



The effects of variability in the timing of electrical brain stimulation pulse sequences on dopamine release and single-unit activity in the nucleus accumbens

Hamilton, A.R.¹, Vishwanath, A.², Weintraub, N.C.¹, Winter, G.M.², Lin, K.K.³, Lewis, T.J.⁴, Cowen, S.L.², Heien, M.L.¹

¹Department of Chemistry & Biochemistry, ²Department of Psychology, ³Department of Mathematical Sciences, University of Arizona, Tucson, AZ,

⁴Department of Mathematics, University of California Davis, Davis, CA

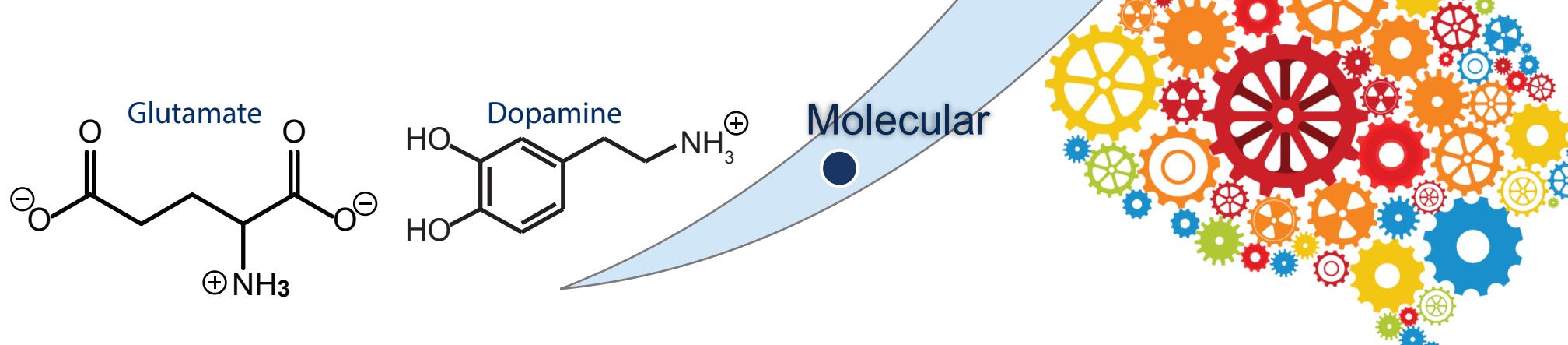
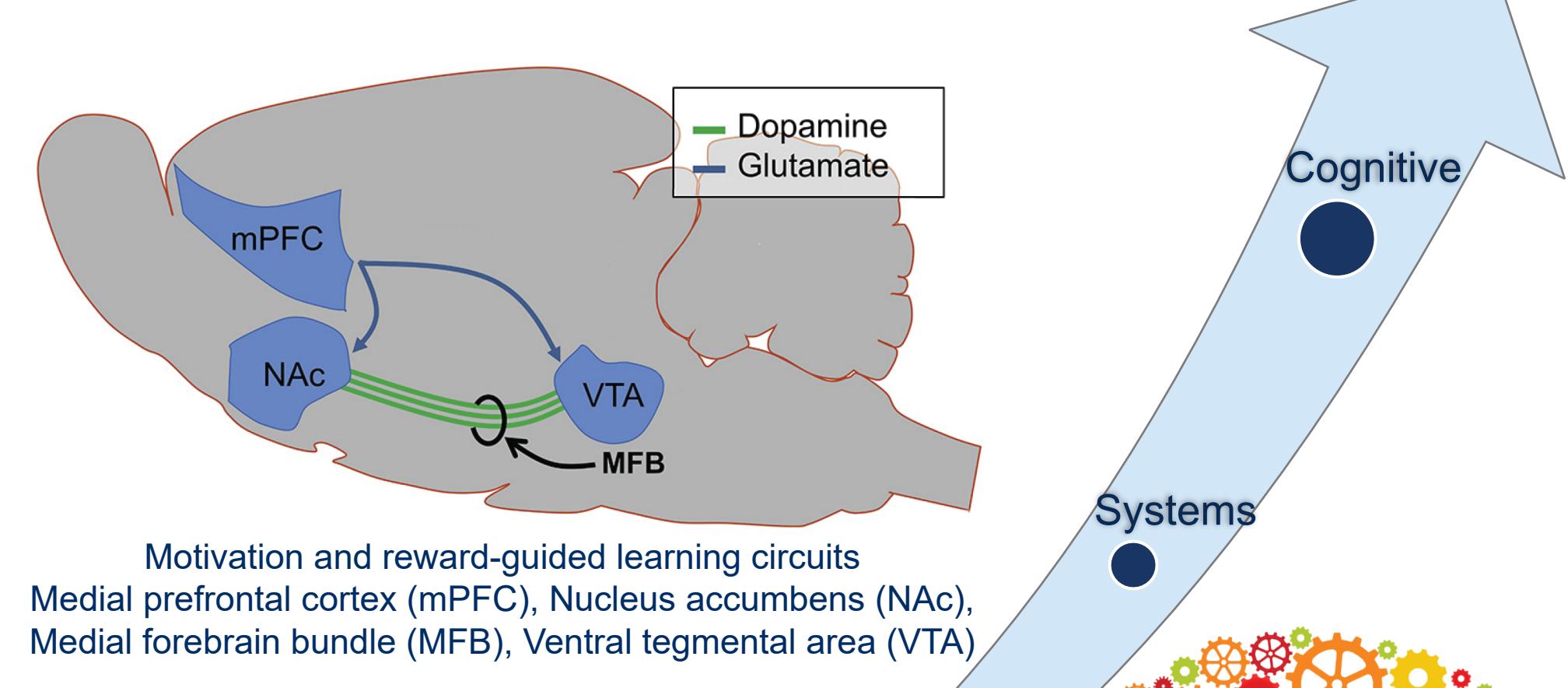
Abstract

Dopamine release in the striatum is integral to motor control, reward-guided learning, and decision making. Electrical deep brain stimulation (DBS) is an important tool for the causal investigation of neural circuits and treatment of diseases such as Parkinson's disease. Traditionally, DBS has been applied using fixed inter-pulse interval stimulation at a given frequency. However, past research has shown neural circuits are often more responsive to variable and unpredictable input. We seek to explore the effects of inter-pulse variability on evoked dopamine release and single-unit activity in the nucleus accumbens (NAc) and whether these effects differ by the anatomical target of stimulation. We hypothesize that NAc dopamine release and single-unit responses will be most robust when inter-pulse intervals are variable or 'bursty'. Methods: Anesthetized (isoflurane) male Sprague-Dawley rats (345-400 g, n = 8) were implanted with a carbon-fiber microelectrode and/or a Neuropixels probe placed in the NAc and a stimulating electrode placed in the medial forebrain bundle (MFB) or the medial prefrontal cortex (mPFC). Ten-second stimulation trains with varying inter-pulse interval statistics were delivered while sub-second changes in dopamine concentration were measured using fast-scan cyclic voltammetry (FSCV) and neural ensemble activity was measured using Neuropixels probes. Data from dopamine measurement indicate that the effects of pulse variability on release depends on the stimulation target. For example, dopamine release followed the pattern of stimulation more closely during MFB stimulation relative to mPFC stimulation. Pulse variability may also increase peak release when delivered to the MFB but decrease release when delivered to the mPFC. Data from neural ensemble recordings indicated that the effects of stimulation on ongoing neural activity differed by neuronal subtype (putative medium spiny neurons (MSNs) and interneurons (INs)). MSNs increased activity during stimulation while INs expressed reduced firing activity. Stimulation also reduced network measures of sparsity and increased overall population activity for minutes following stimulation offset.

Results from these experiments may enhance the understanding of how the timing and variability of DBS pulse sequences modulates the time course of release and ensemble activity in the striatum.

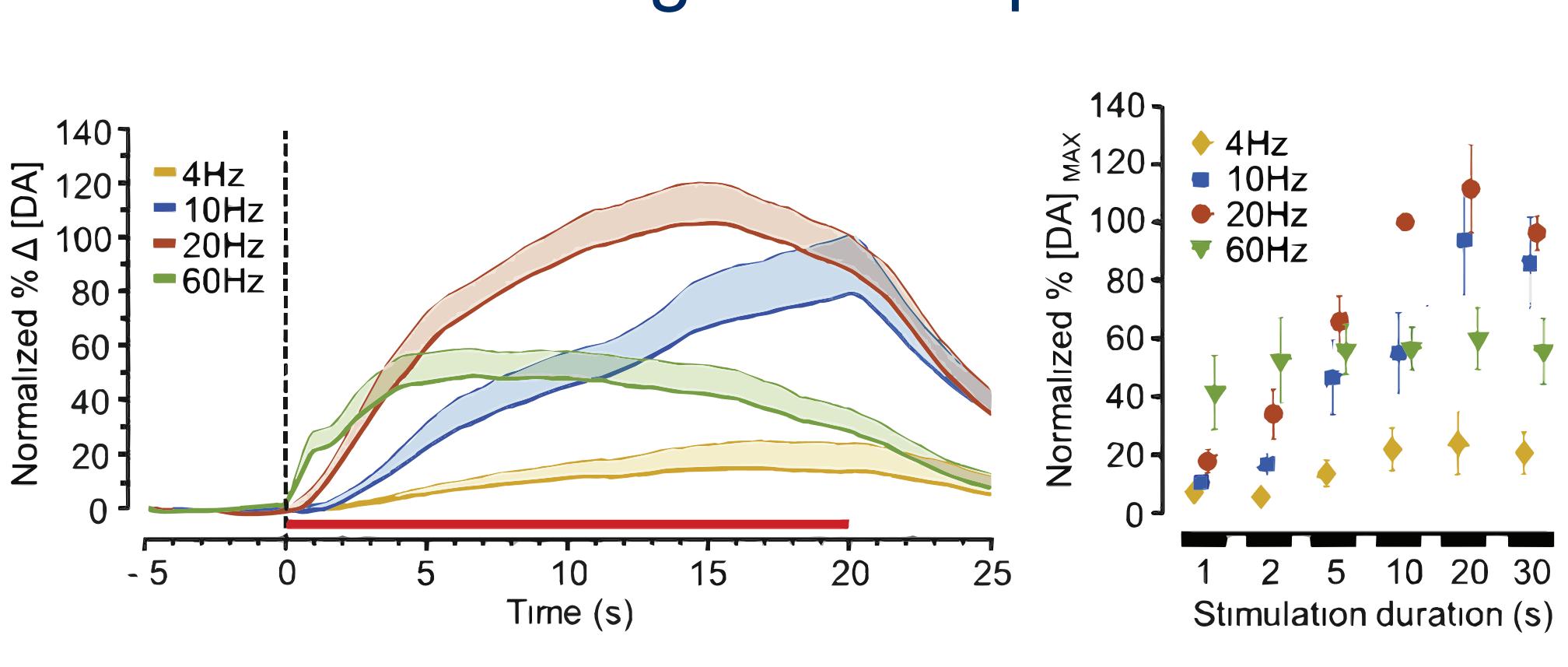
Motivation

Electrical brain stimulation is an important tool to investigate neural circuits and treat neurological diseases

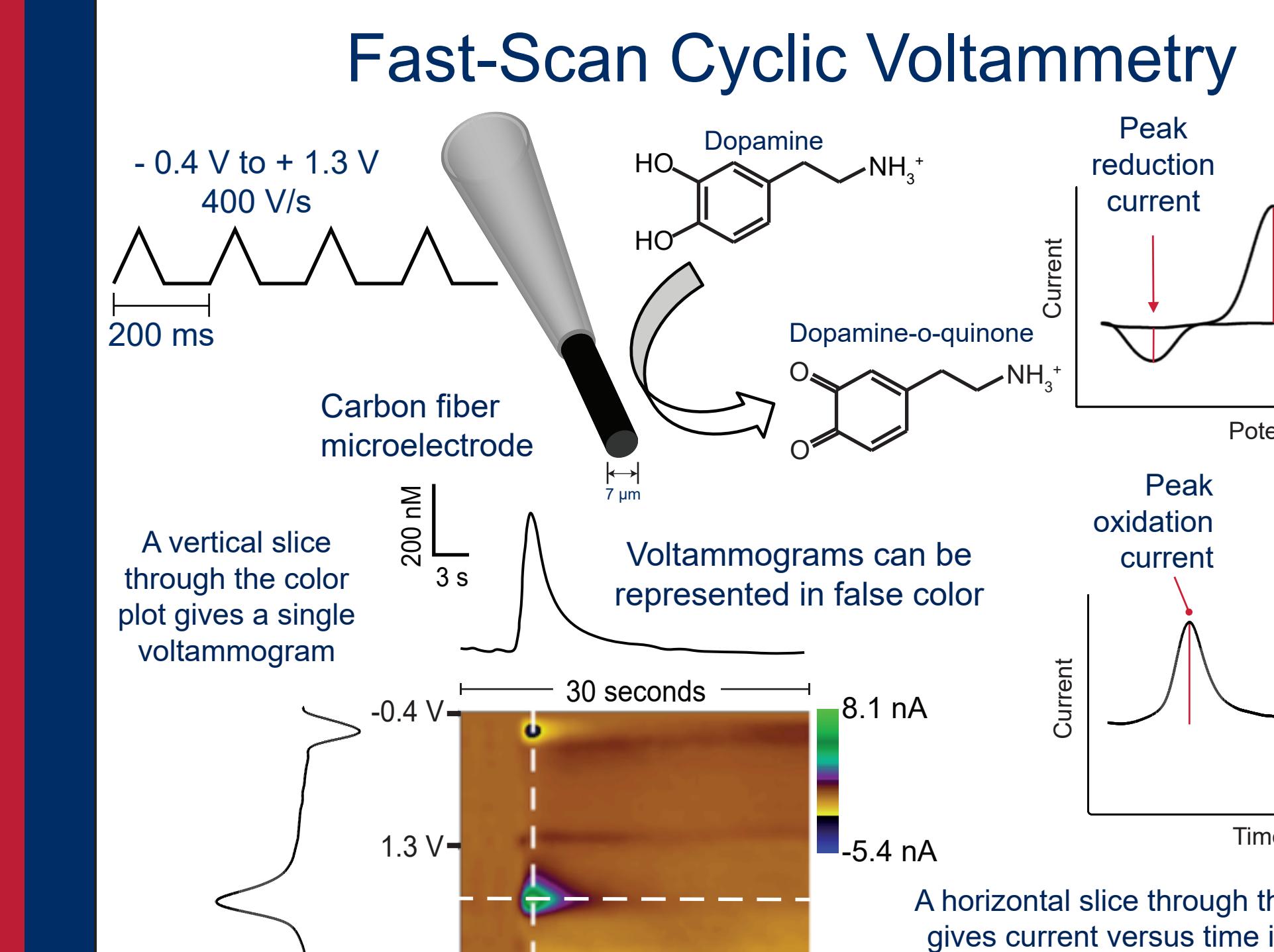


Background

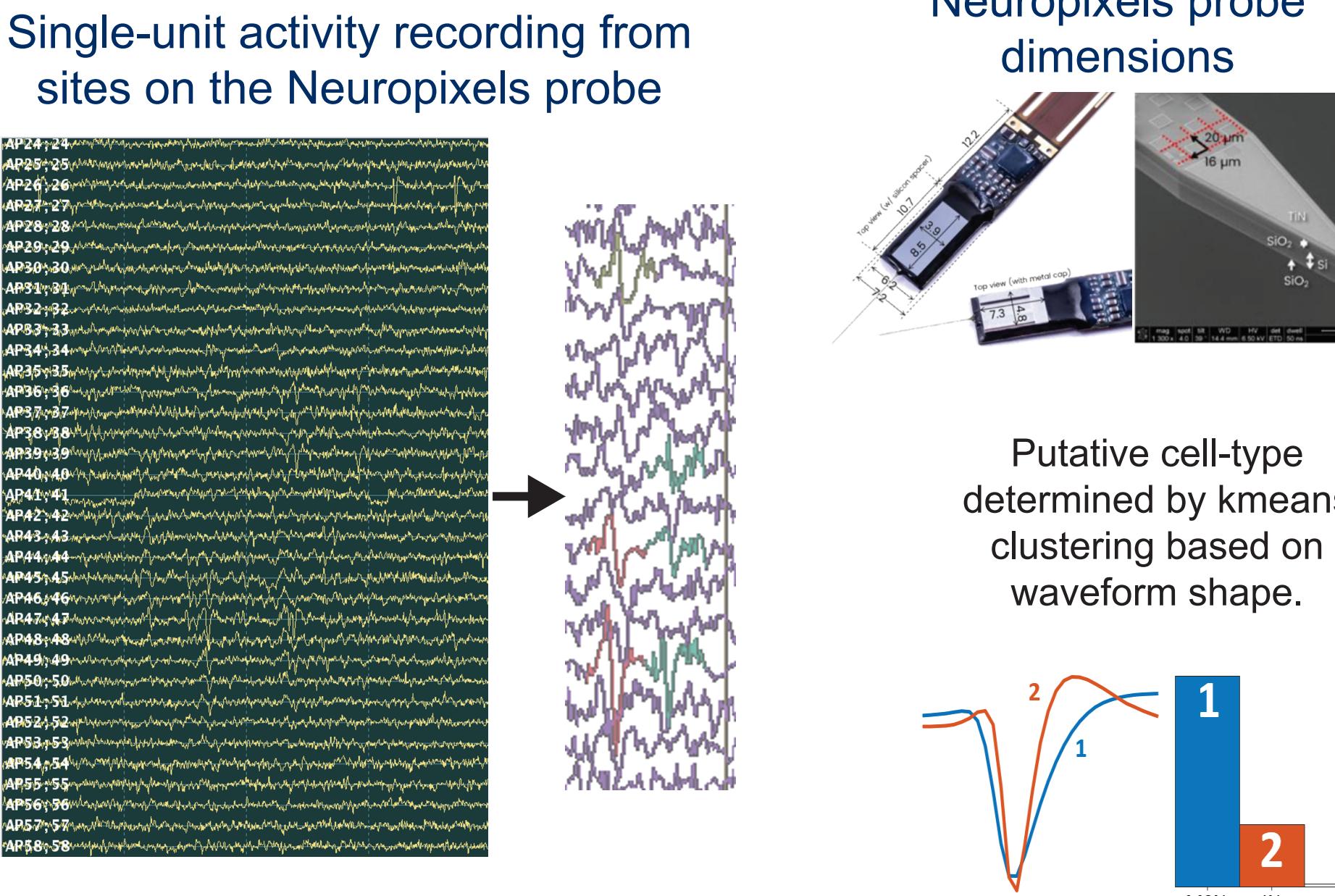
Low frequency, longer duration mPFC stimulation elicits greater dopamine release³



Methods

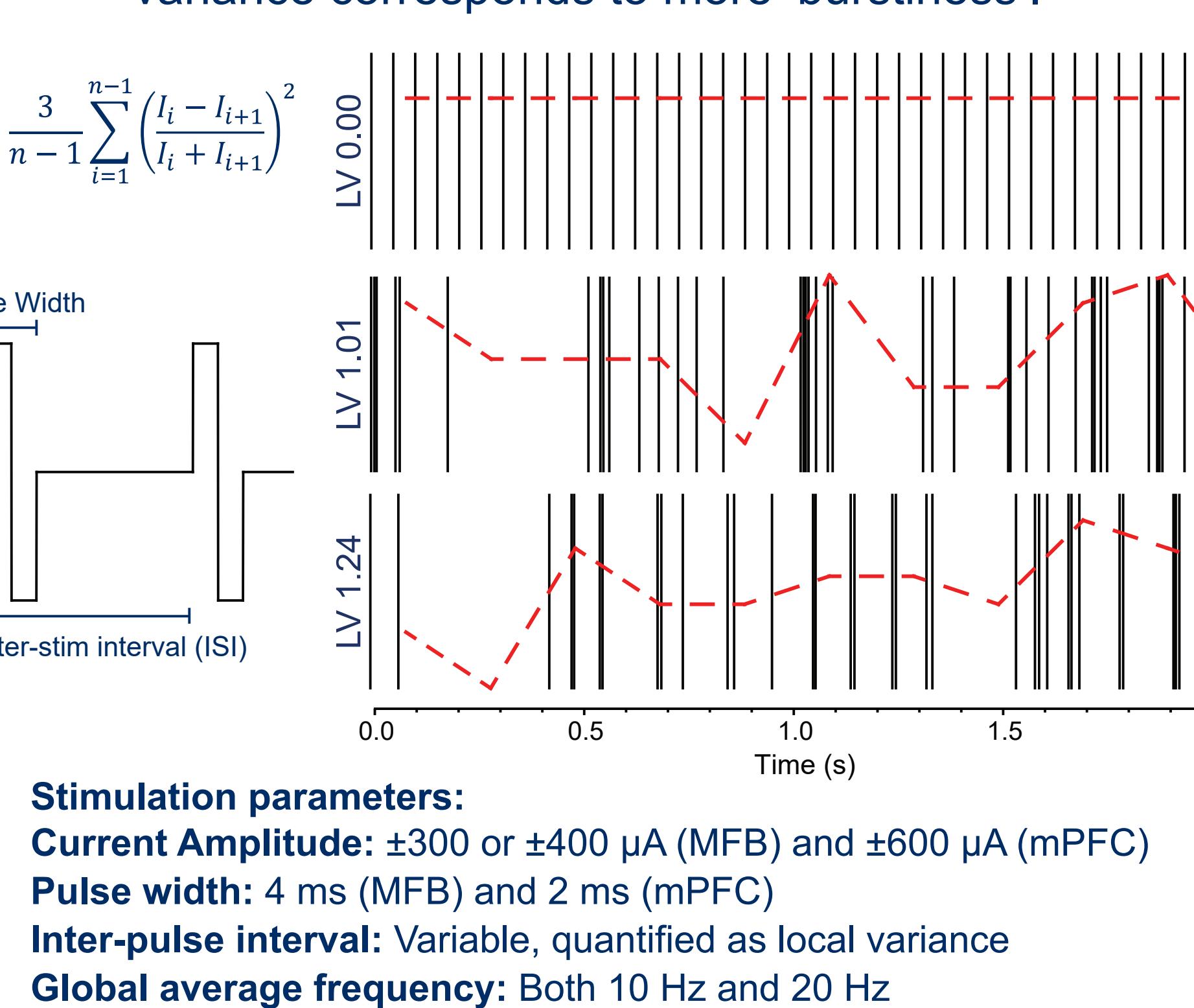


Single-unit Neural-ensemble Activity



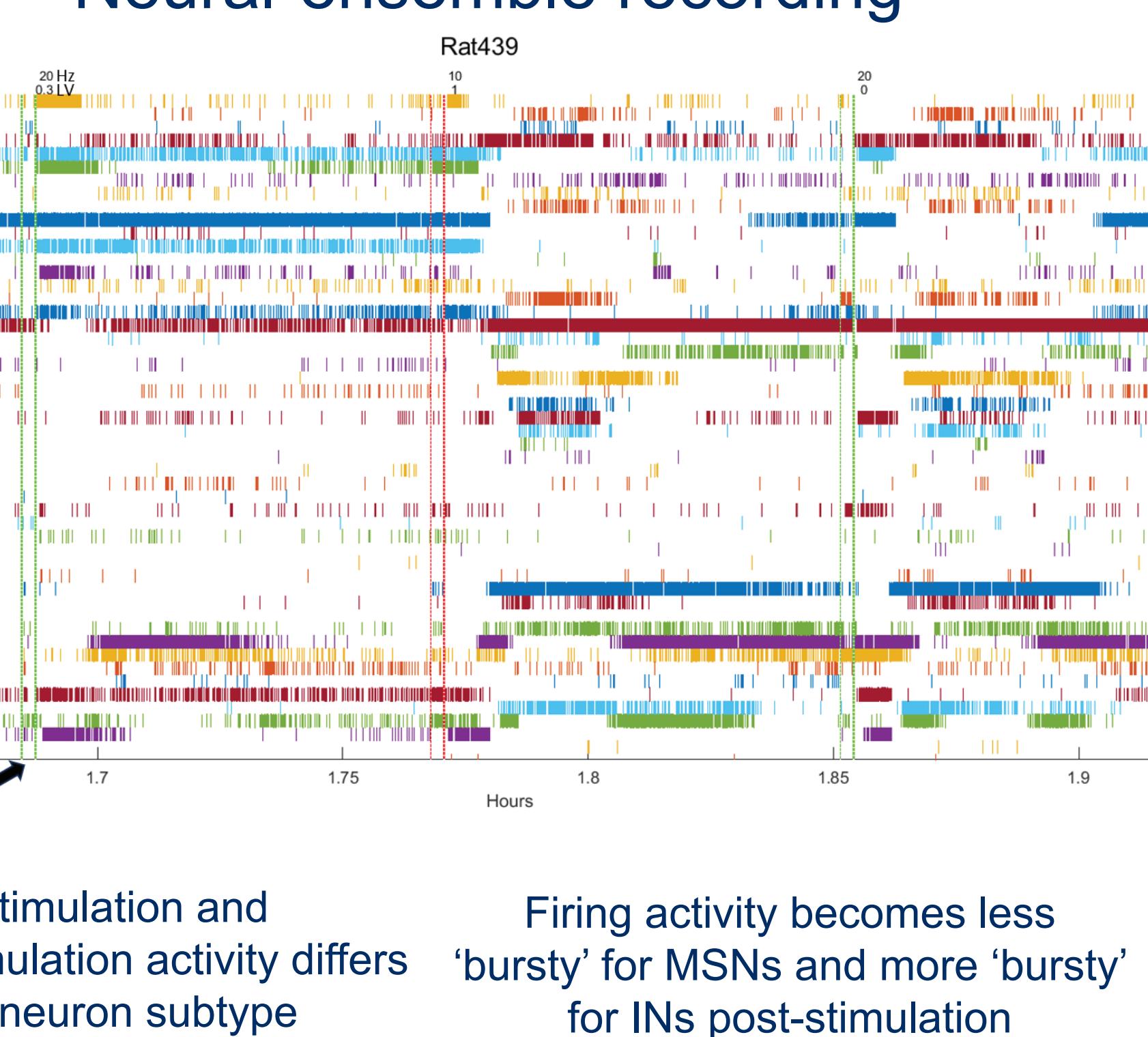
Local Variance

Measure of the variance of the inter-pulse interval, or the 'burstiness' of the stimulation patterns. A higher local variance corresponds to more 'burstiness'.²

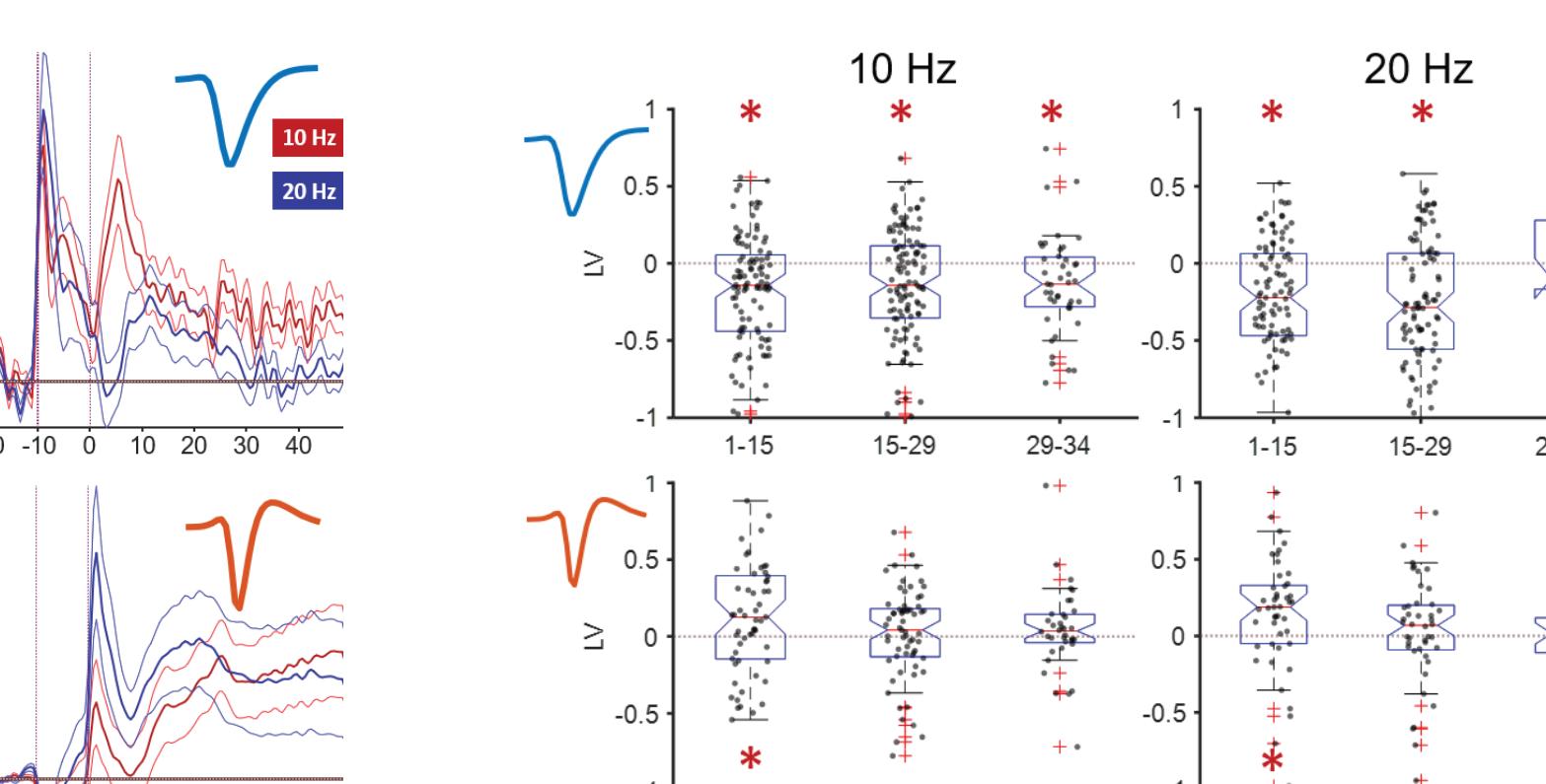


Results

Neural-ensemble recording

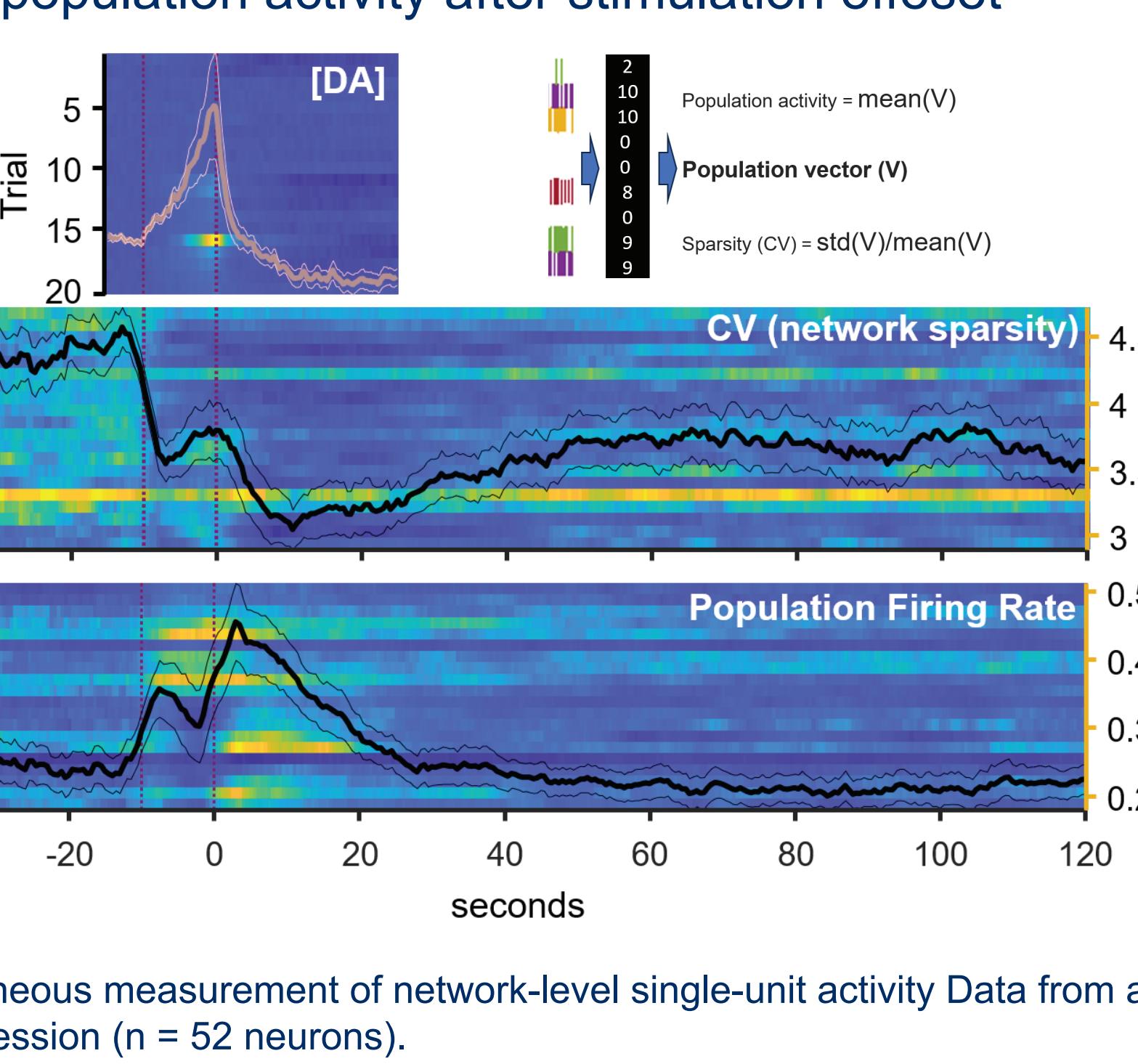


Stimulation and post-stimulation activity differs by neuron subtype



MSNs: Activated and adapt during stimulation. Rebound at stim termination (n = 138)
INs: Inhibition during stimulation, large rebound. Sustained activity for >2 min post stim (n = 41).
* Indicates difference from baseline (t-test).

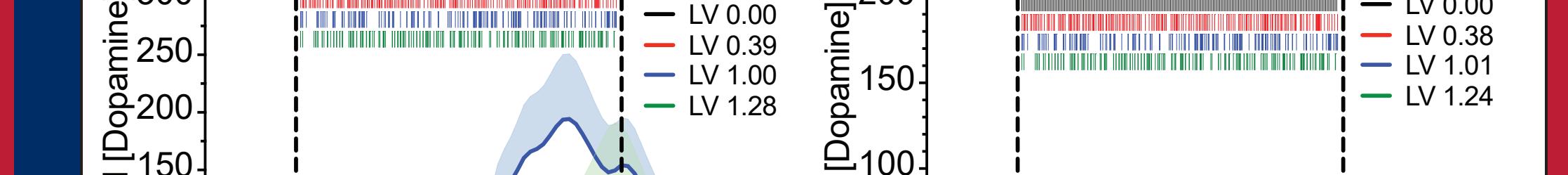
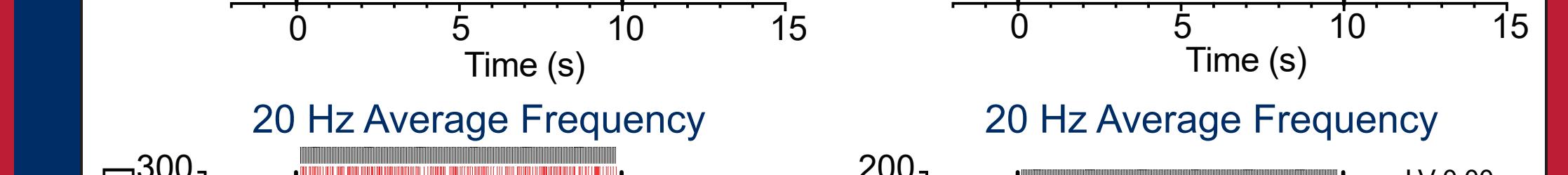
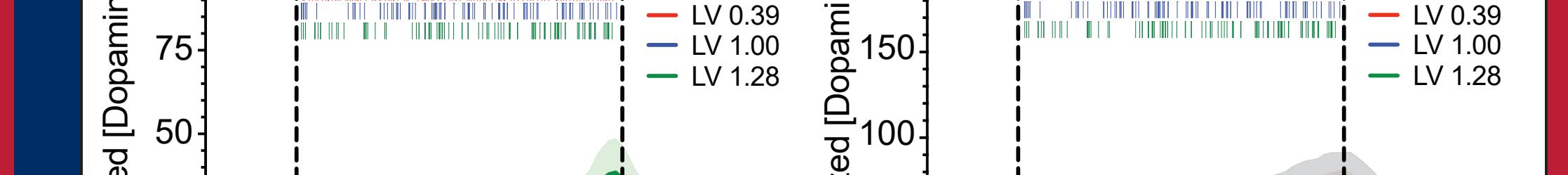
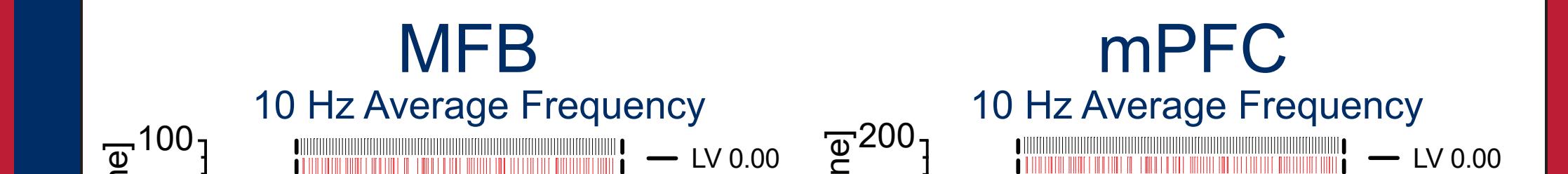
MFB stimulation reduces network sparsity but increases population activity after stimulation offset



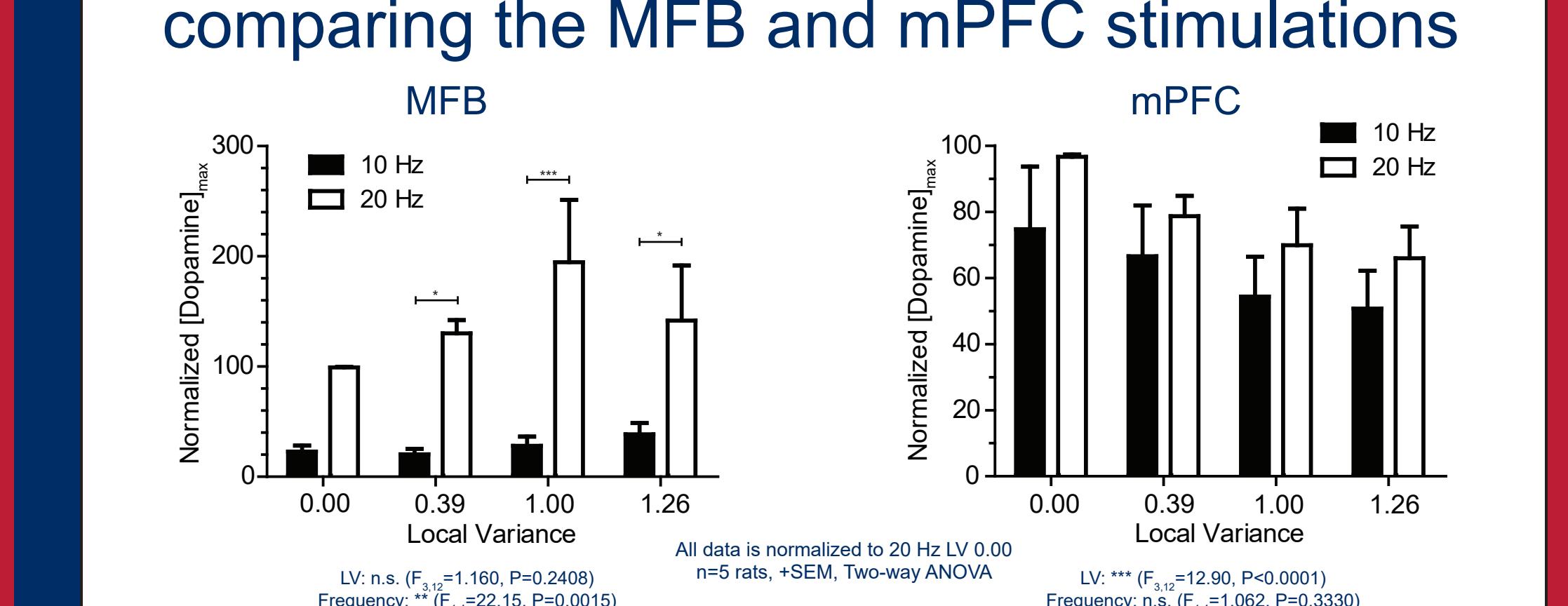
Simultaneous measurement of network-level single-unit activity Data from a single session (n = 52 neurons).

Results

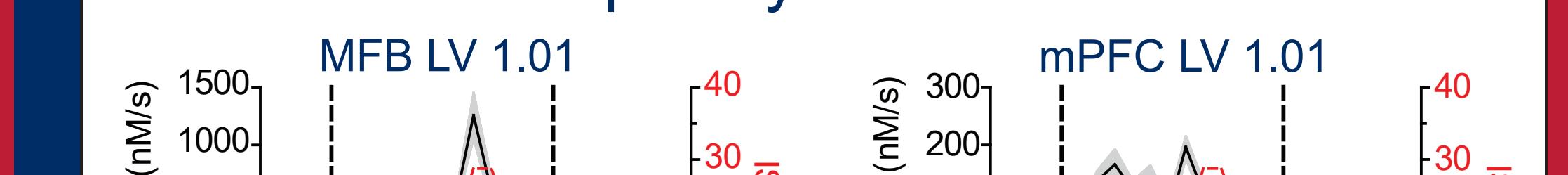
Pulse variability affects the shape of the release of the MFB and mPFC stimulations



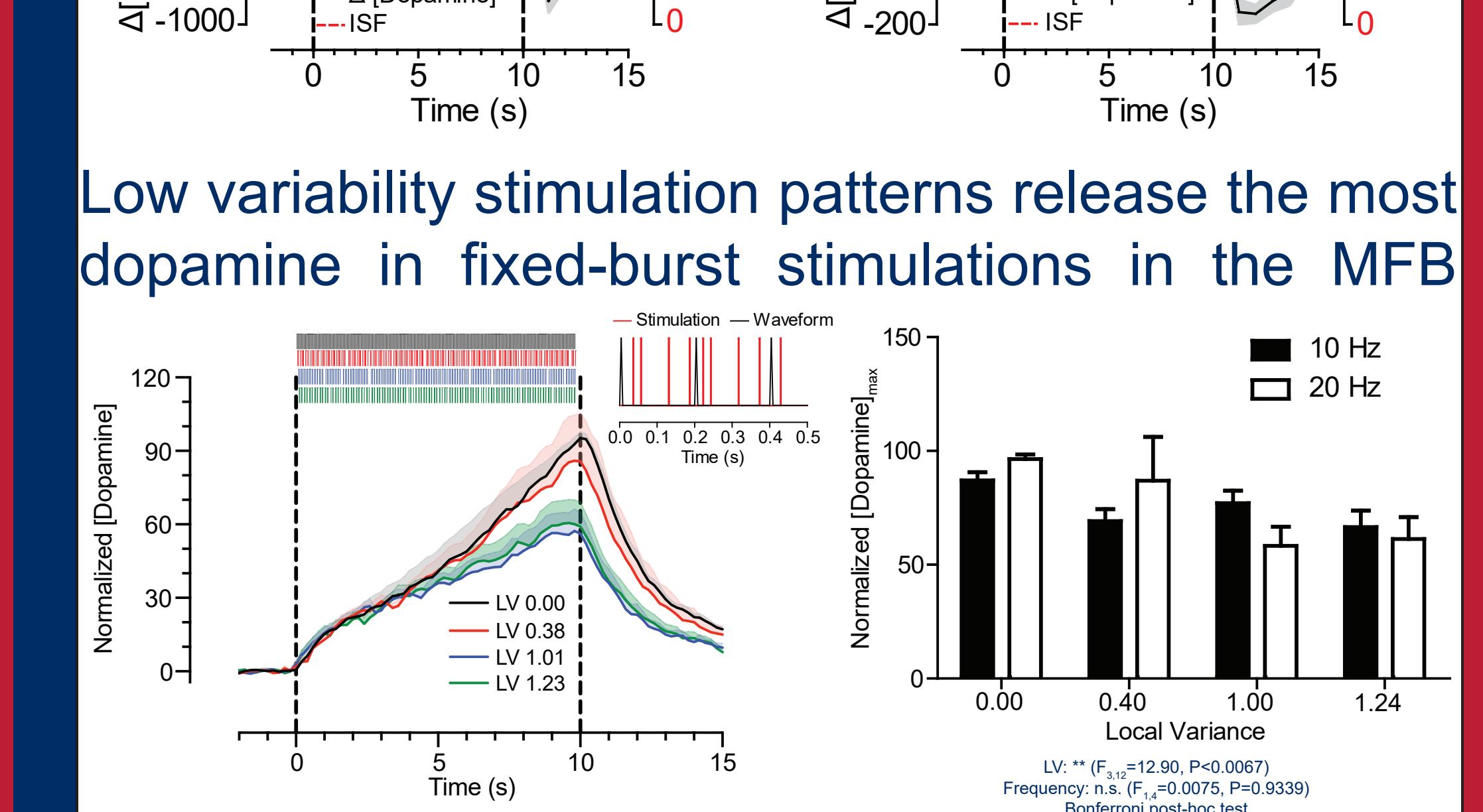
Pulse variability has opposite trends when comparing the MFB and mPFC stimulations



Dopamine release aligns to the instantaneous stimulation frequency in MFB but not mPFC



Low variability stimulation patterns release the most dopamine in fixed-burst stimulations in the MFB



Conclusions

- Ongoing MFB stimulation increases MSN but reduces IN activity. Both MSNs and INs have heightened activity long after stimulation offset
- MFB stimulation reduces network sparsity for >60 seconds post stimulation
- Variable pulses delivered to the MFB but not mPFC results in temporally aligned NAc DA release
- Variable MFB stimulation may increase DA release but variable mPFC stimulation may reduce release

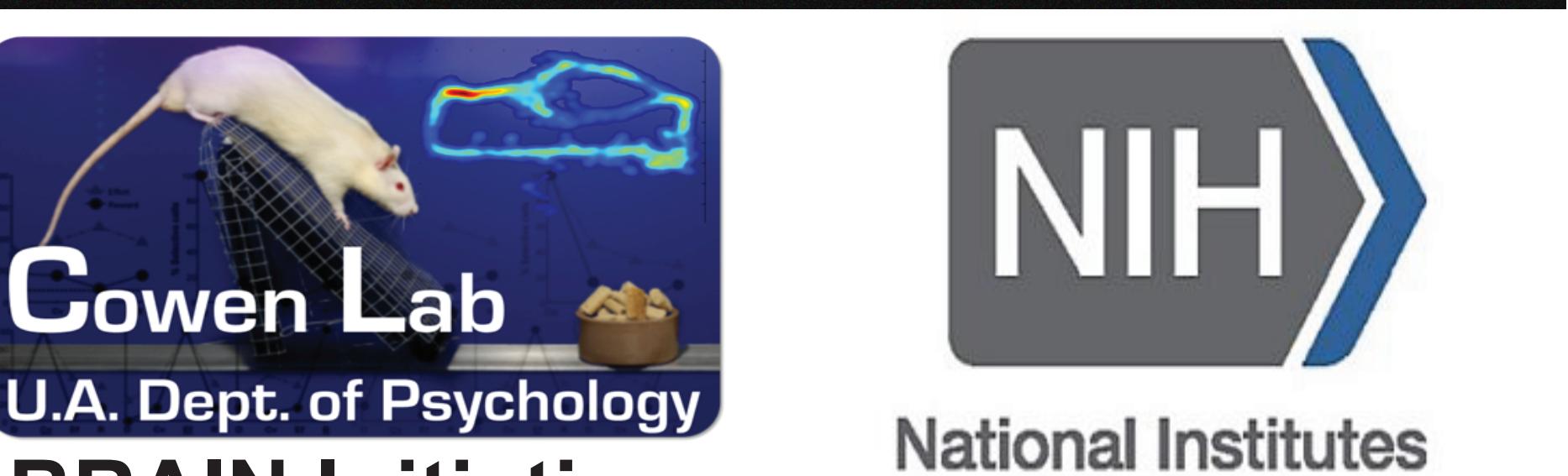
Future Directions

- Investigate how tonic (i.e., basal) dopamine is modulated by pulse variability
- Develop a computational model to predict the effect of pulse variability on dopamine release and neural ensemble activity
- Identify millisecond-scale effects of dopamine release and stimulation variability on NAc ensemble activity
- Chronic freely moving experiments with closed loop optimization of stimulation patterns

References

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- Shinomoto et al. Neural Comput.. 2003, 15(12):2823-42
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Acknowledgments



Funding

R01 NS123456-01
T32 GM008804