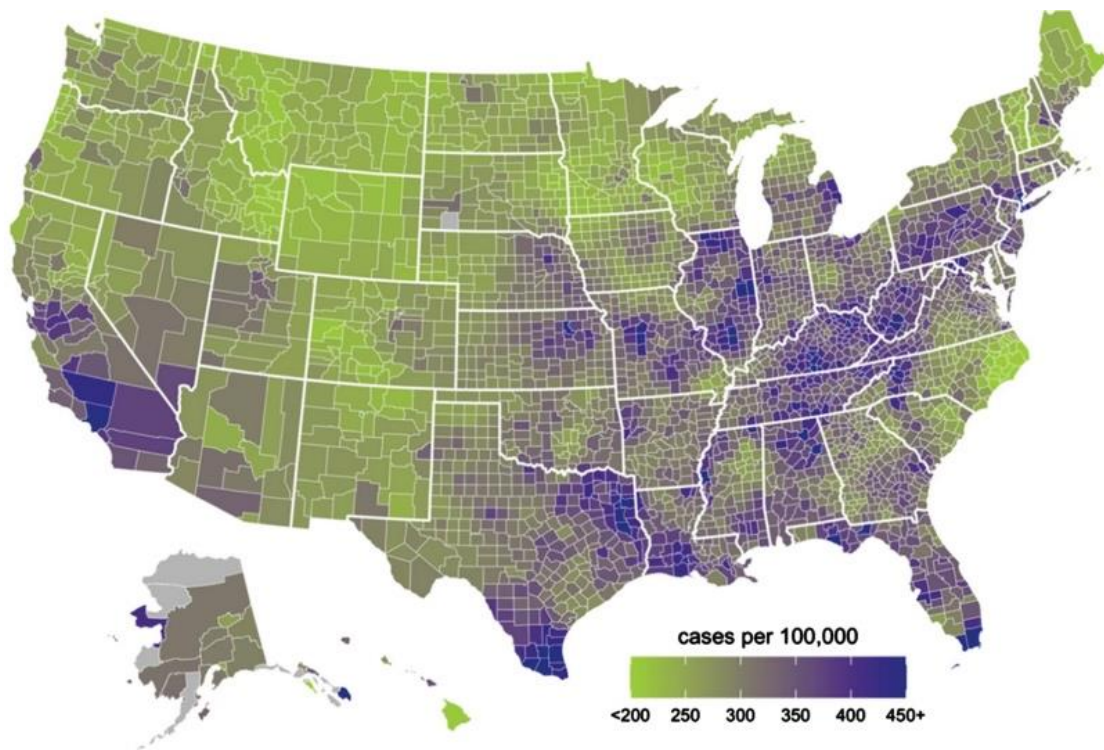
Braingeneers
October 17, 2025



Agenda

- A little about Parkinson's Disease
- Construction of an *in vitro* model
- Burst detection method
- Population-level burst changes
- Backbone sequence changes

About 90% of PD cases are Linked to Environment

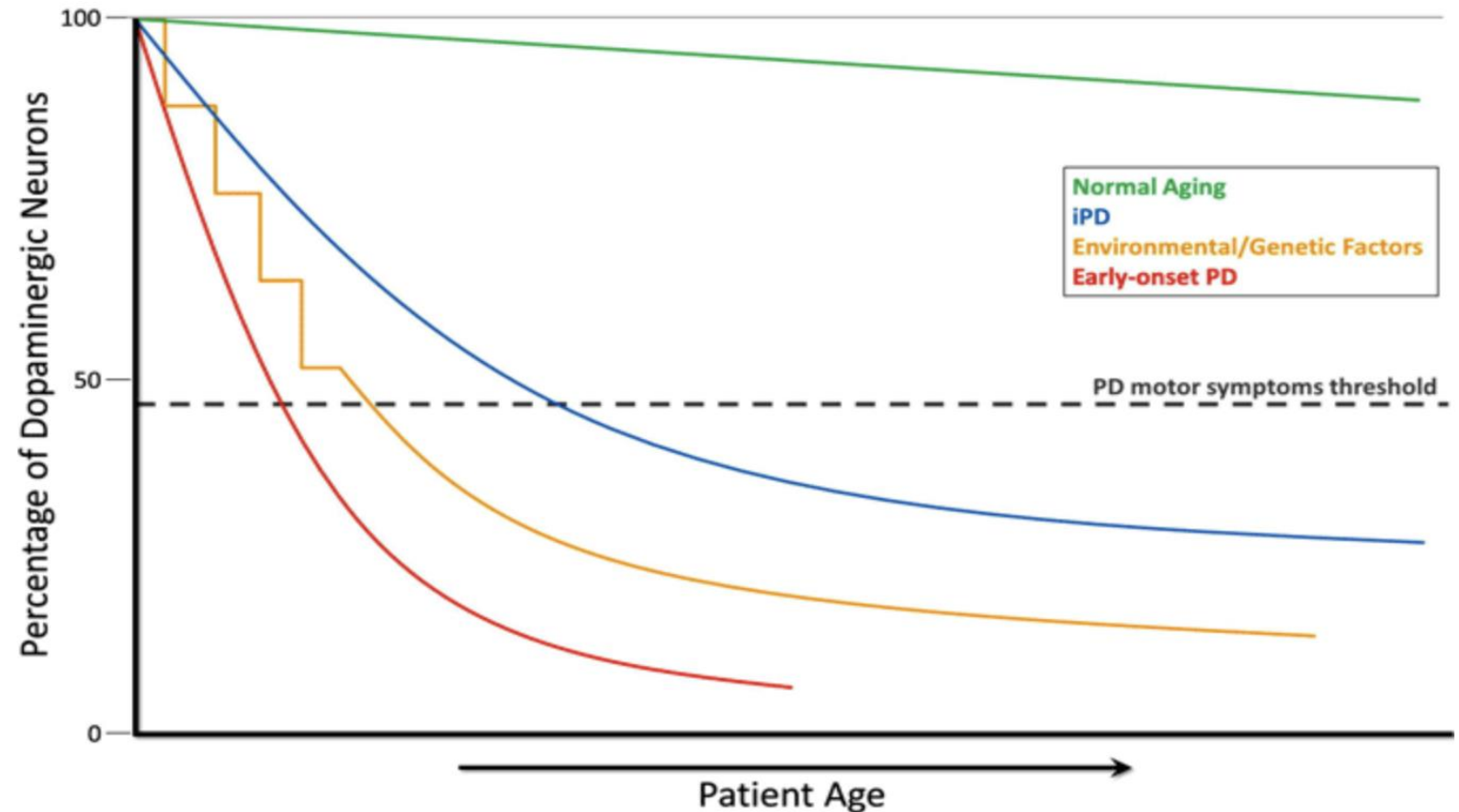


To understand the majority of PD cases, we need models that can capture how environmental insults lead to circuit-level dysfunction.

Key Pathology: Loss of Midbrain Dopaminergic Neurons

PD symptoms typically arise after ~55% of mDA neurons are lost, with motor symptoms reflecting a loss of neural synchrony.

Circuit-level effects are difficult to study in animals, but organoids are a promising alternative.

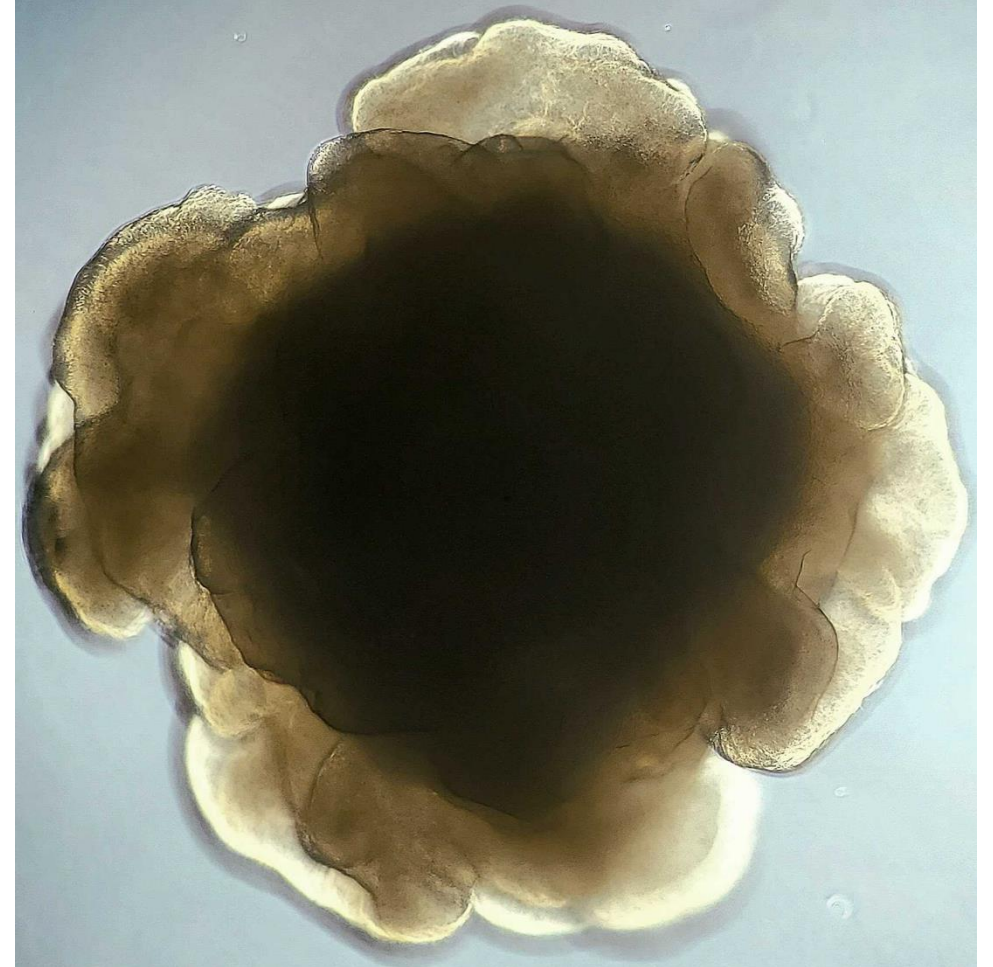


Building a Late-Stage Parkinsonian Midbrain in a Dish

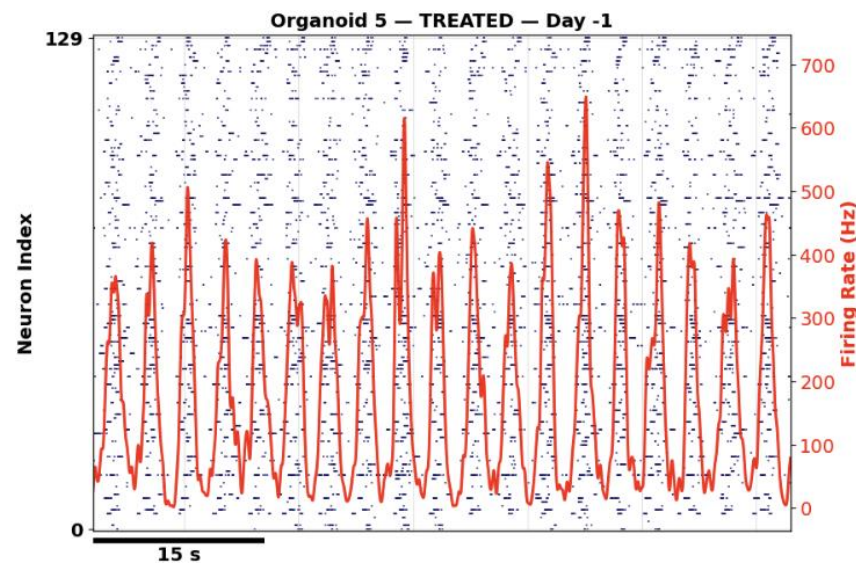
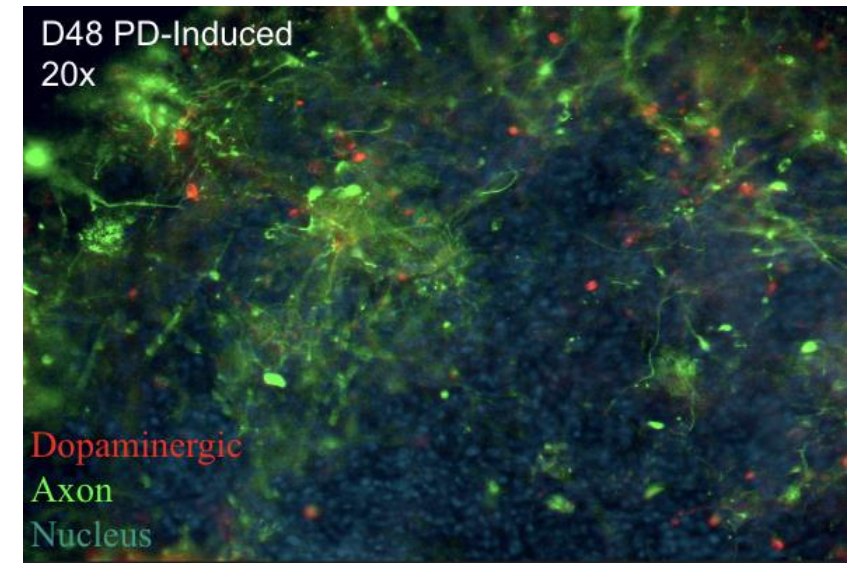
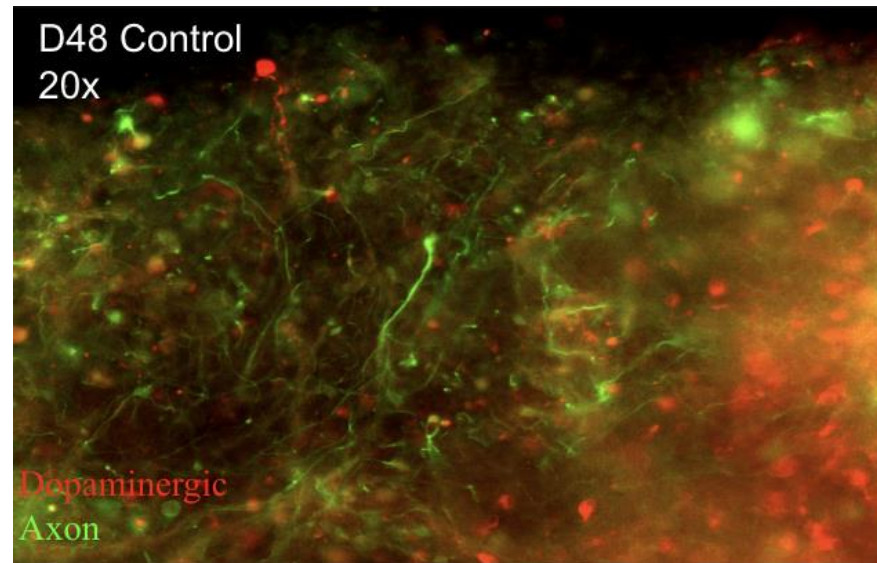
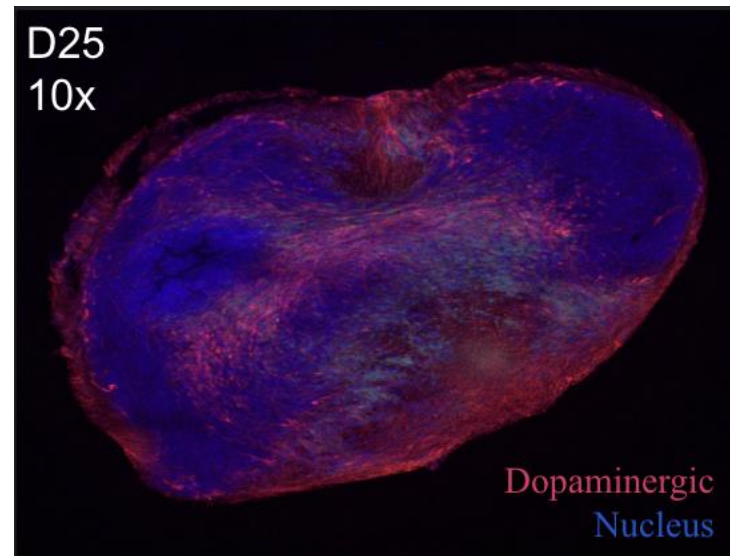
Our first aim: create a simple chemical induction model of PD (based on Nickels *et al.* (2019) protocol).

6-OHDA selectively destroys midbrain dopaminergic (mDA) neurons, mimicking PD pathology.

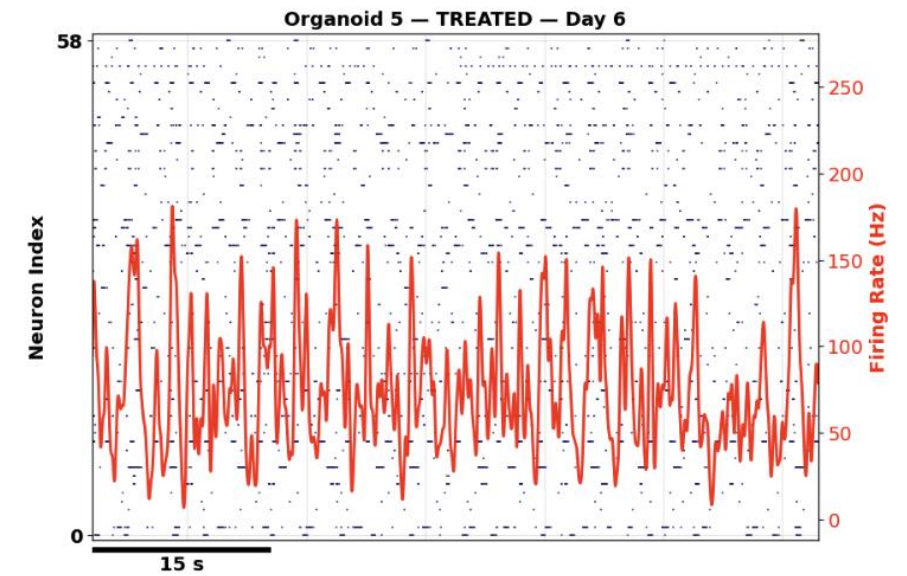
This *in vitro* approach replicates key features of late-stage Parkinsonian midbrain.



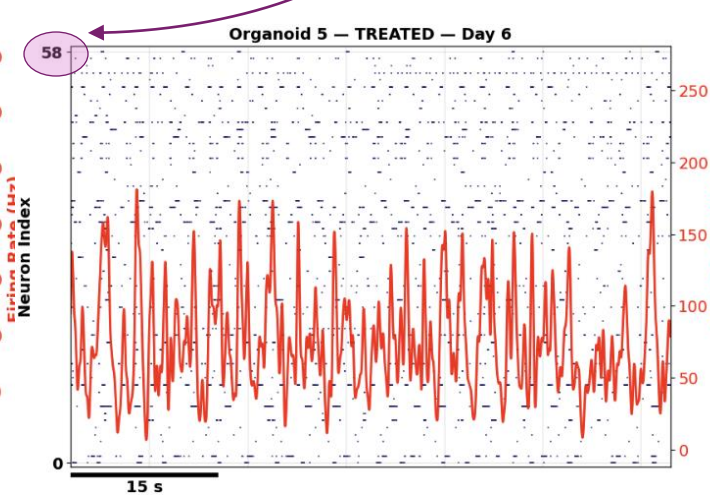
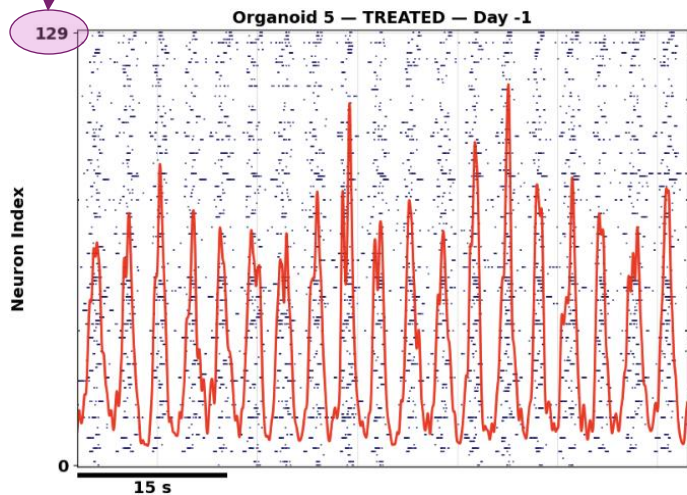
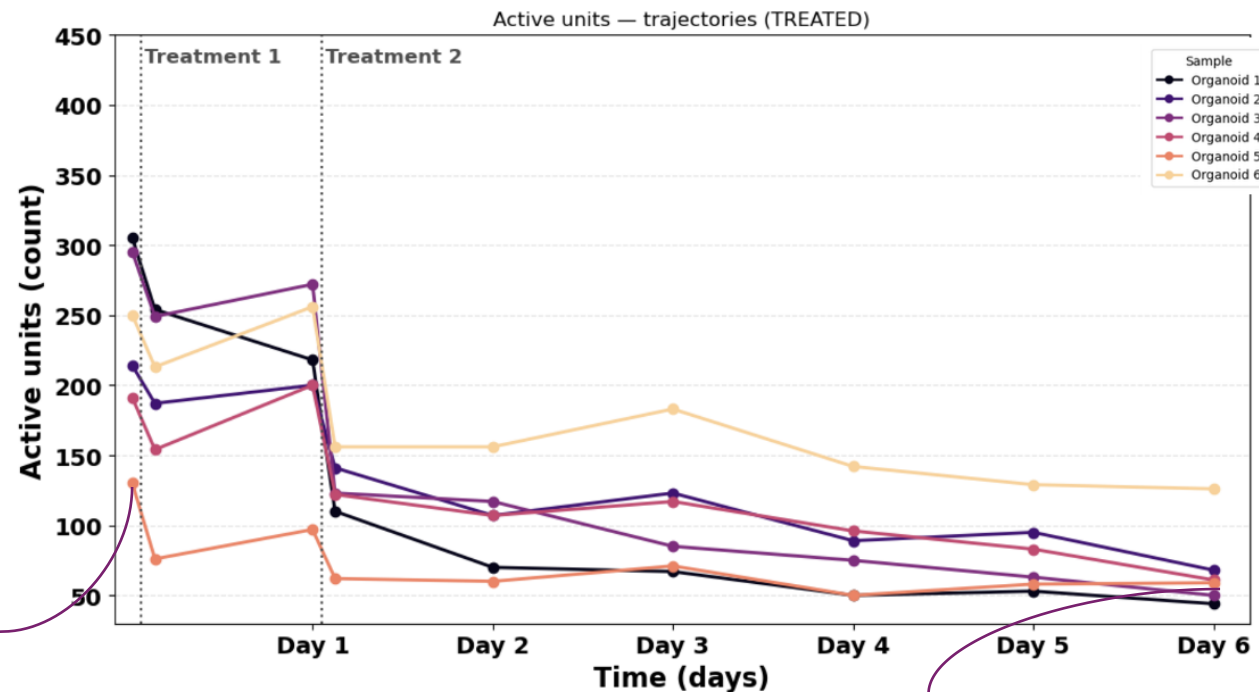
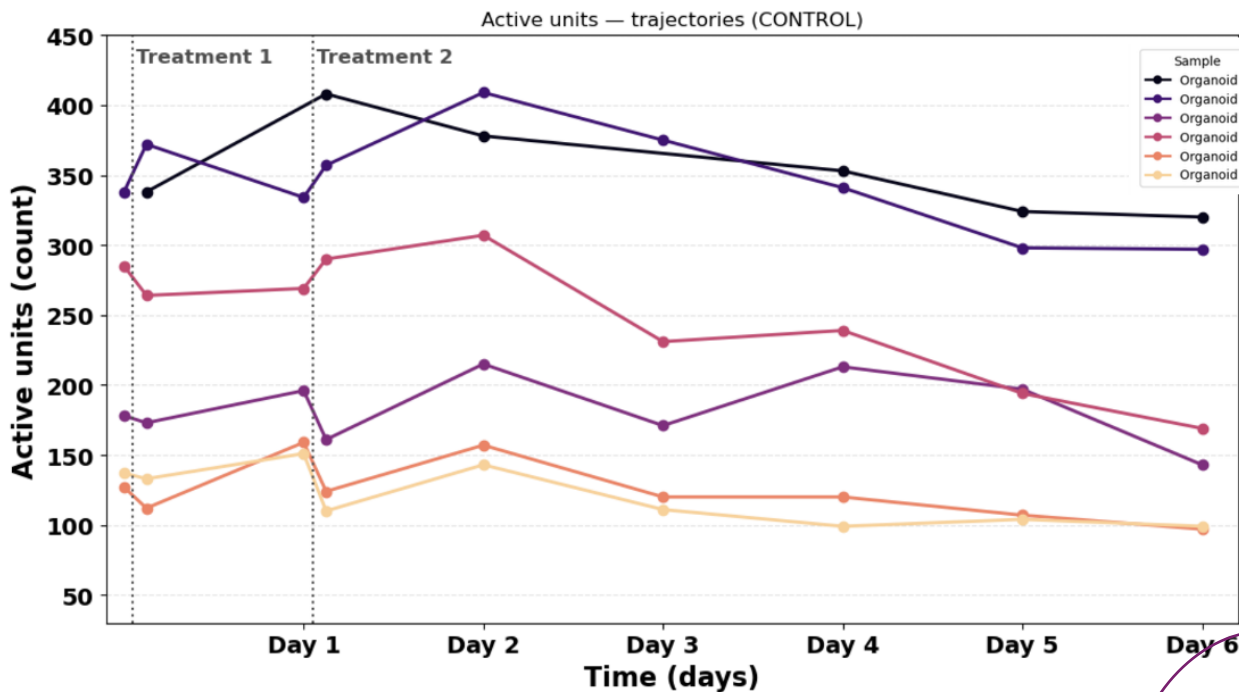
IHC Confirms Selective mDAN Depletion



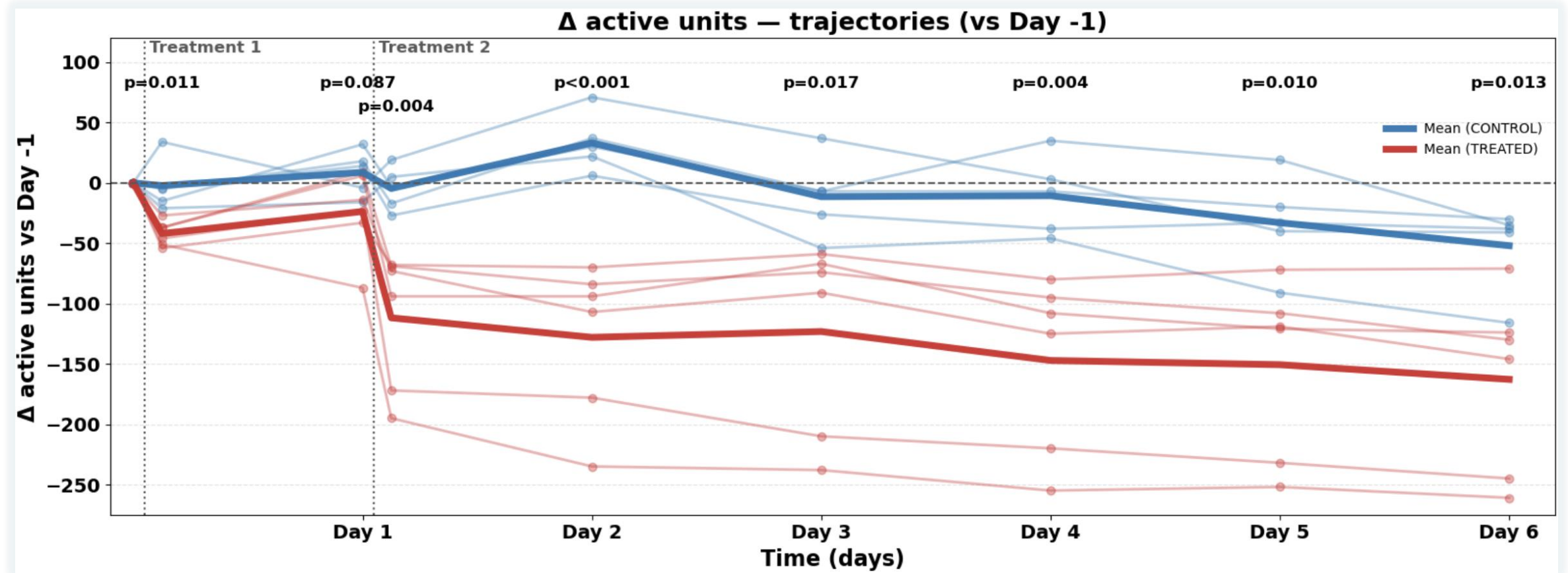
6-OHDA →



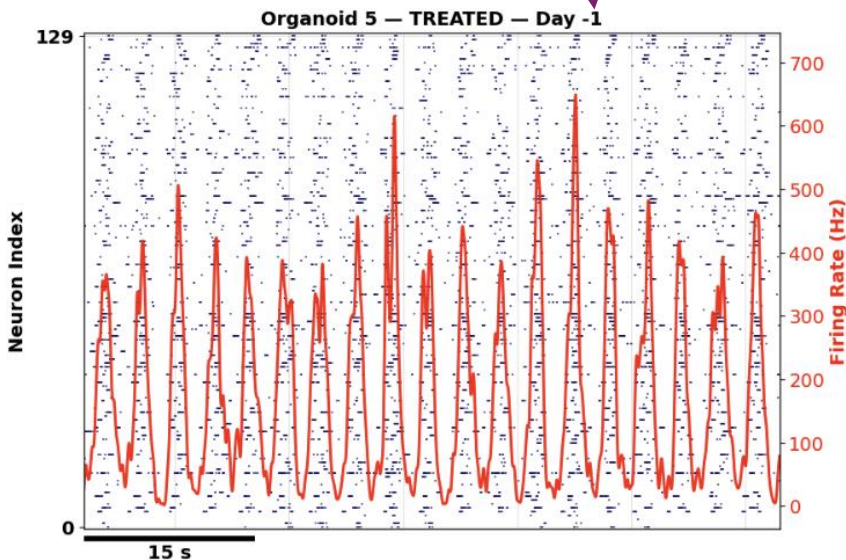
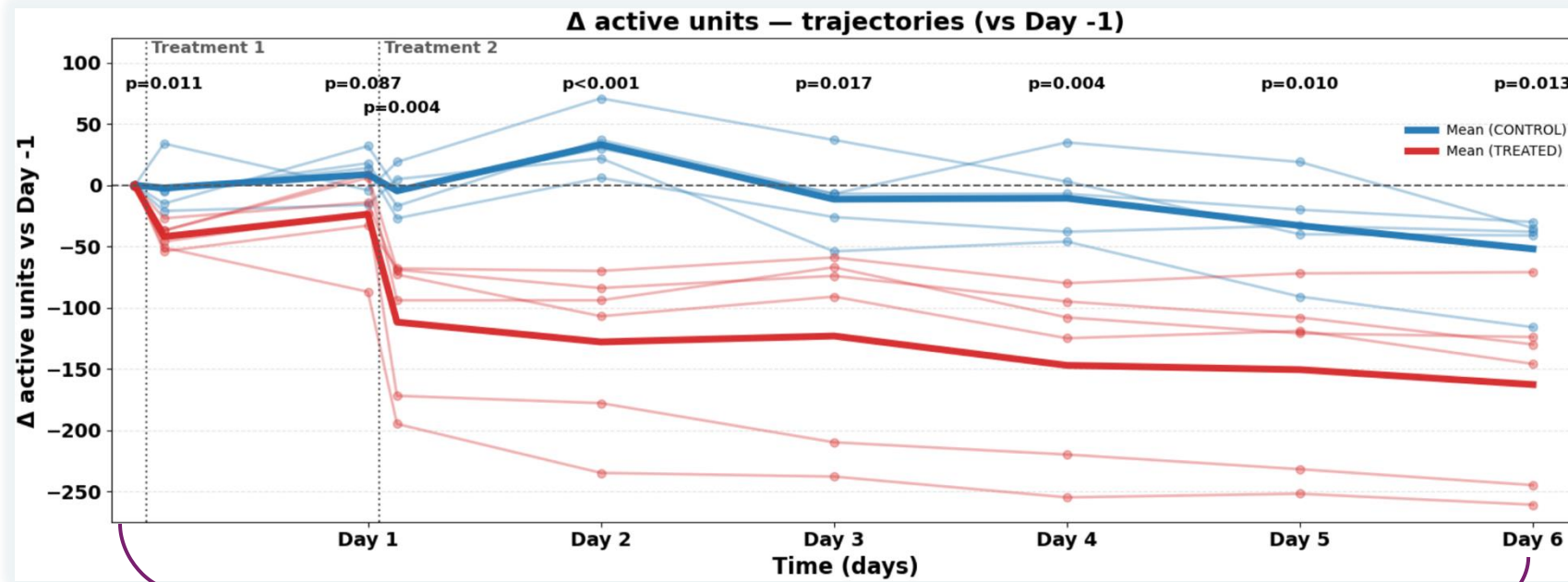
Unit Counts Dipped Dramatically After Treatment 2



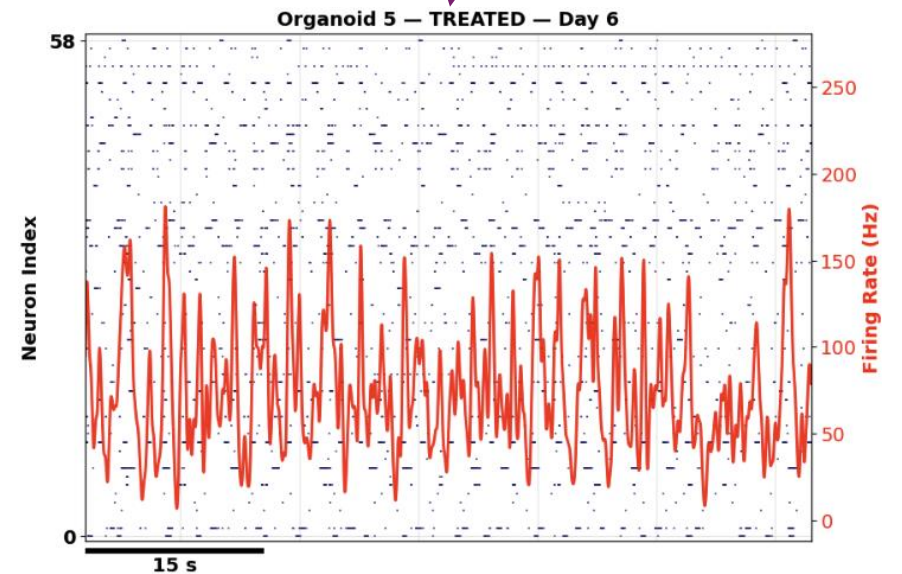
Unit Count Changes are Significant



Interesting Changes in Burst Features Observed



Apply 6-OHDA



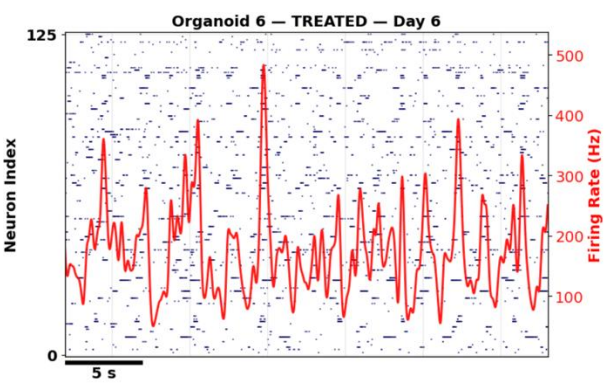
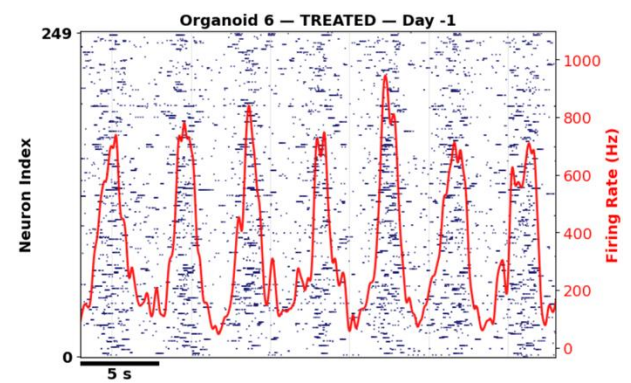
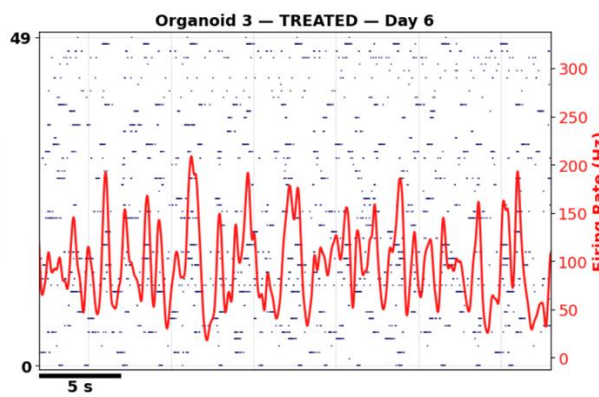
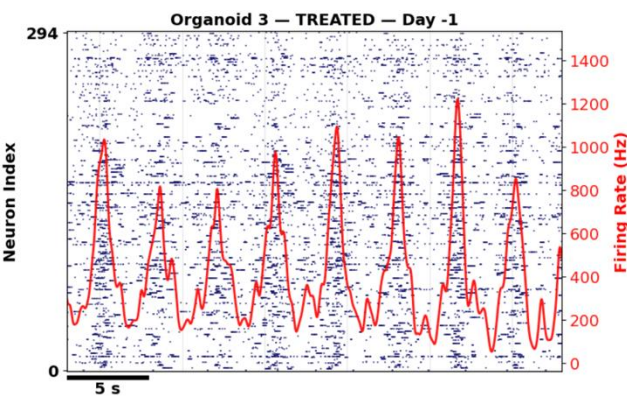
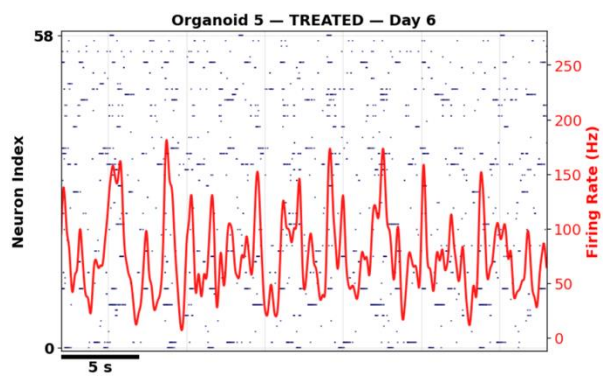
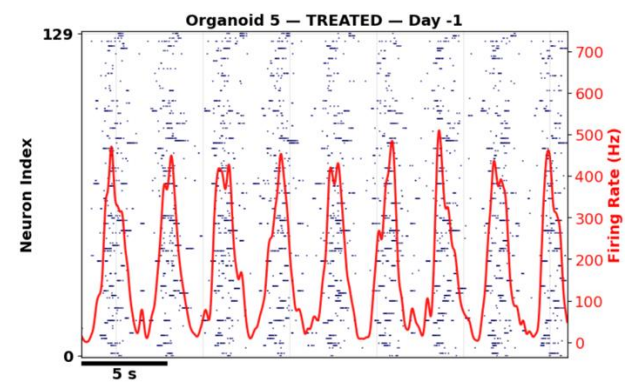
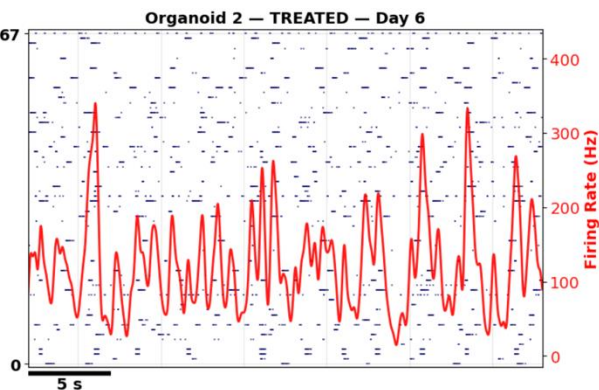
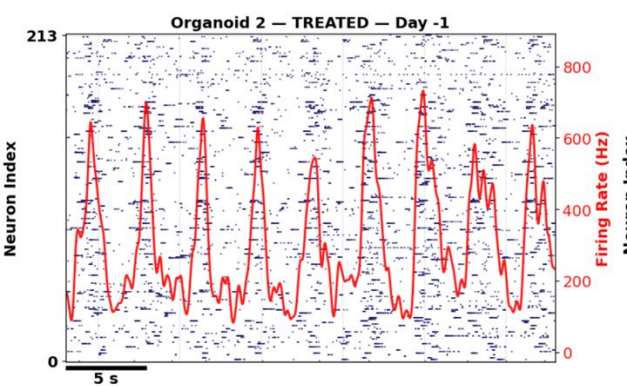
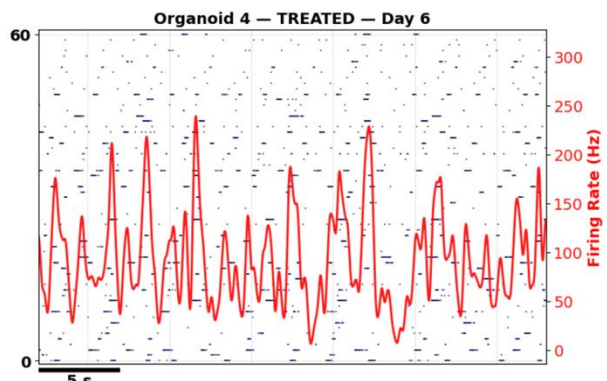
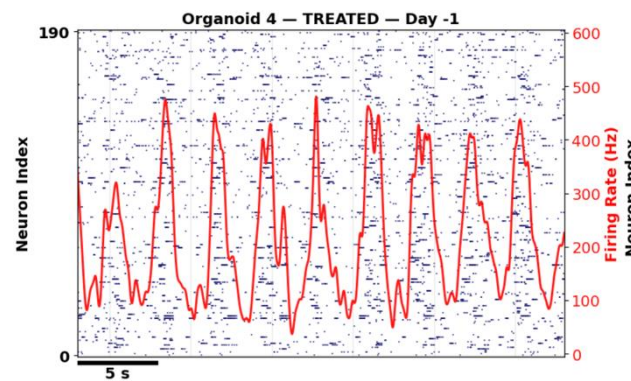
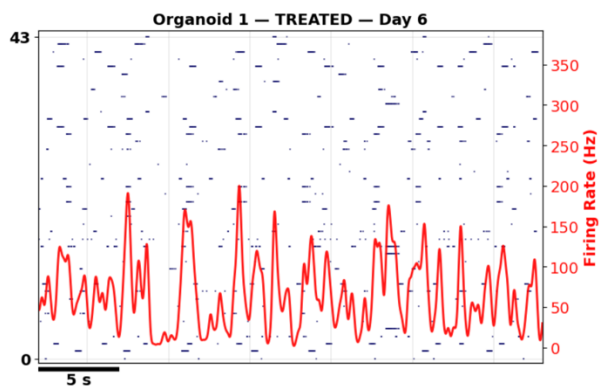
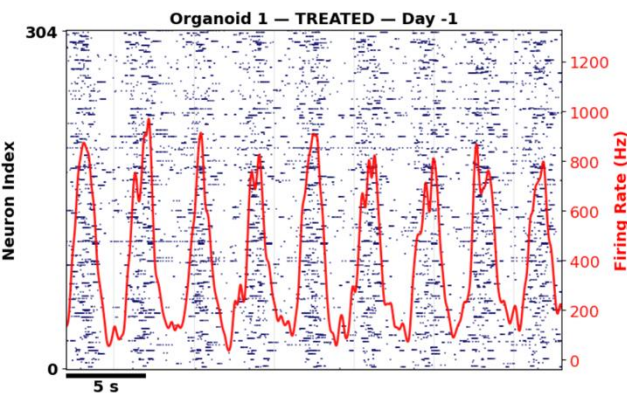
Pre-Treatment versus 6 Days Post-Treatment

PRE

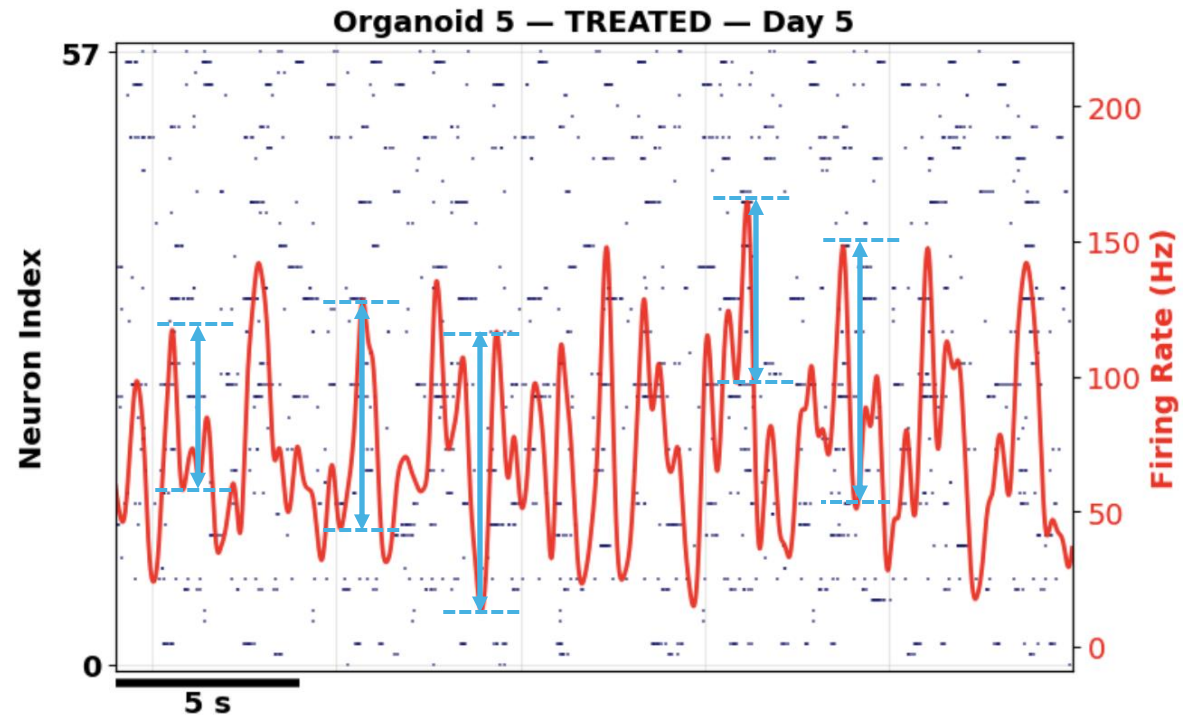
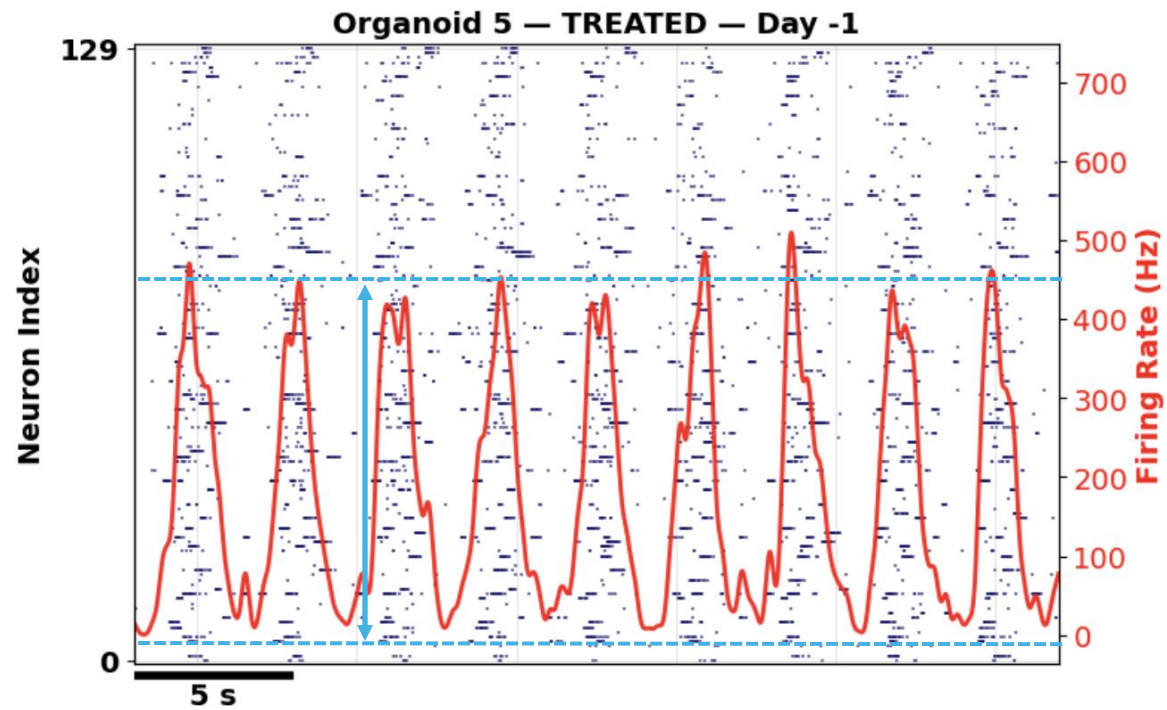
POST

PRE

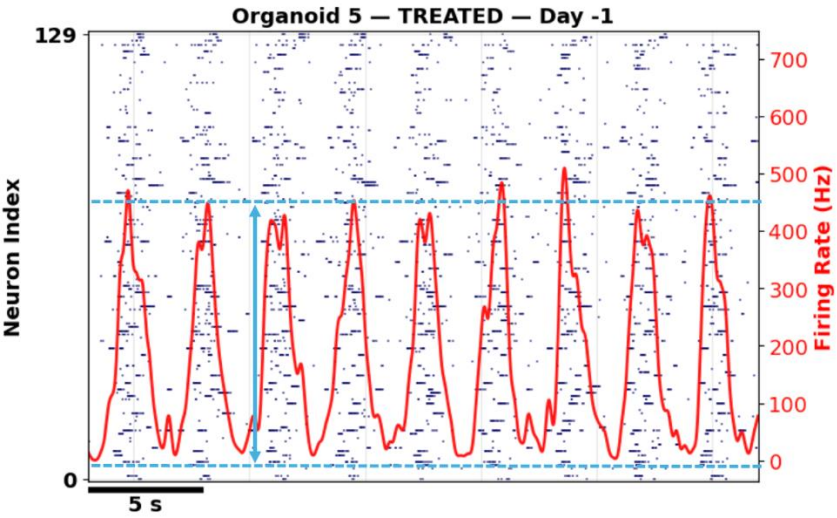
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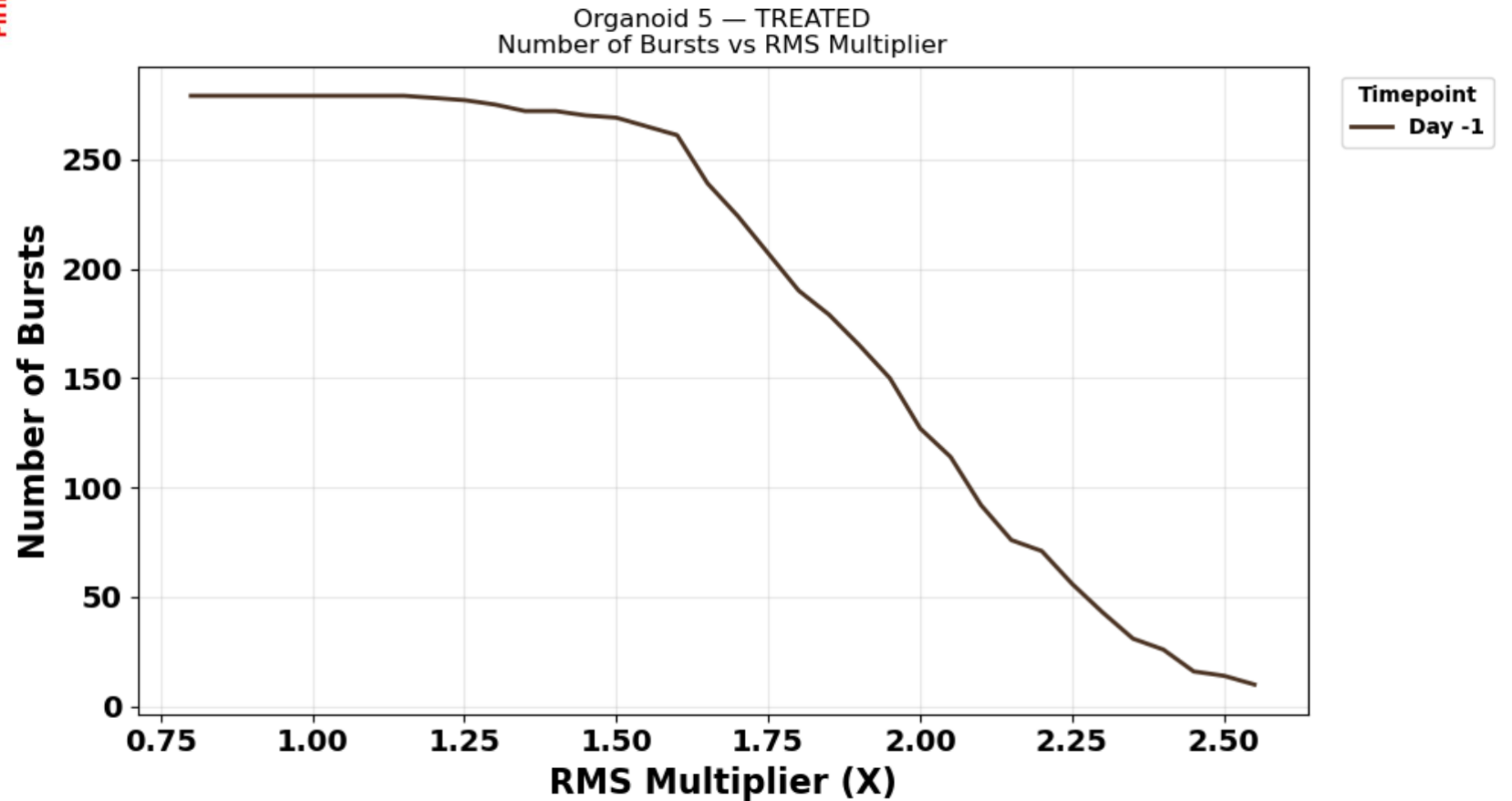
Prior Methods to Measure Bursts Don't Hold Up With Variability



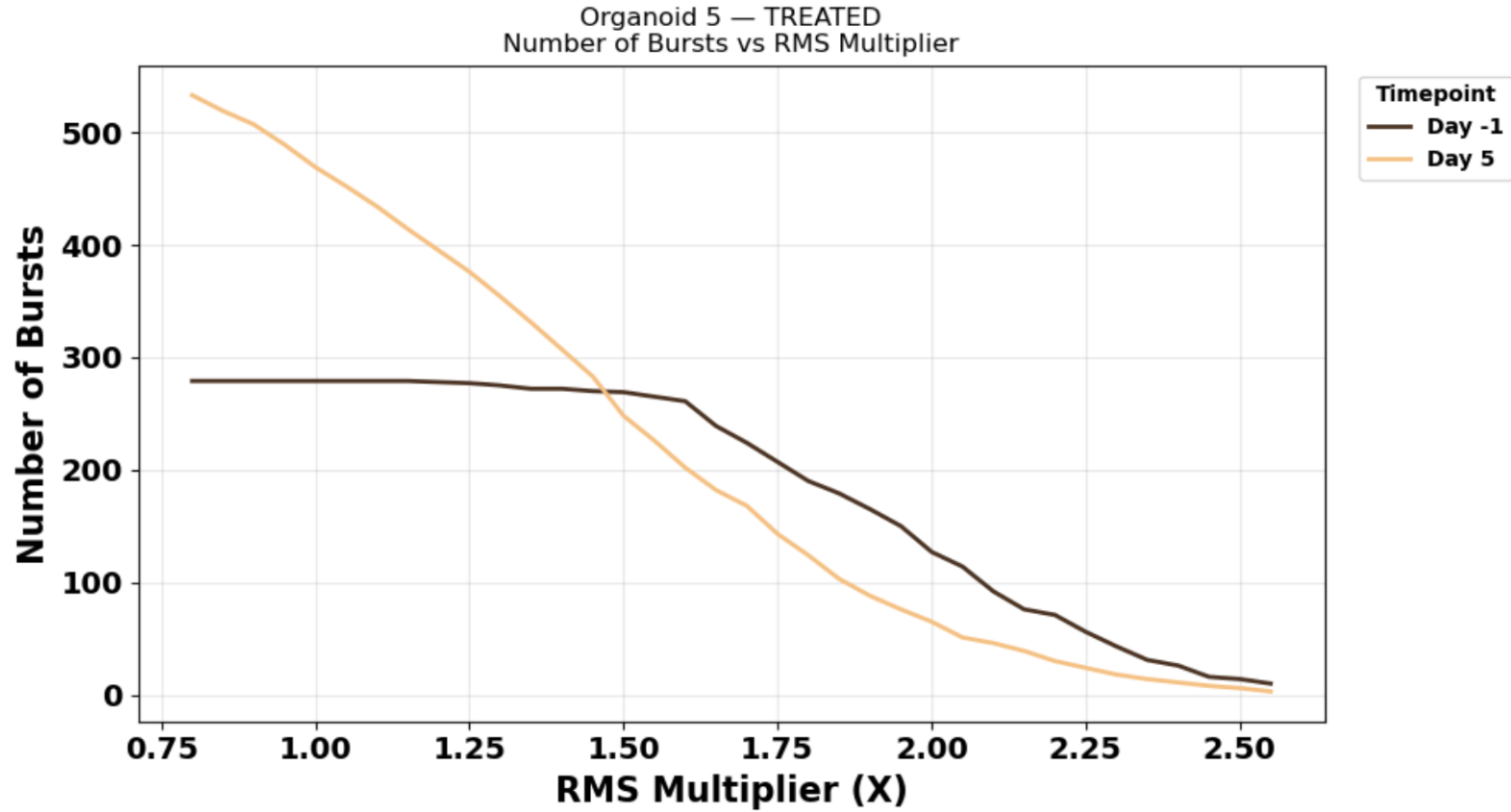
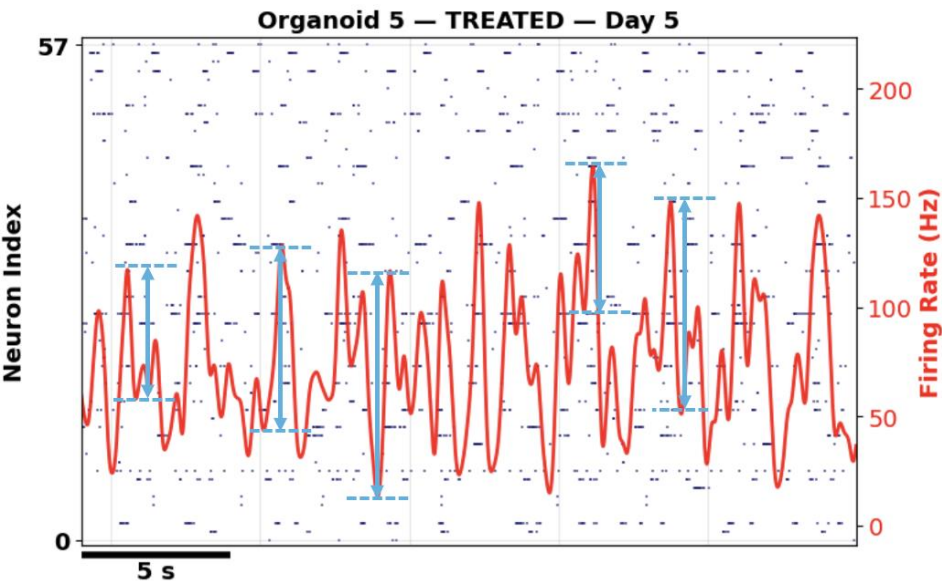
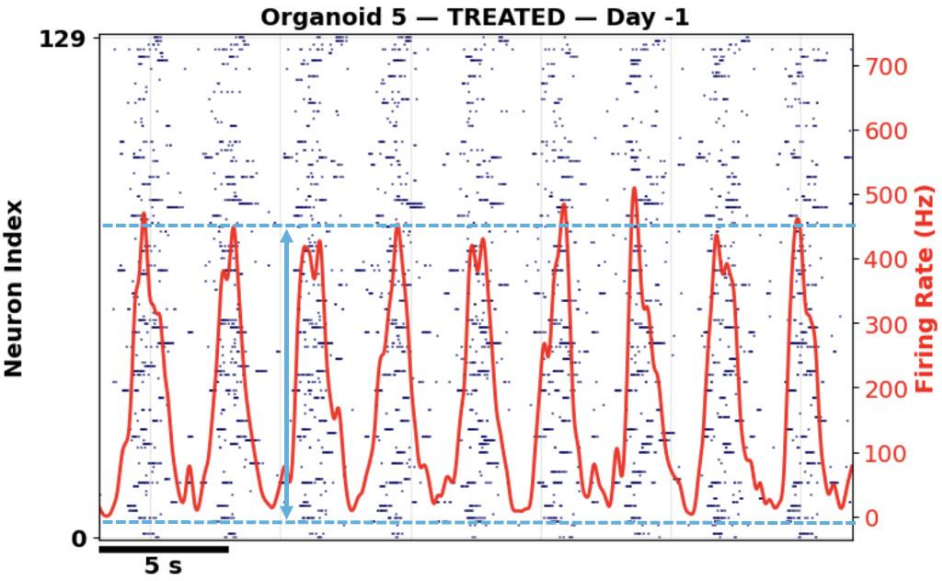
Burst Peak Threshold Multiplier



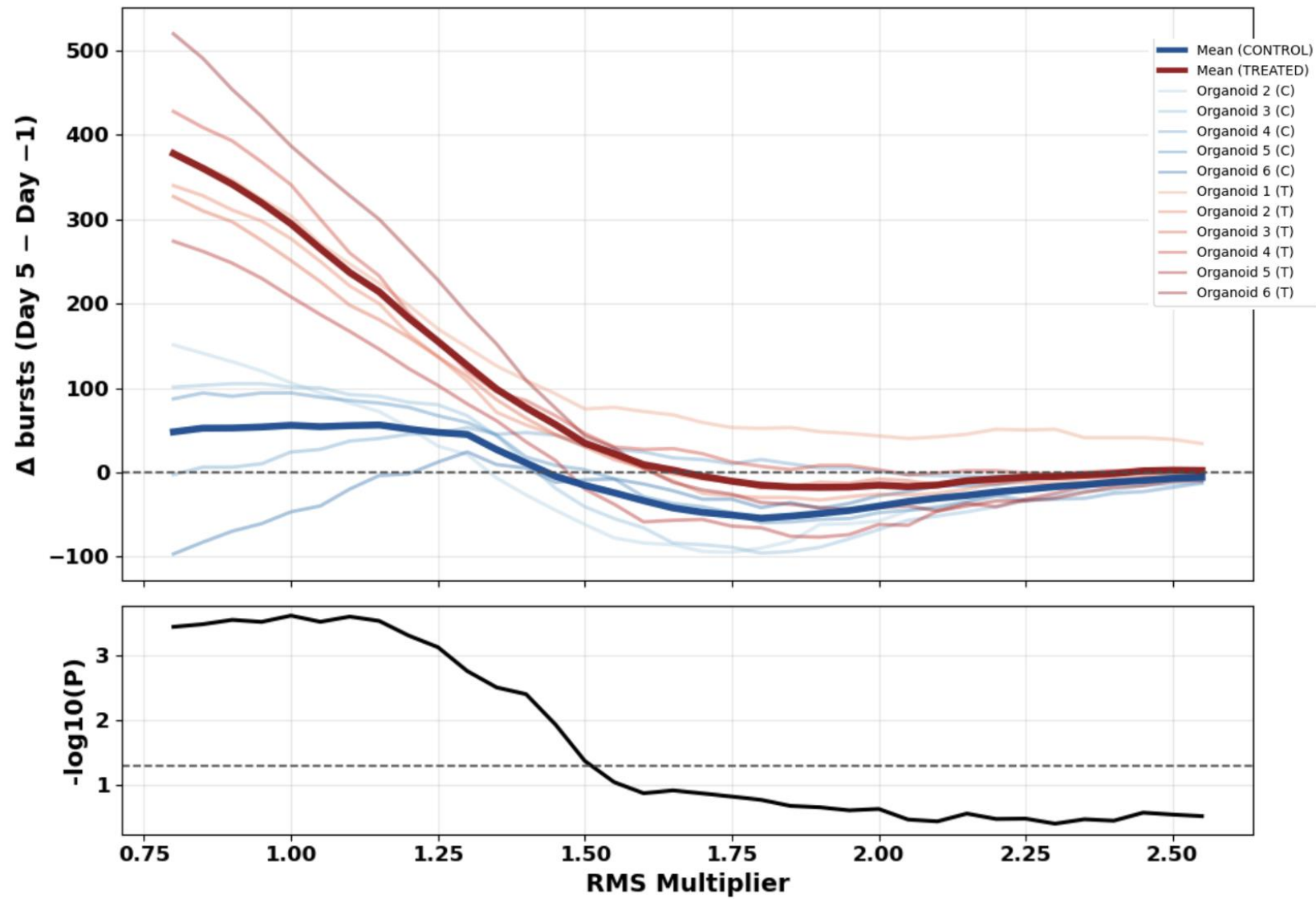
$$\text{Threshold} = X \cdot \text{RMS}(\text{Population Firing Rate})$$



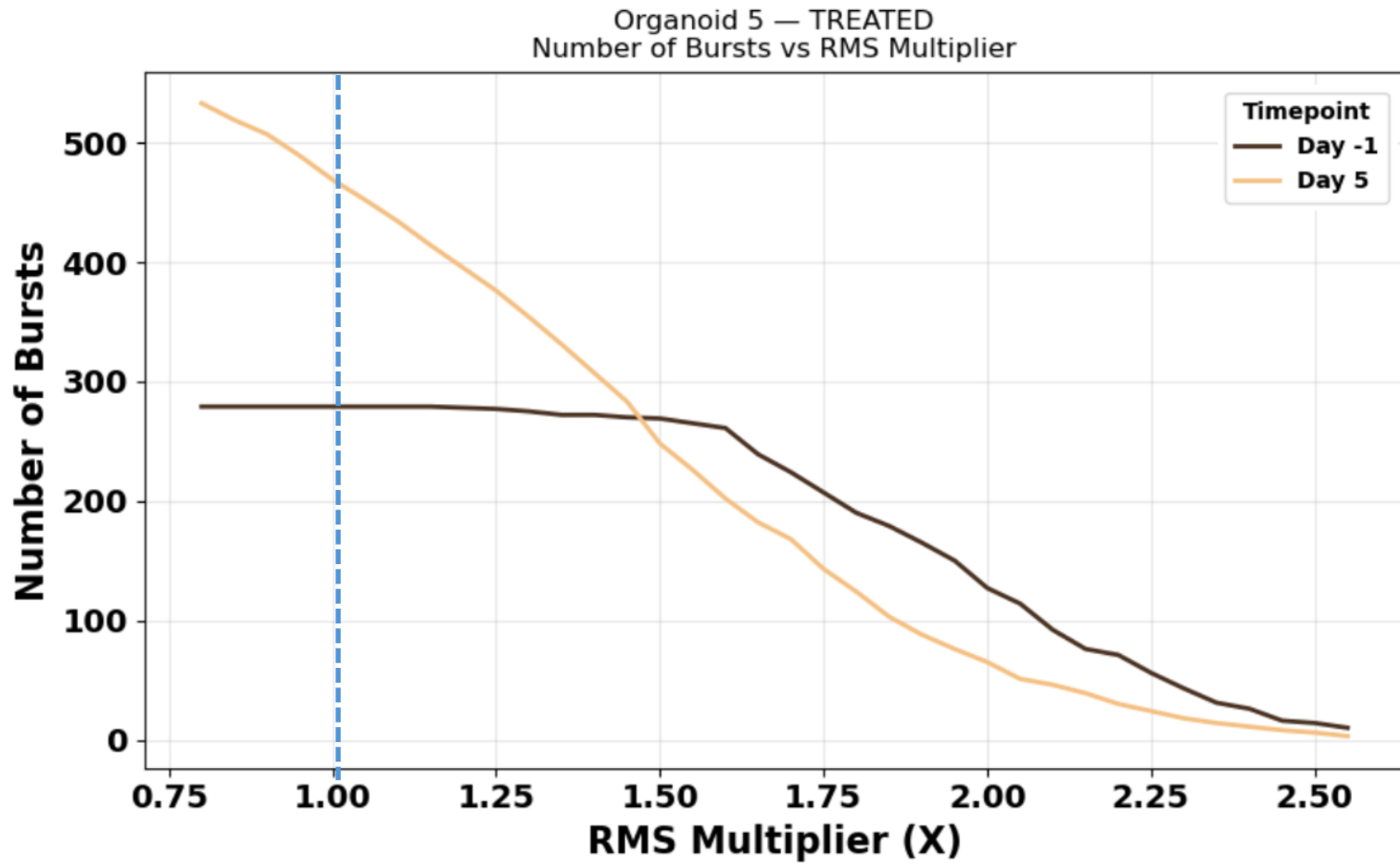
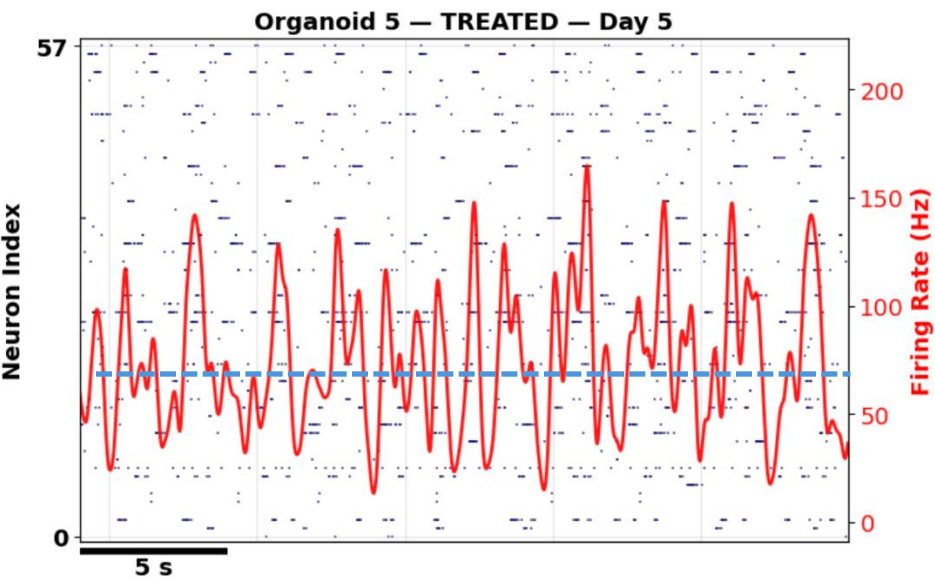
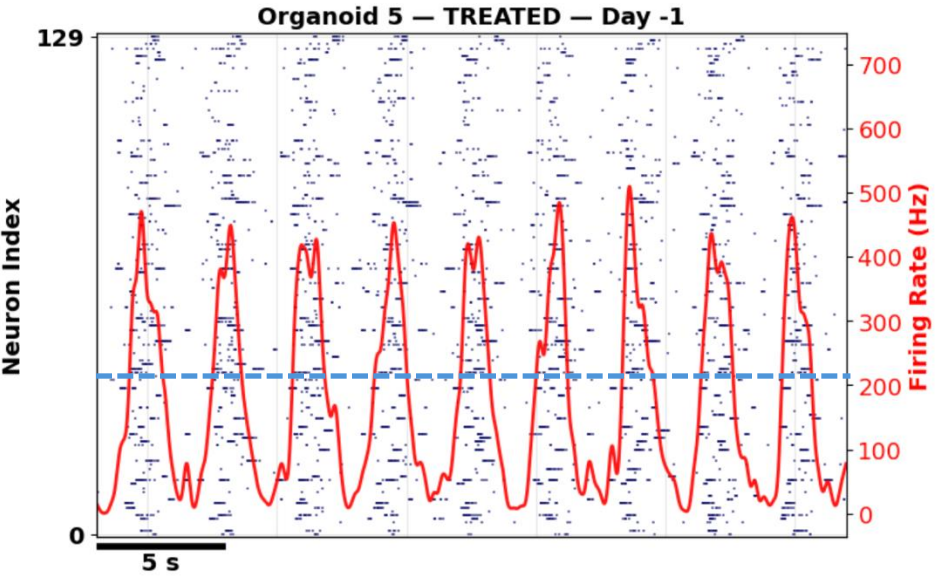
Burst Peak Threshold Multiplier



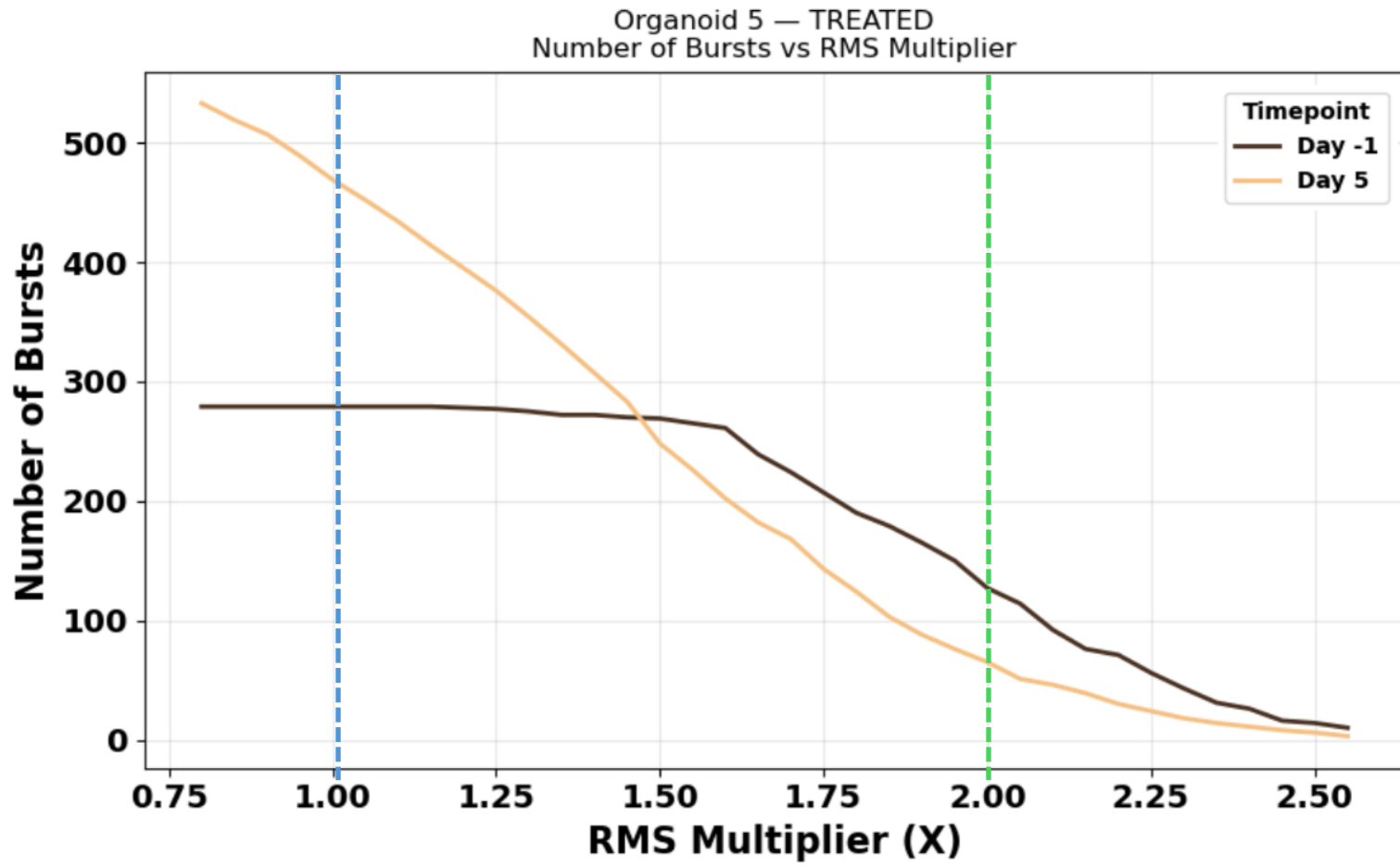
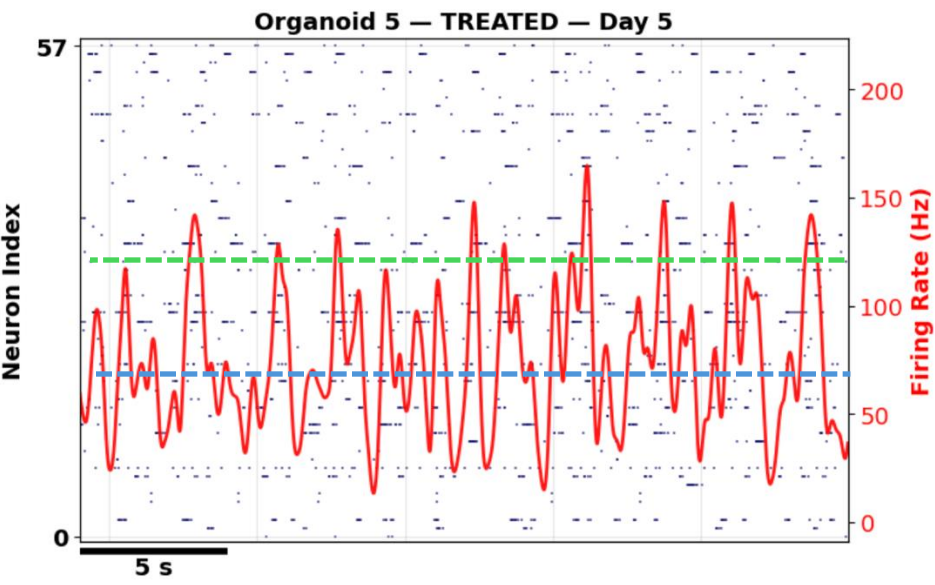
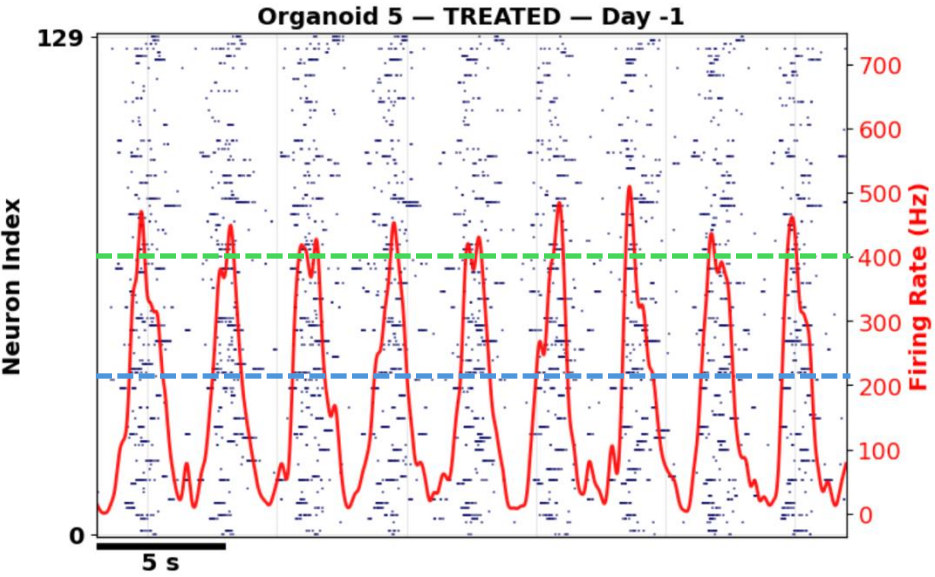
Peaks Get Much Smaller After Treatment



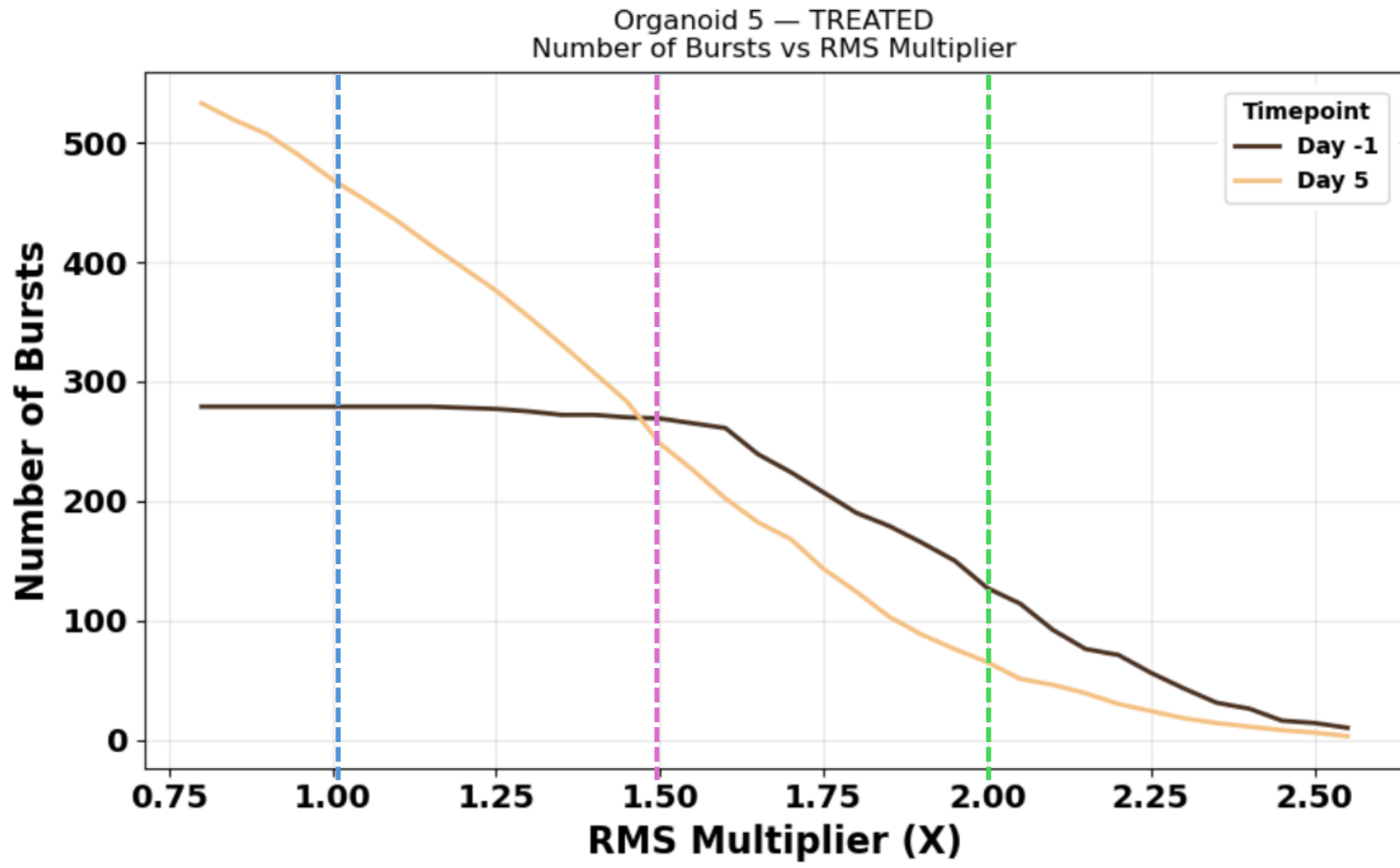
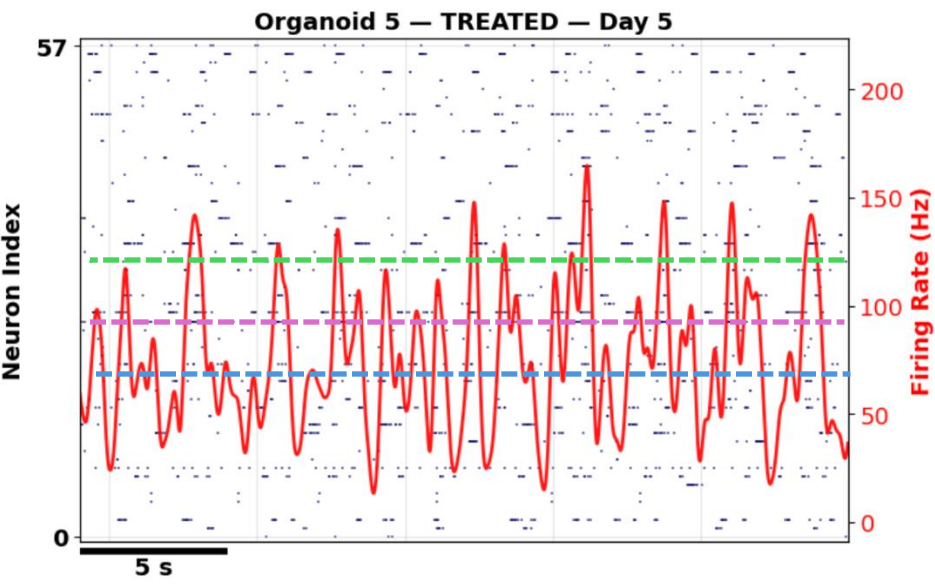
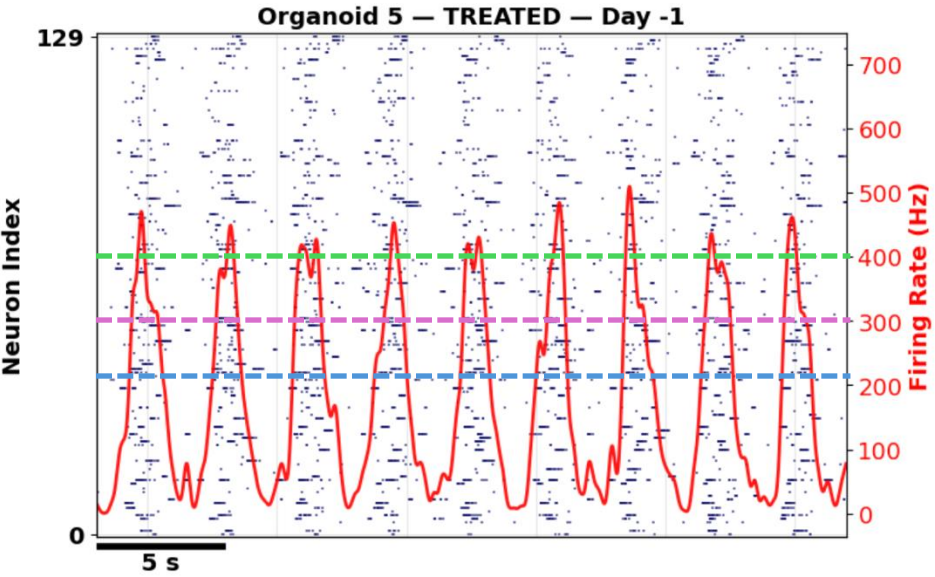
Burst Peak Threshold Multiplier



Burst Peak Threshold Multiplier

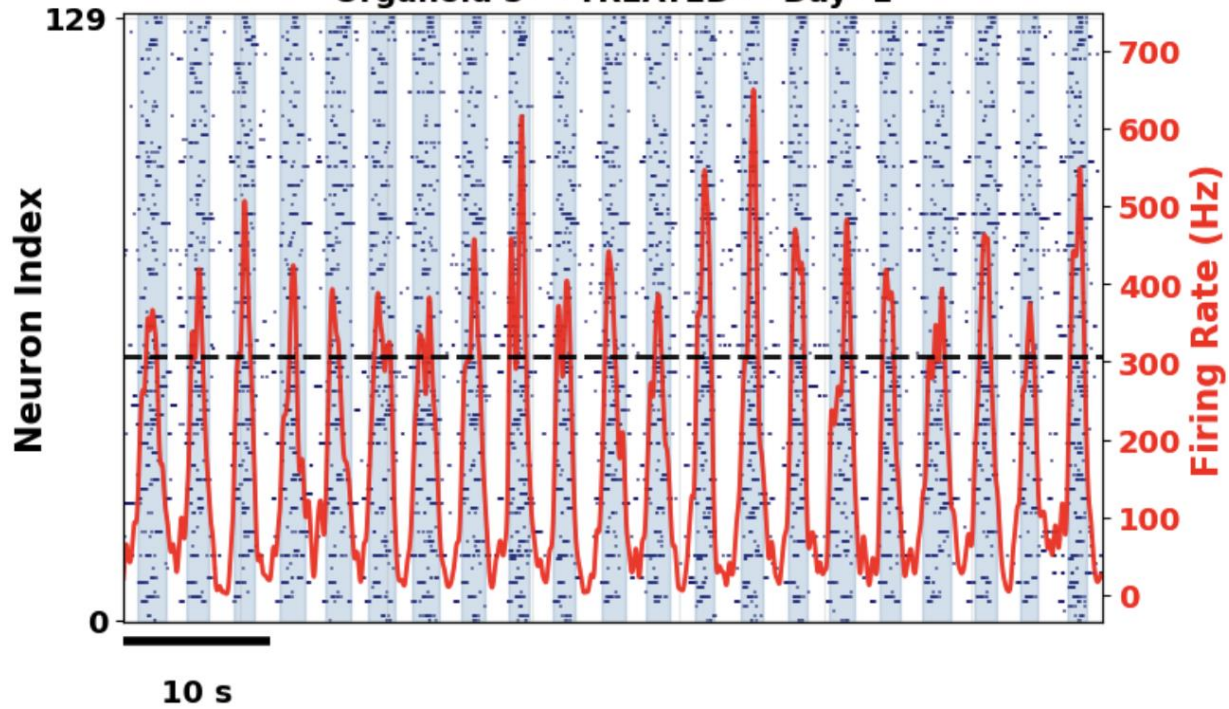


Burst Peak Threshold Multiplier

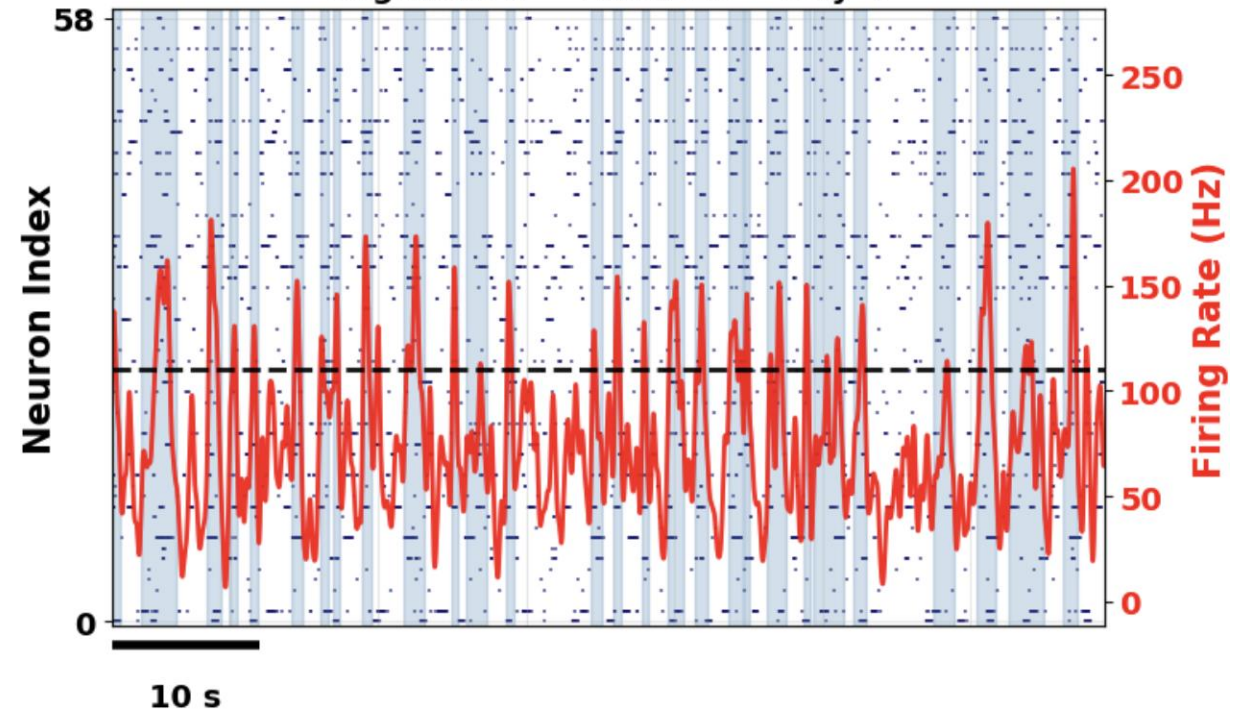


Per-Organoid Mean RMS Threshold Applied

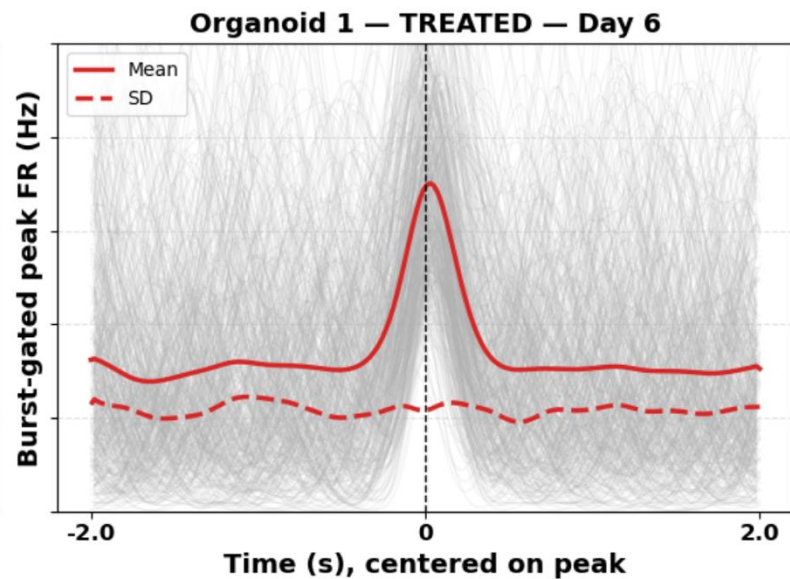
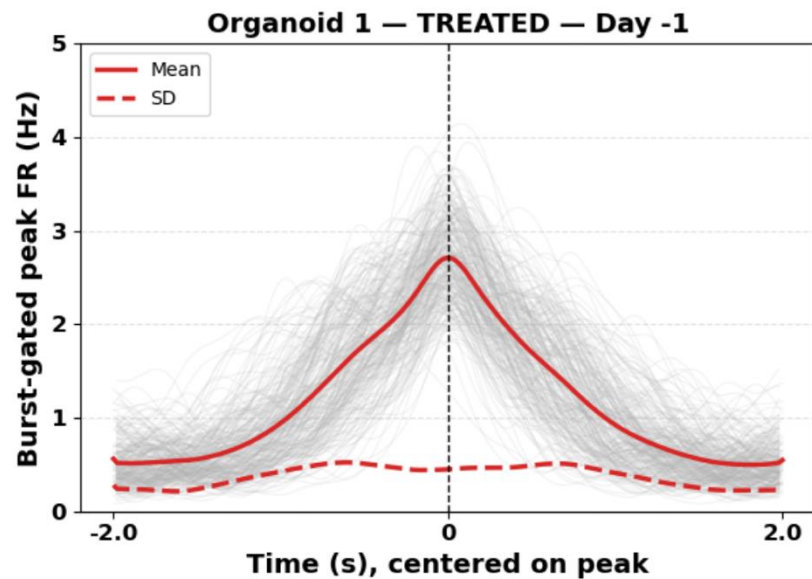
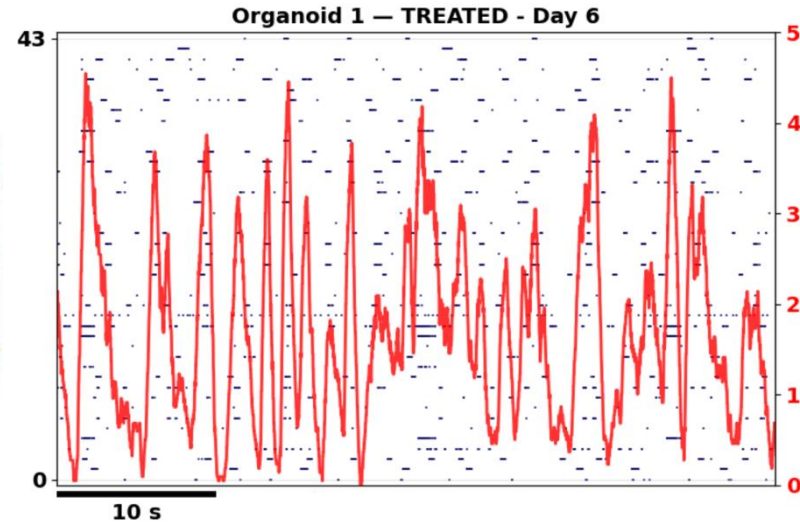
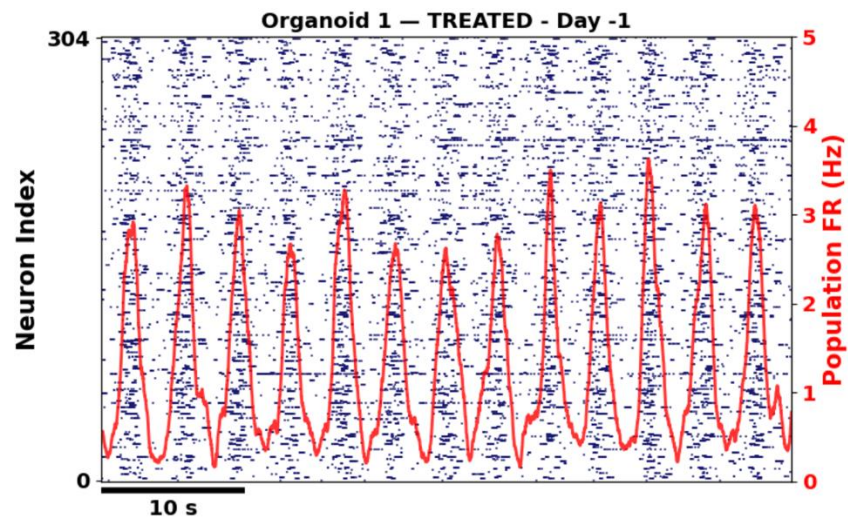
Organoid 5 — TREATED — Day -1



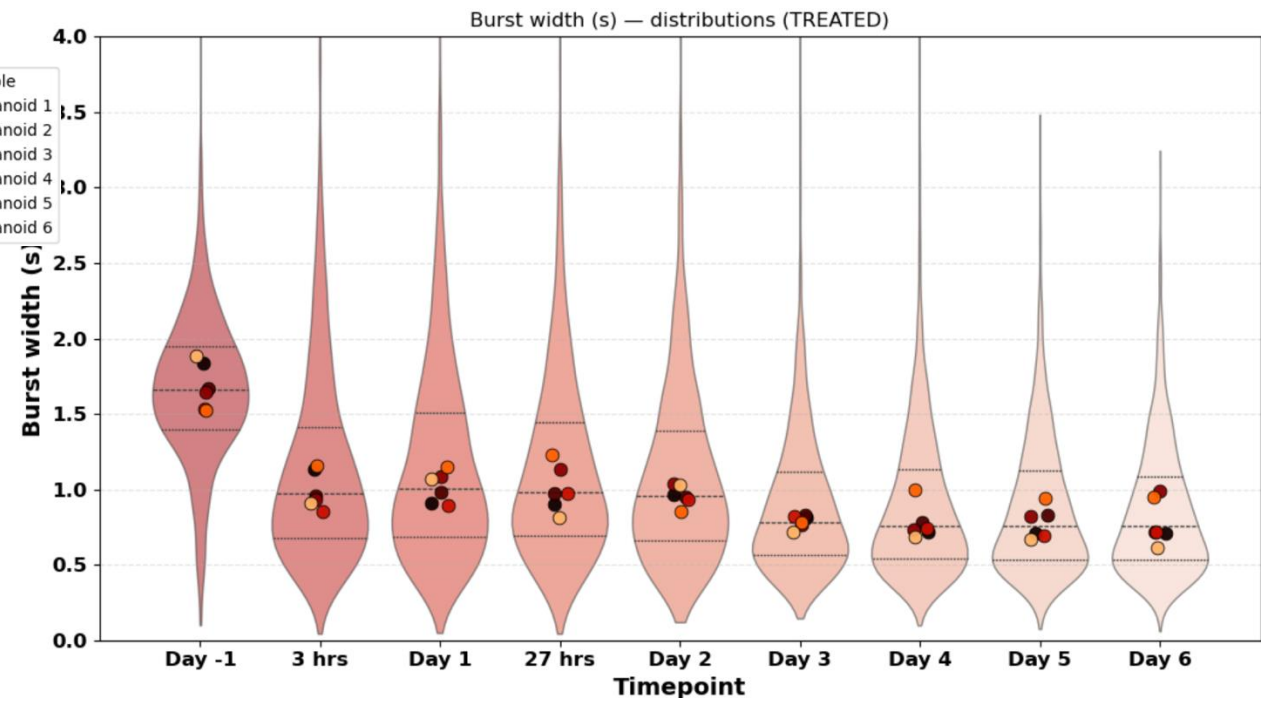
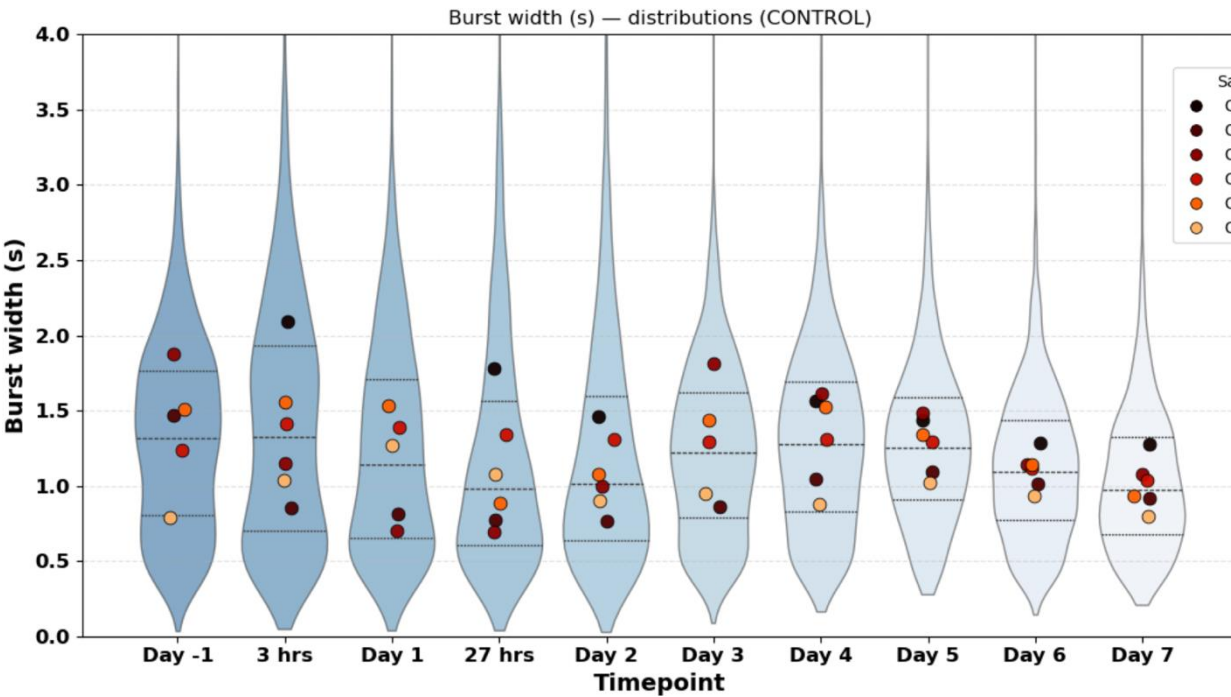
Organoid 5 — TREATED — Day 6



Peak Events Got Narrower After Treatment

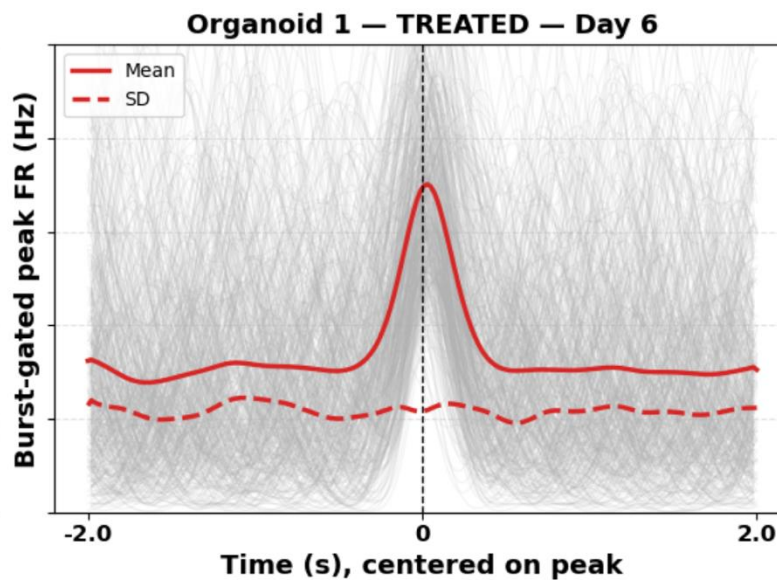
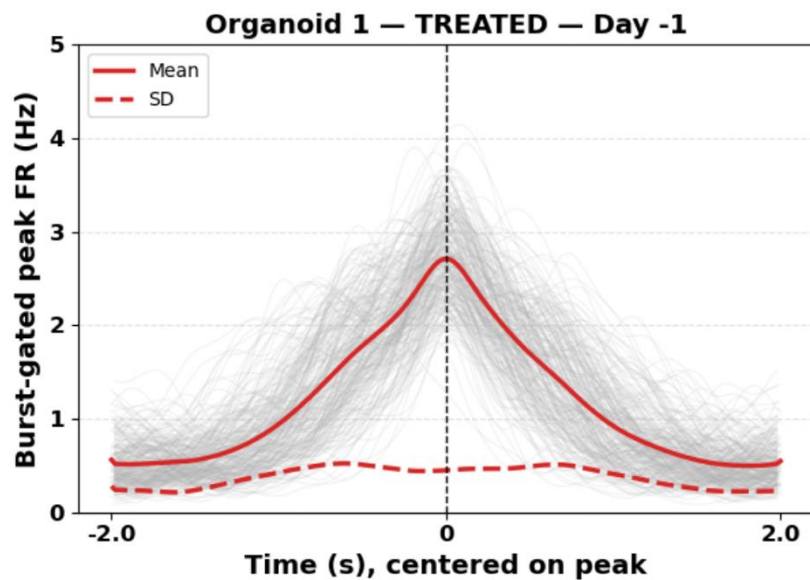
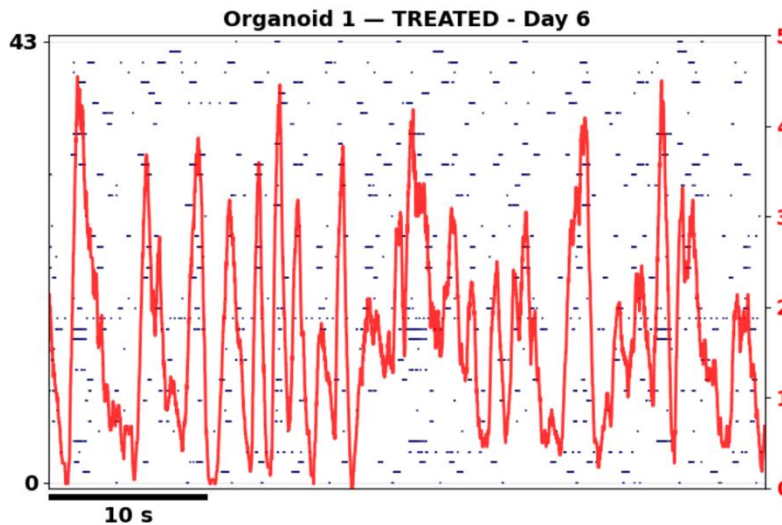
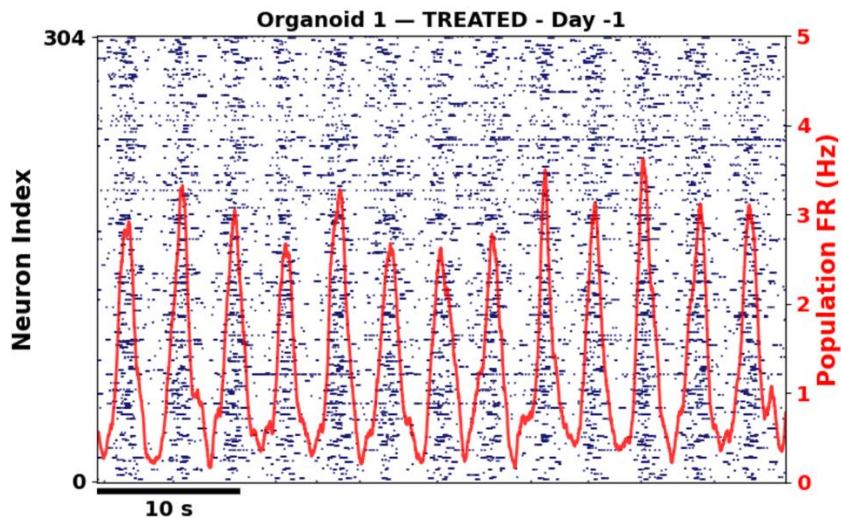


Setting Median Burst Widths as Min Burst Distance



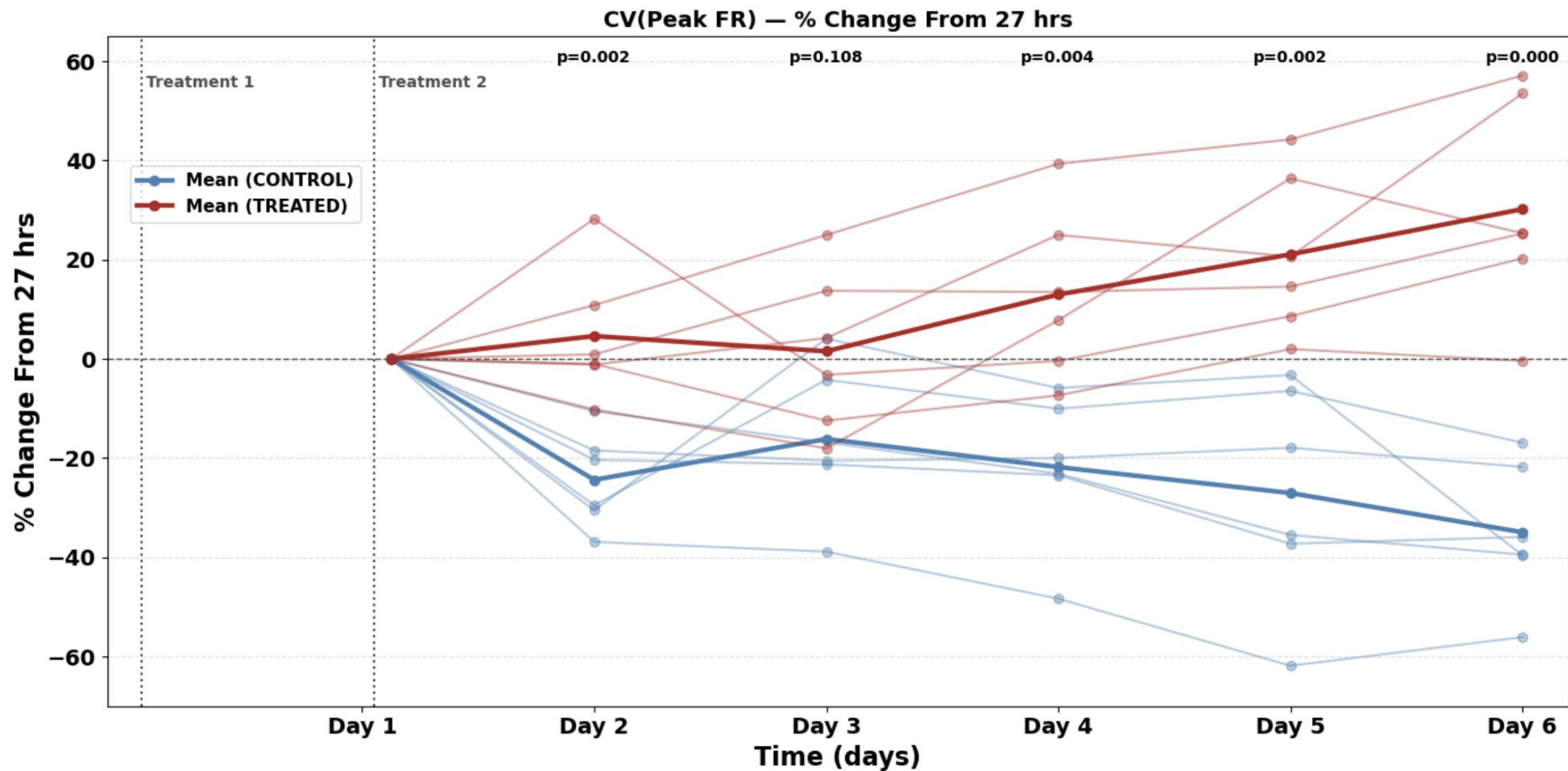
Dots are medians per organoid while the violin contains all widths

Peak Amplitudes Got More Variable After Treatment

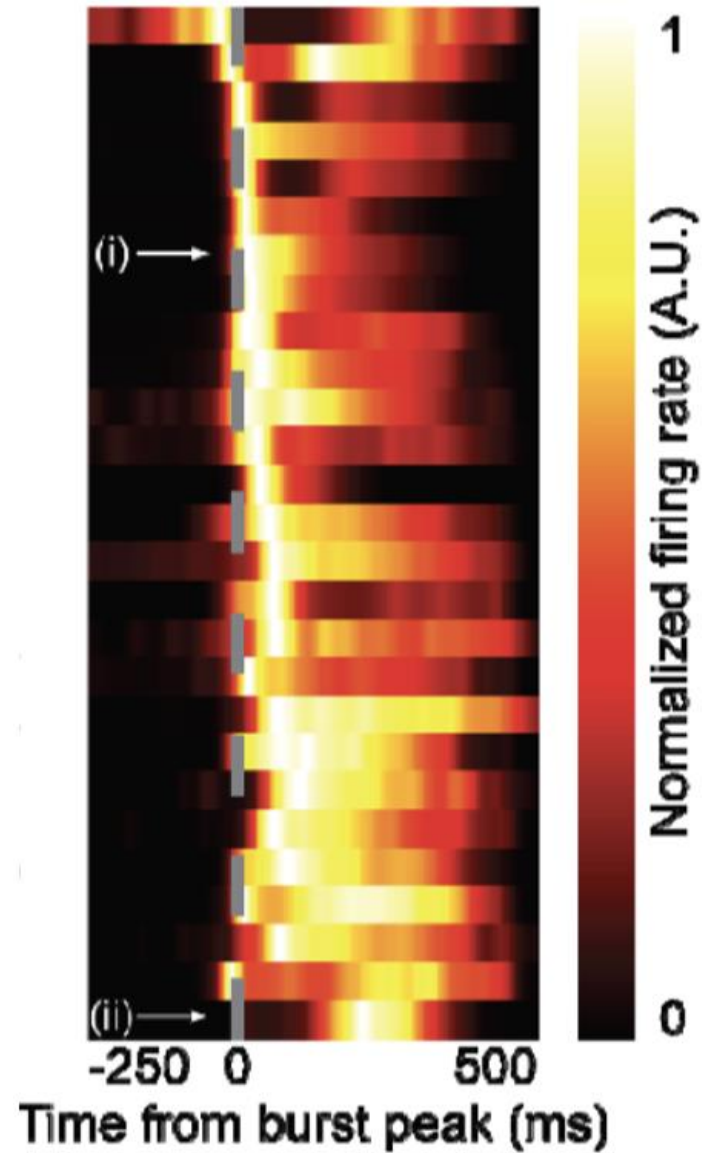


$$\frac{SD}{Mean} = CV$$

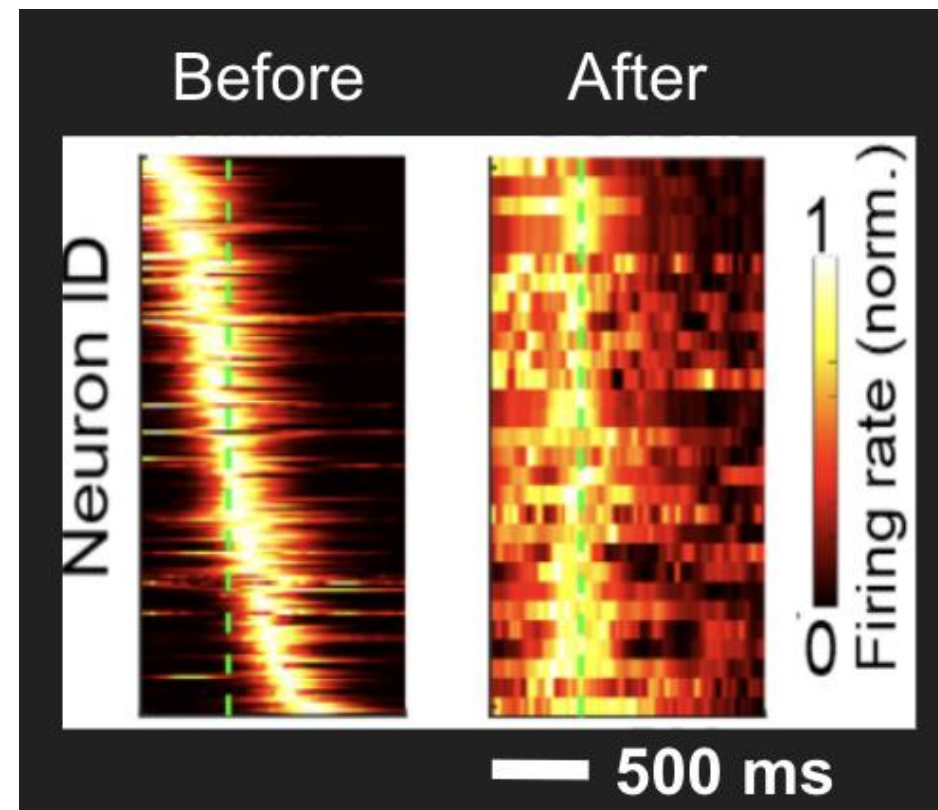
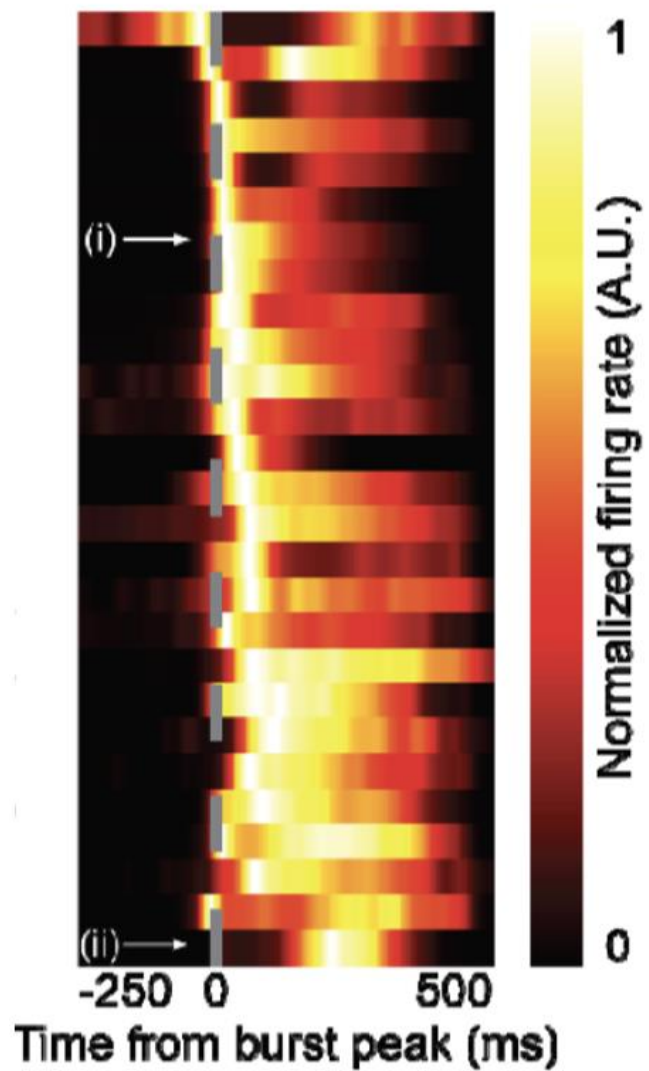
Peak Amplitudes Got More Variable After Treatment



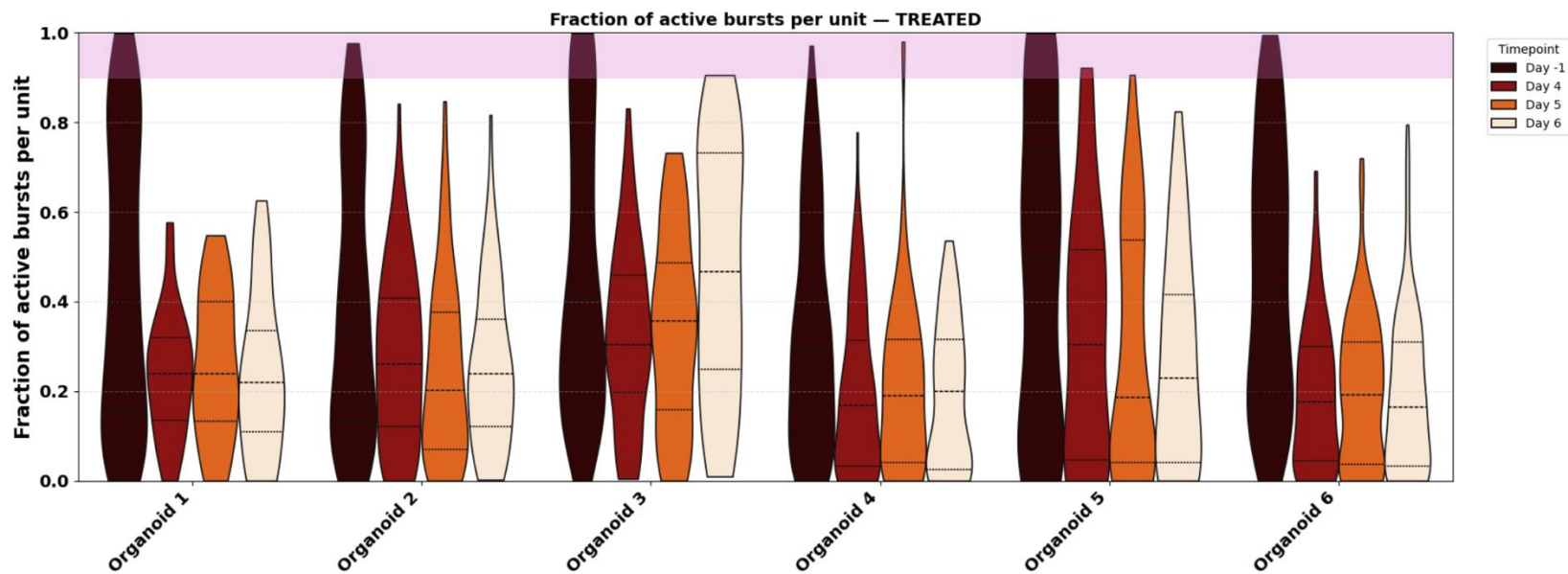
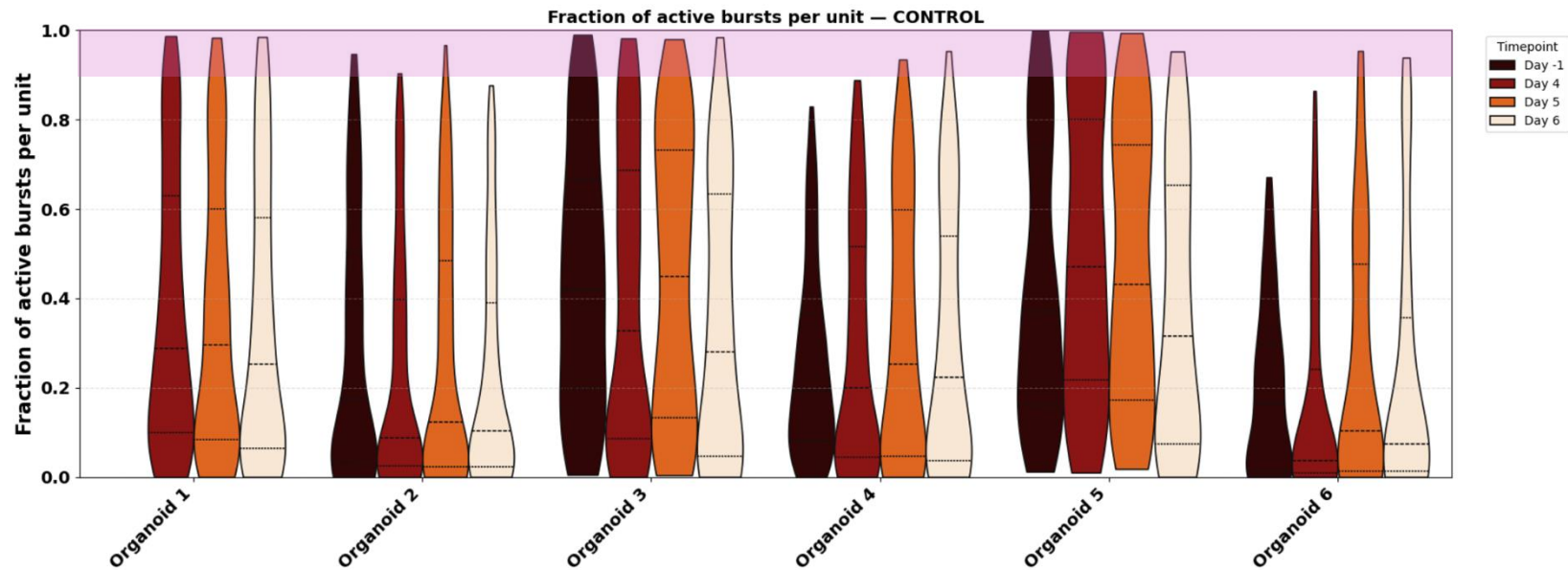
Post-Treatment Variability in Backbone Units



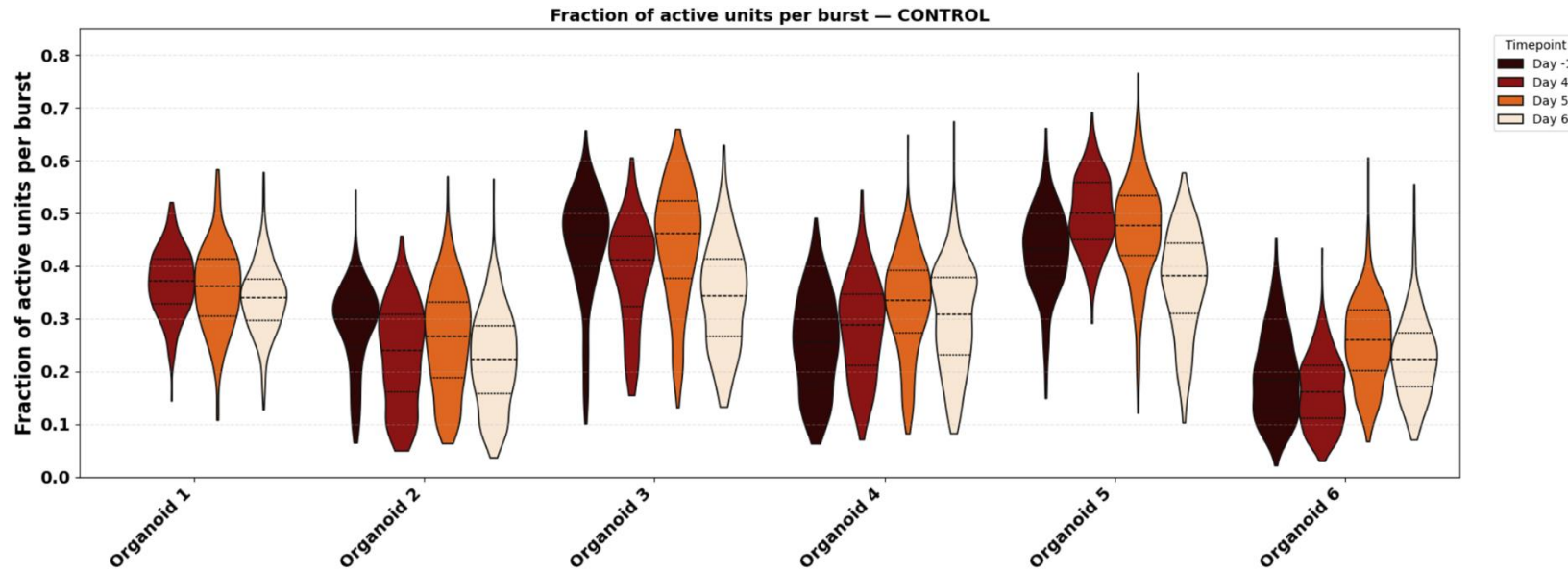
Backbone Units are Abolished After Treatment



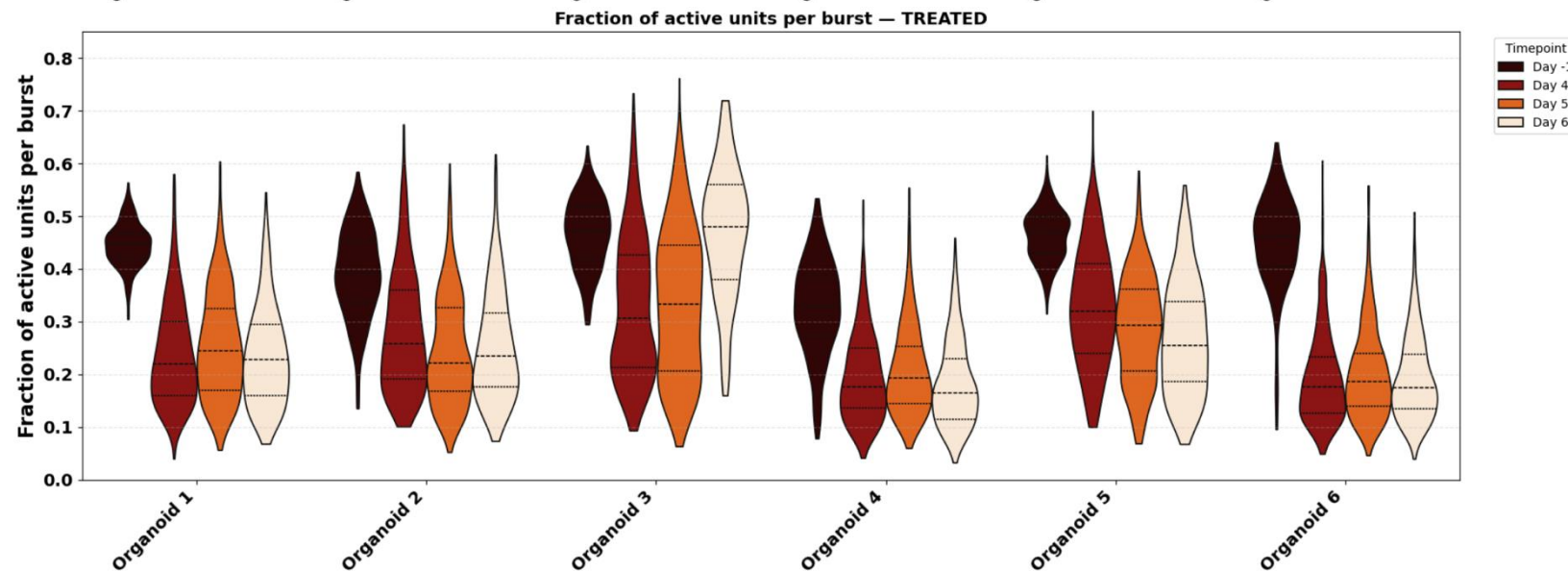
Backbone Units are Abolished After Treatment



Backbone Units are Abolished After Treatment



Fraction of active units per burst
= $\frac{\# N \geq 2 \text{ spikes in burst}}{\text{Total } N}$



Wrapping Up

Completed

- Generated a scalable model to study neurodegenerative diseases in a human-relevant context
- Developed an imperfect, but workable, method to manage highly-variable firing in treated organoids
- Identified persistent population-level feature changes: peak firing & burst width
- Found backbone sequences were destroyed after treatment

Next:

- Continue to refine methods and dig deeper into ensemble and unit-level changes
- Potentially develop experiments around microplastics and if/how they promote neurodegeneration

References

Dorsey, ER & Bloem, BR. Parkinson's Disease Is Predominantly an Environmental Disease. *Journal of Parkinson's disease*, 14(3), 451–465 (2024).

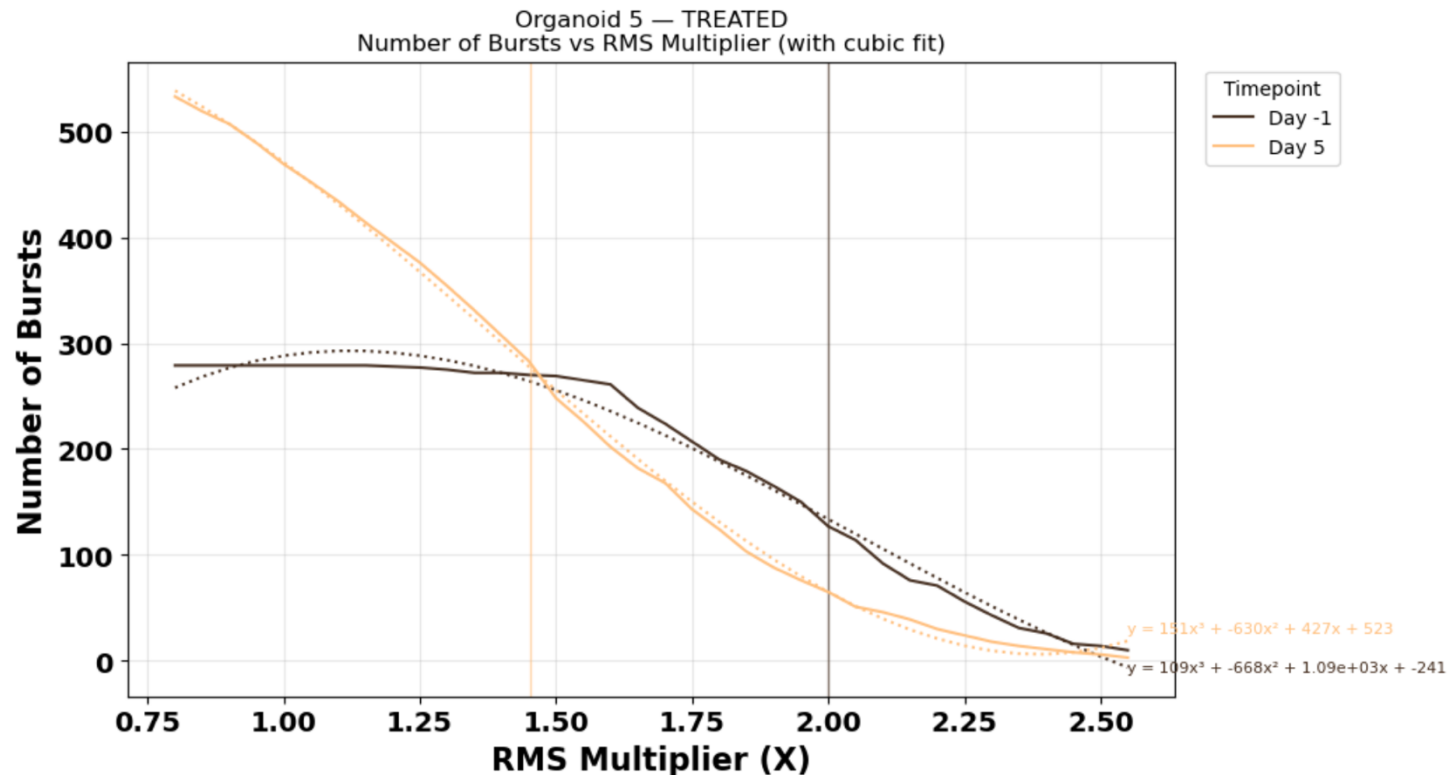
Cookson MR. alpha-Synuclein and neuronal cell death. *Molecular Neurodegeneration*. Feb 4;4:9 (2009).

Nickels, SL et al. Reproducible generation of human midbrain organoids for in vitro modeling of Parkinson's disease. *Stem cell research*, 46, 101870 (2020).

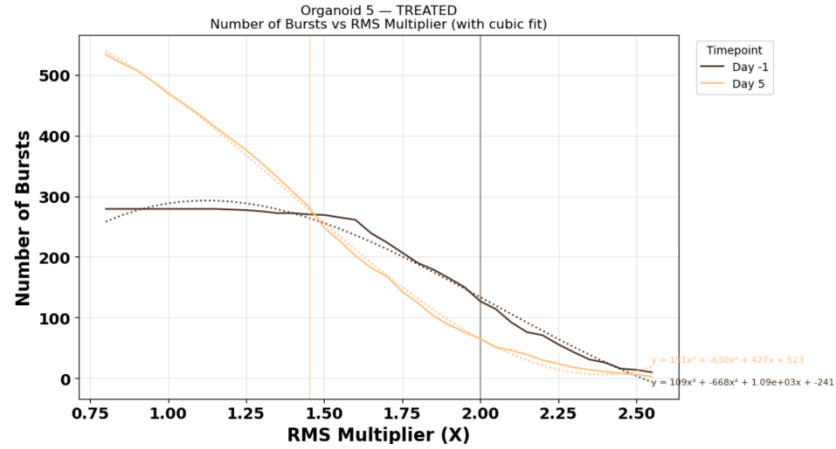
van der Molen T *et al.* Protosequences in brain organoids model intrinsic brain states. *bioRxiv* [Preprint]. Jan 8:2023.12.29.573646 (2025).

Sharf, T *et al.* Functional neuronal circuitry and oscillatory dynamics in human brain organoids. *Nature Communications* 13, 4403 (2022).

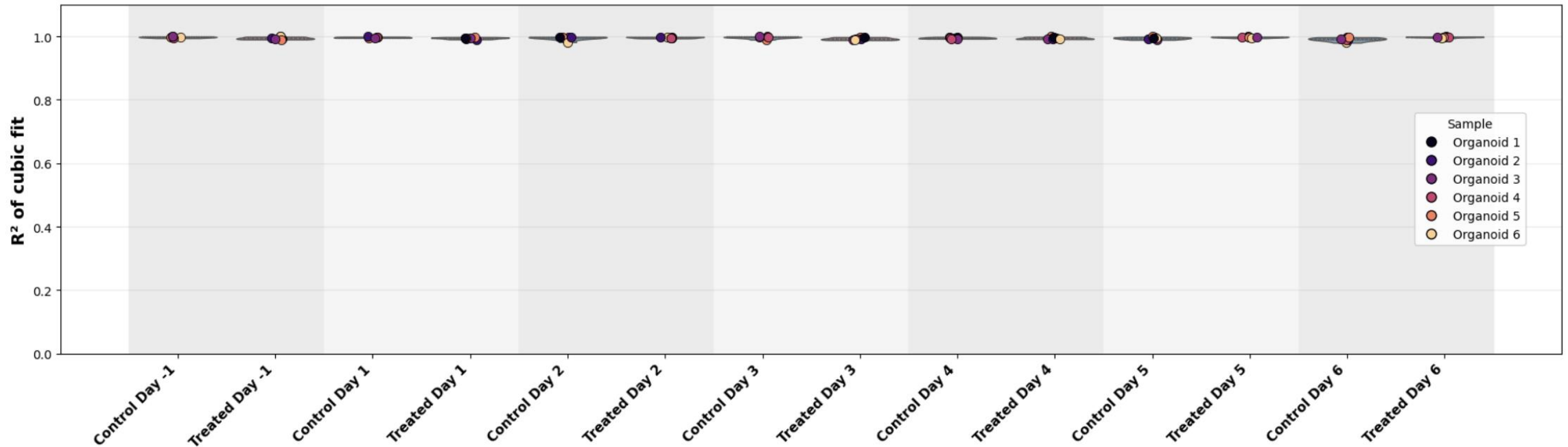
Fitting the Curves

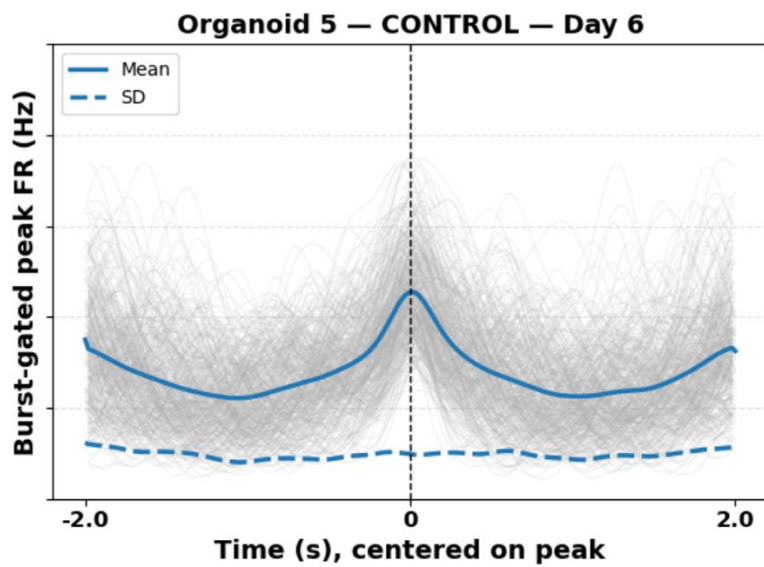
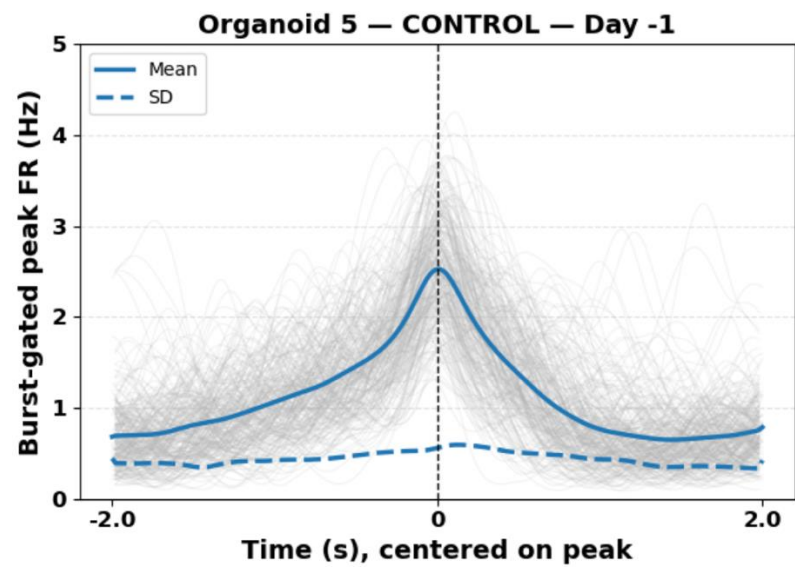
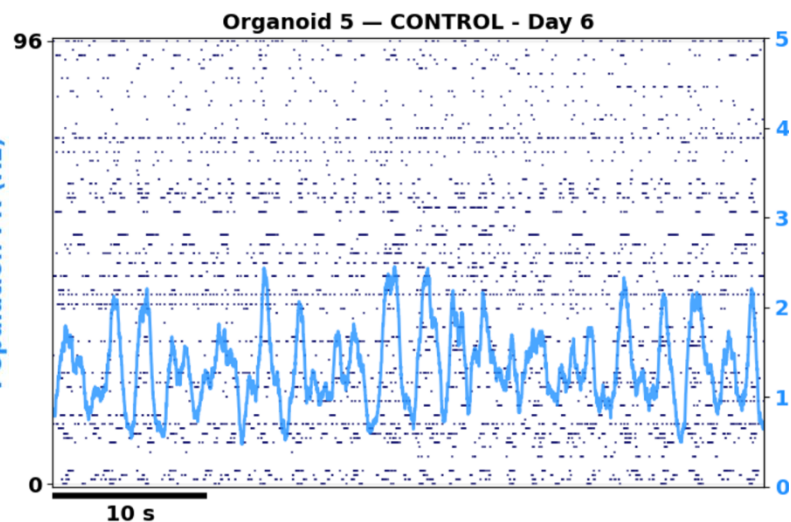
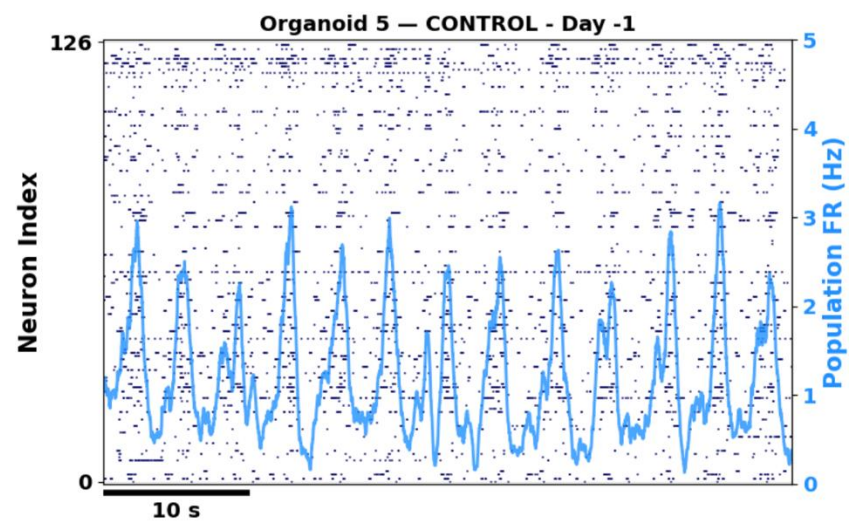


Running a Goodness of Fit Test

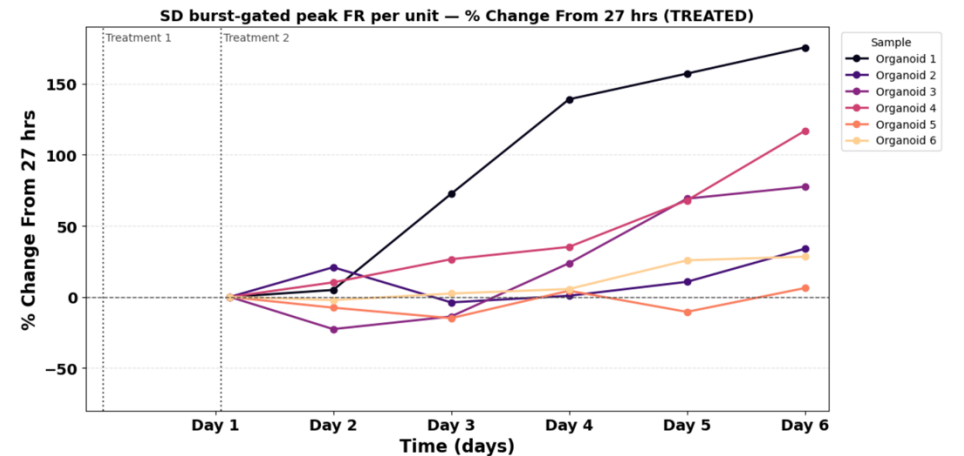
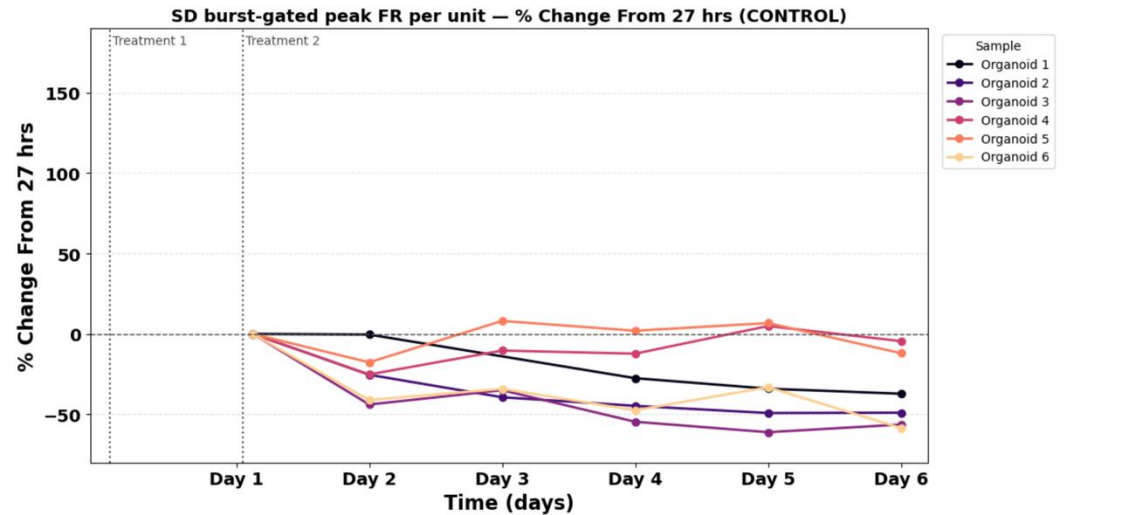
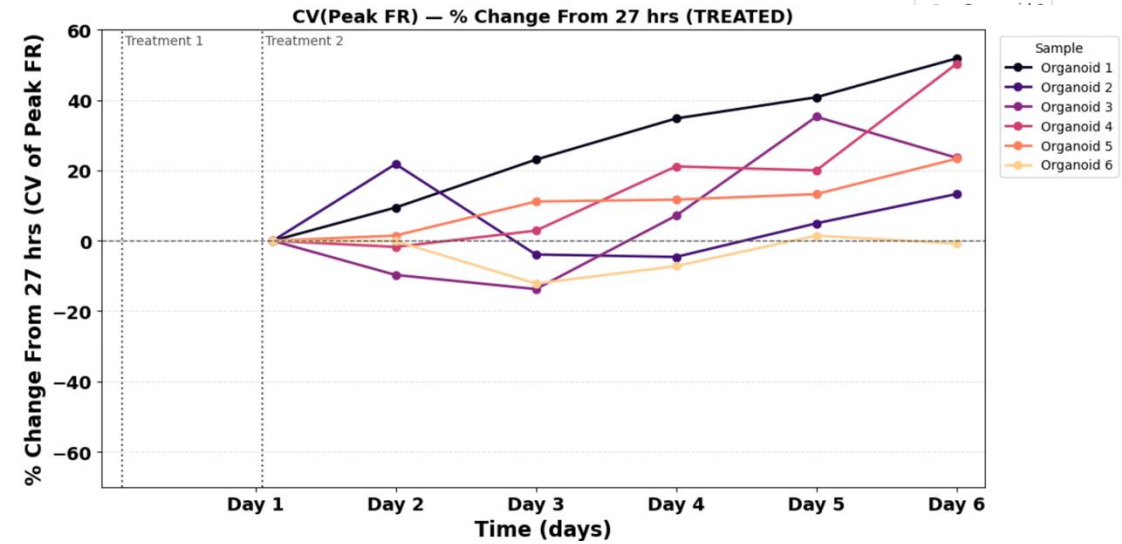
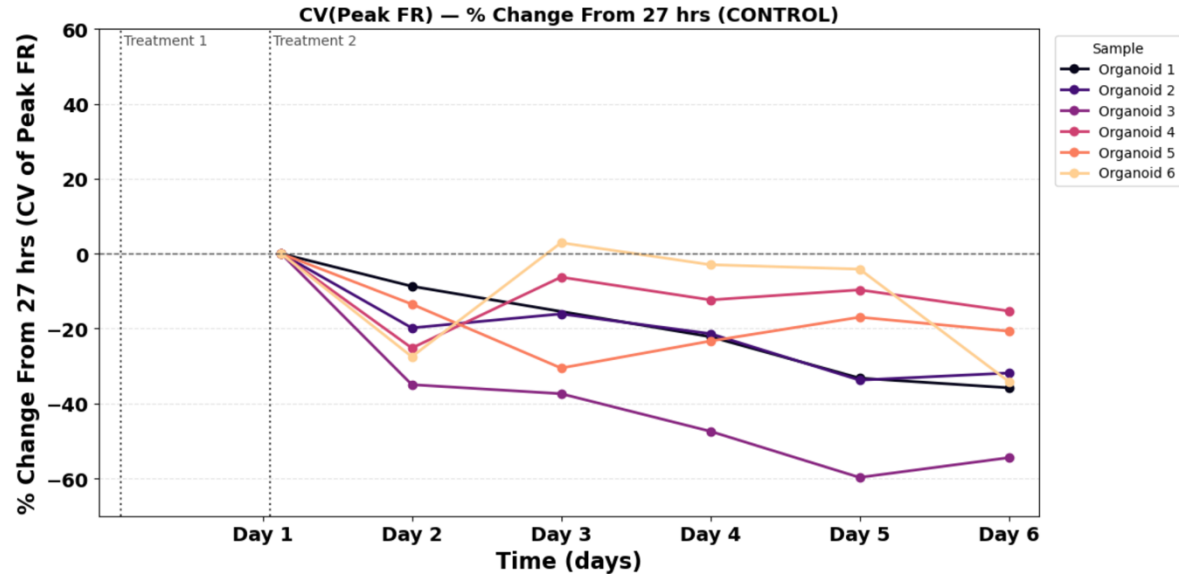


Cubic Fit R^2 - Days -1 to 6

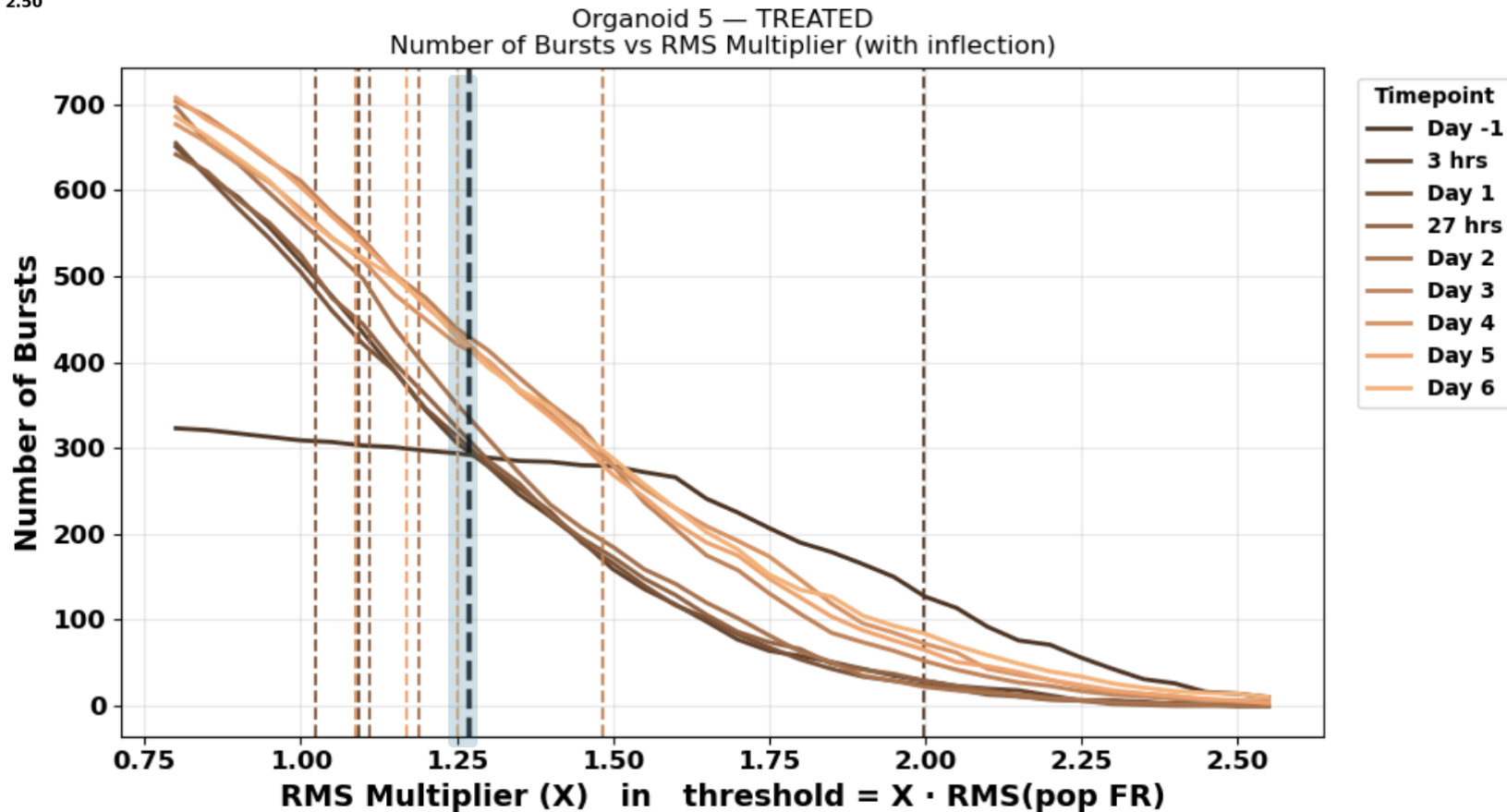
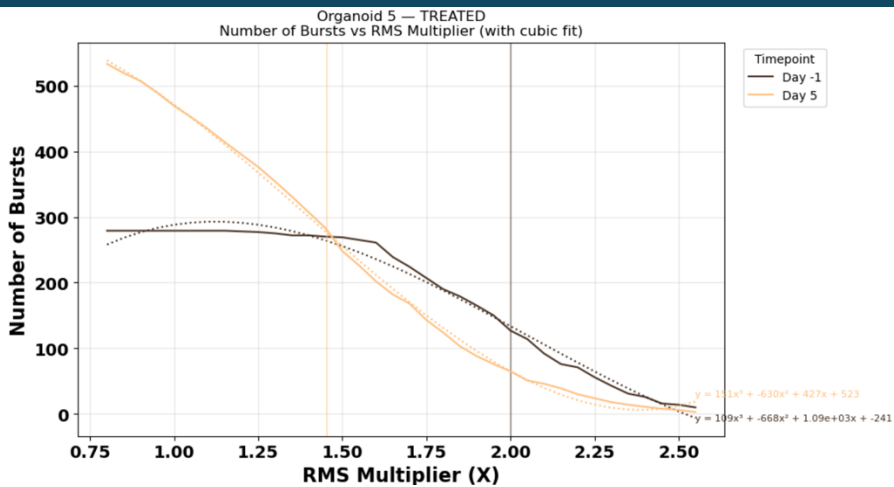




$$CV = (SD \text{ of peak firing rates}) / (\text{Mean of peak firing rates}) \times 100\%$$



Taking the Mean RMS Multiplier at Inflection For Each Recording



Organoid 2 – TREATED – Day 5

