Modeling the Effects of Buprenorphine during Morphine Withdrawal in Ventral Tegmental Area Dopamine Neurons

Lawrence Long, Aiden Kim, Luke Shao, Oviya Kalaivanan

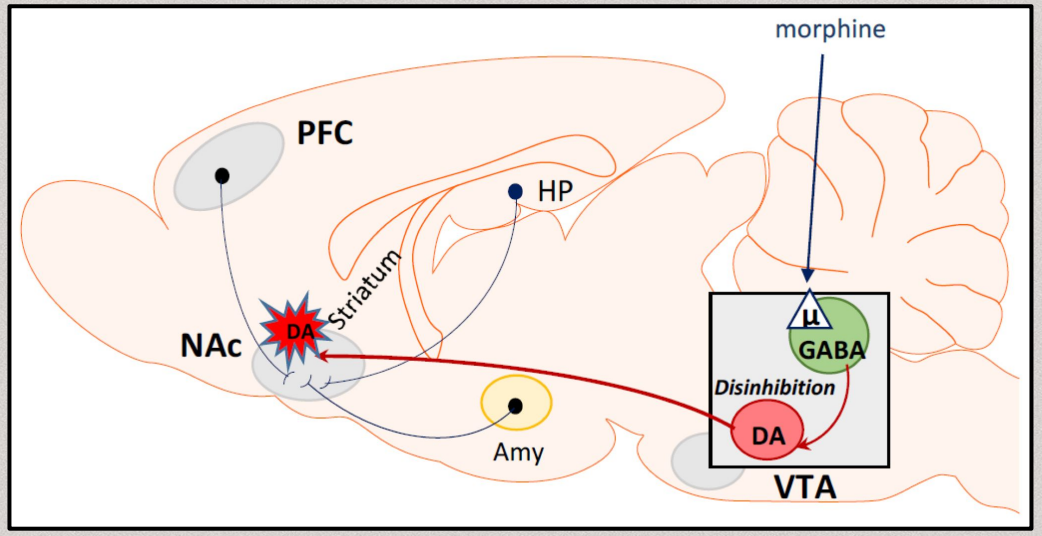
Outline

16,000,000

individuals worldwide have had or currently suffer from opioid use disorder (OUD)

VTA & Morphine

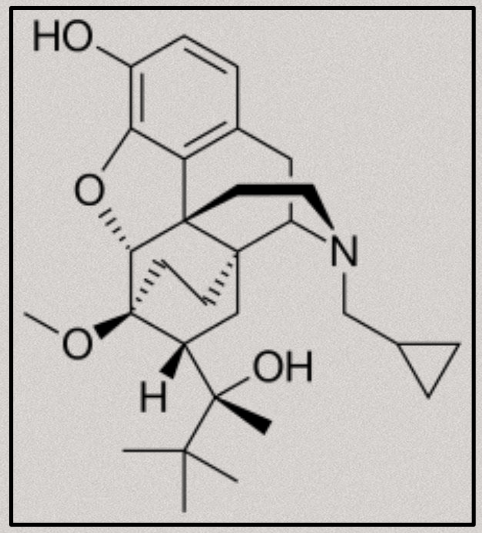
- The **ventral tegmental area** (VTA) is responsible for dopamine synthesis & release
  - Brain's reward system → addiction
- **Morphine** (MOR) binds to μ-opioid receptors in the brain → inhibits GABA and increases glutamate → increases dopamine transmission from VTA



Mechanisms of morphine induced rewarding effects.

MOR Withdrawal & BUP

- MOR withdrawal causes symptoms such as muscle pain, anxiety, diarrhea, vomiting, & insomnia
- **Buprenorphine** (BUP) is a partial opioid agonist -- high affinity binding to μ-opioid receptors, but less severe of a response
    - Used for the treatment of opioid addiction → milder withdrawal symptoms for the patient



Molecular structure of buprenorphine.

Research Objective: To model the effects of buprenorphine and morphine on the firing pattern and dopamine output of a VTA neuron undergoing withdrawal

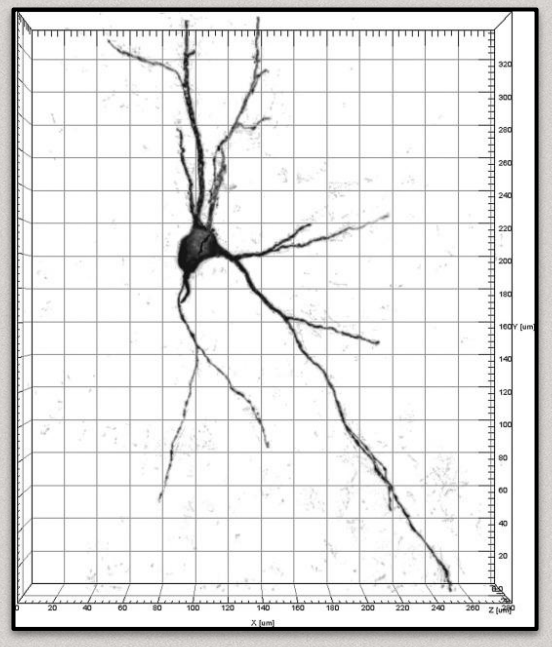
Our Model

Ventral tegmental area dopamine-releasing neuron single cell model:

- 10 second simulation of neuronal activity
- **Parameters**: GABA and glutamate
- **Outputs**: firing pattern and dopamine output

Morphofunctional alterations in ventral tegmental area dopamine neurons in acute and prolonged opiates withdrawal. A computational perspective

P. Enrico [a], M. Migliore [b], S. Spiga [c], G. Mulas [c], F. Caboni [c], M. Diana [d]



Reconstructed morphology of VTA neuron used in model.

Simulation Conditions

Decrease soma diameter by 30%	-46% GABA +30% Glutamate	+47% GABA +57% Glutamate
Control: Withdrawal	**Withdrawal + Morphine**	**Withdrawal + Buprenorphine**

Withdrawal

European Journal of Neuroscience, Vol. 17, pp. 605–612, 2003

Morphine withdrawal-induced abnormalities in the VTA: confocal laser scanning microscopy

Saturnino Spiga,[1] Giuliana P. Serra,[1] M. Cristina Puddu,[1] Marzia Foddai[2] and Marco Diana[2]
[1]Department of Animal Biology and Ecology, University of Cagliari, Italy
[2]Department of Drug Sciences, University of Sassari, Italy

Withdrawal + Morphine

Morphine selectively disinhibits glutamatergic input from mPFC onto dopamine neurons of VTA, inducing reward

Li Yang, Ming Chen, Qianqian Ma, Huan Sheng, Dongyang Cui, Da Shao, Bin Lai, Ping Zheng

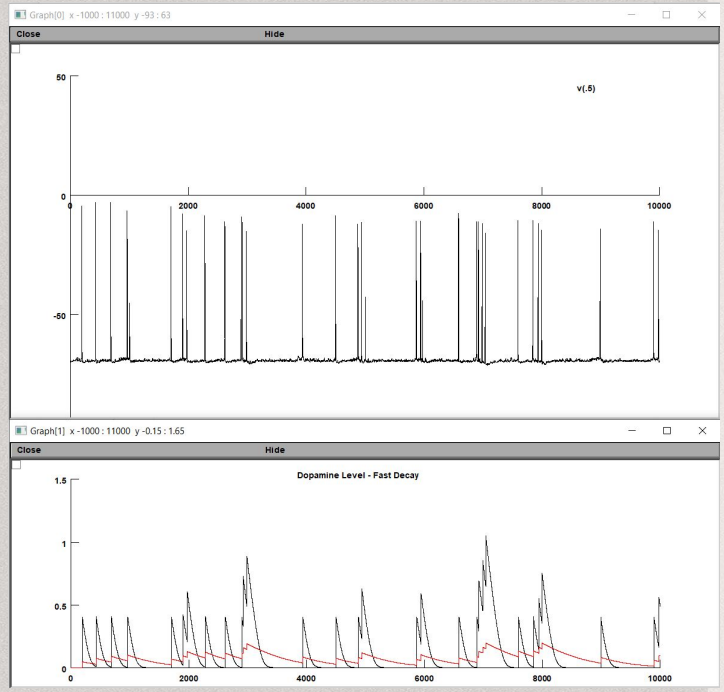
Withdrawal + Buprenorphine

Alterations in neurotransmitter levels and transcription factor expression following intranasal buprenorphine administration

Sanelisiwe P. Xhakaza [a], Leon J. Khoza [a], Advaitaa M. Haripershad [a], Terisha Ghazi [b], Shanel Dhani [b], Cosmas Mutsimhu [c], Molopa J. Molopa [c], Nithia P. Madurai [c], Lorna Madurai [c], Sanil D. Singh [a], Nirmala D. Gopal [d], Hendrik G. Kruger [a], Thavendran Govender [e], Anil Chuturgoon [b], Tricia Naicker [a], Sooraj Baijnath [a]

Data Analysis

- Compared results for the three conditions
- **Single spikes**, **burst firing**, **spikes/burst**, and **DA output**
  - Spike = depolarization to -30mV
  - Burst = 2+ spikes in 80ms
- t-test to confirm significance
  - $p < 0.05$ = significant



Graphs from NEURON GUI

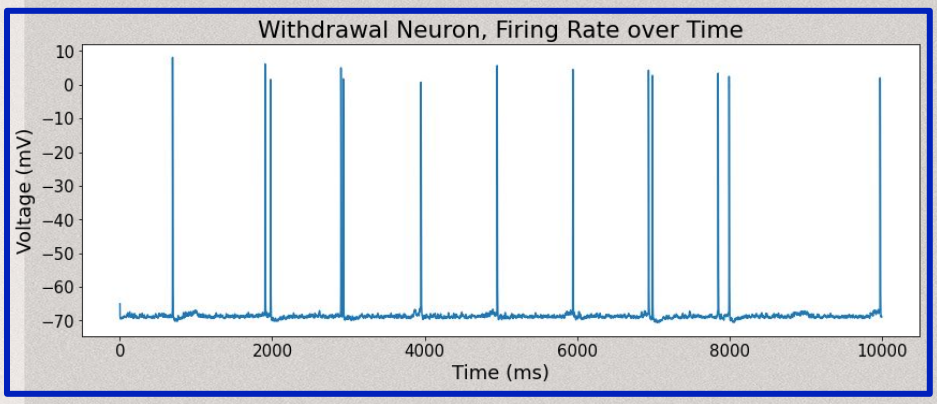
Spreadsheet to keep track of the 4 variables for all 30 runs

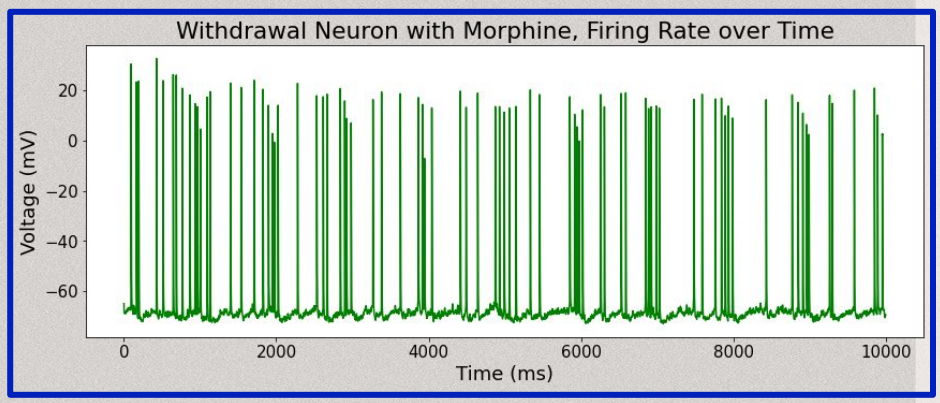
type	Single Spikes	Burst Firing	Spikes/Burst	DA Output
Control	7	3	2	454.6763038
Control	3	7	2.167	746.6640734
Control	8	3	2	576.4565344
Control	8	3	2.3333	580.7742783
Control	14	4	2.33333	843.4806333
Control	8	1	2	349.4443544
Control	7	3	2	493.7638773
Control	7	3	3	709.9306
Control	6	6	2	662.7185
Control	7	4	2	536.1582
Morphine	19	18	3.411	5202.576946
Morphine	20	16	4.06666	6193.705
Morphine	20	19	3.6111111	6652.3539
Morphine	23	17	3.6875	6862.47659
Morphine	23	15	4.0714285	5943.46136
Morphine	20	17	4.0625	6853.9382
Morphine	21	17	3.8125	6167.32412
Morphine	20	17	4.125	7587.9286
Morphine	15	19	3.722	6028.089
Morphine	21	16	4.06666	6623.8184
BUP	15	6	2.5	1200.961935
BUP	18	8	2.5	1629.3296

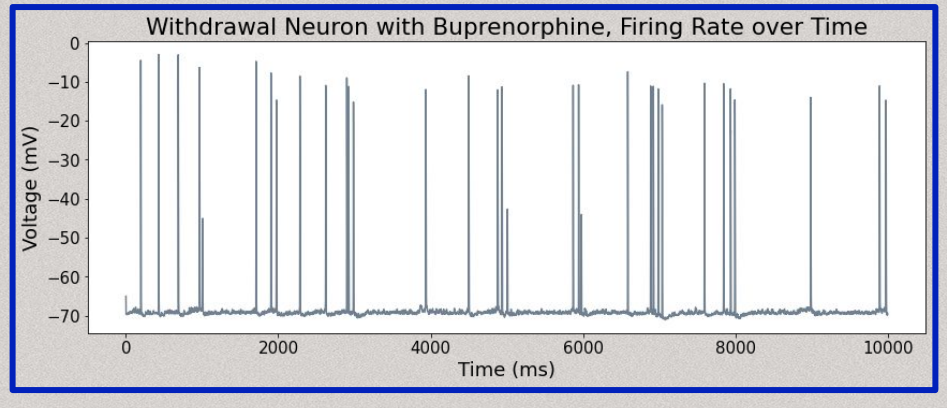
Python code to analyse NEURON simulations

```
def count_single_spikes_and_bursts(info):
    """
    how many single spikes (not bursts) in this 10s simulation
    how many bursts in this 10s simulation

    burst was defined as a train of 2 or more spikes initiated
    by an inter-spike interval (ISI) of 80 ms and terminated by an ISI > 160 ms
    """

    singles = 0
    bursts = 0
    inBurst = False

    spikesperbursts = []
    spb = 2

    prev_start = -1000
    prev_end = -1000
    for spike in info:
        if spike[0] - prev_end > 80:
            #print('single:', spike[0])
            singles += 1
            if inBurst:
                spikesperbursts.append(spb)
            inBurst = False
        else:
```

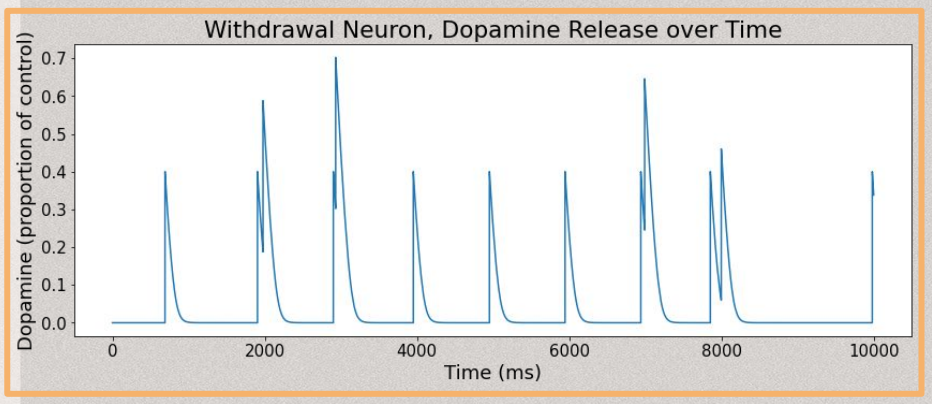
Results - Neuron Firing Rate

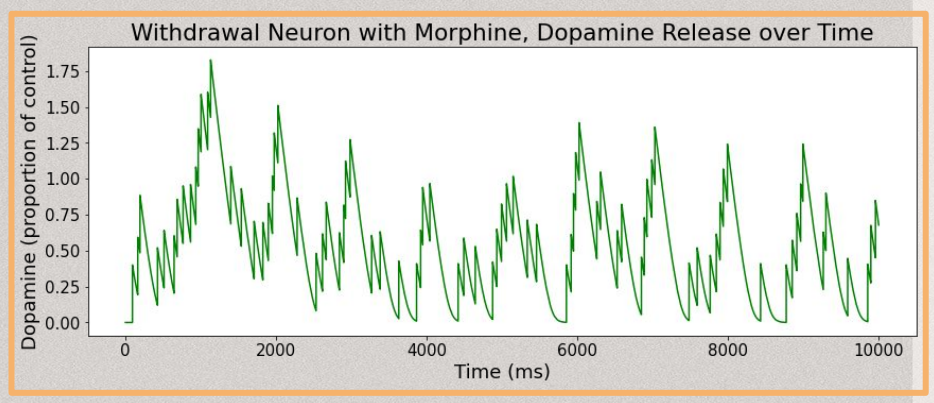


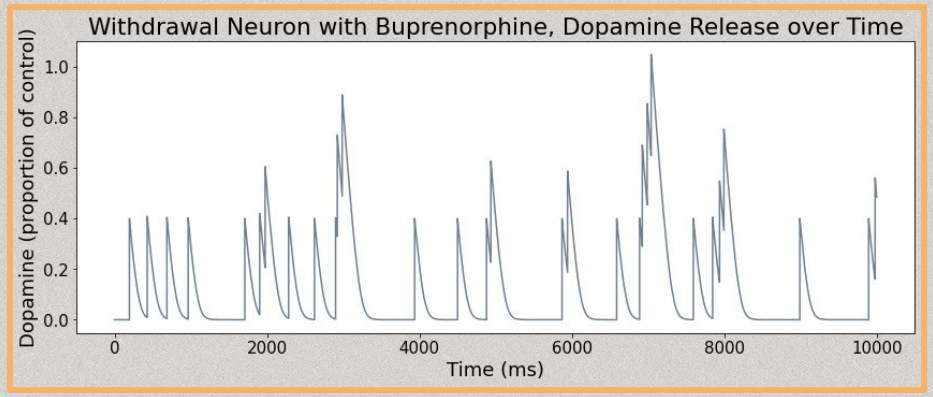




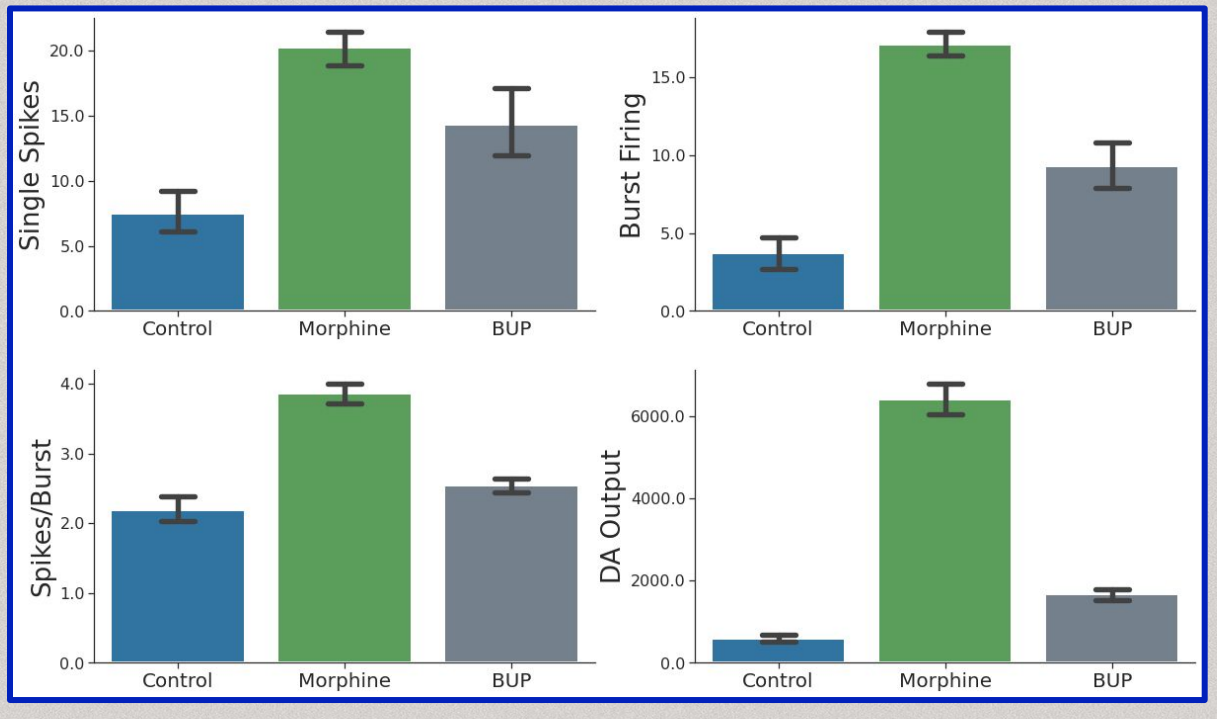
Results - Dopamine Output







Results - Spike, Burst & DA Analysis



- BUP **increased** single spikes, burst firing, spikes/burst, and DA output
- **Intermediate** to the levels reached by the VTA dopamine neuron administered w/ MOR

Results - P values

Categories	Single spikes	Bursts	Spikes/burst	DA output
Control vs Morphine	1.18e-9*	0*	1.14e-10*	0*
Control vs BUP	5.89e-4*	1.50e-5*	5.93e-3*	1.98e-10*
Morphine vs BUP	1.38e-3*	6.34e-8*	0*	0*

* Threshold: $p < 0.05$

Significance of research

BUP's effects remain misunderstood and underutilized

⇩

We determined its effect on DA discharge patterns and firing rates of VTA DA neurons

⇩

Potentially lead to developments in the field of opioid addiction treatment

Support development of personalized doses for different stages of morphine withdrawal

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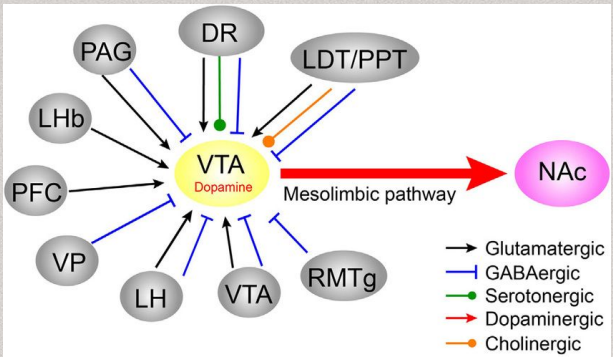
Help decipher the most effective method of treatment

Limitations

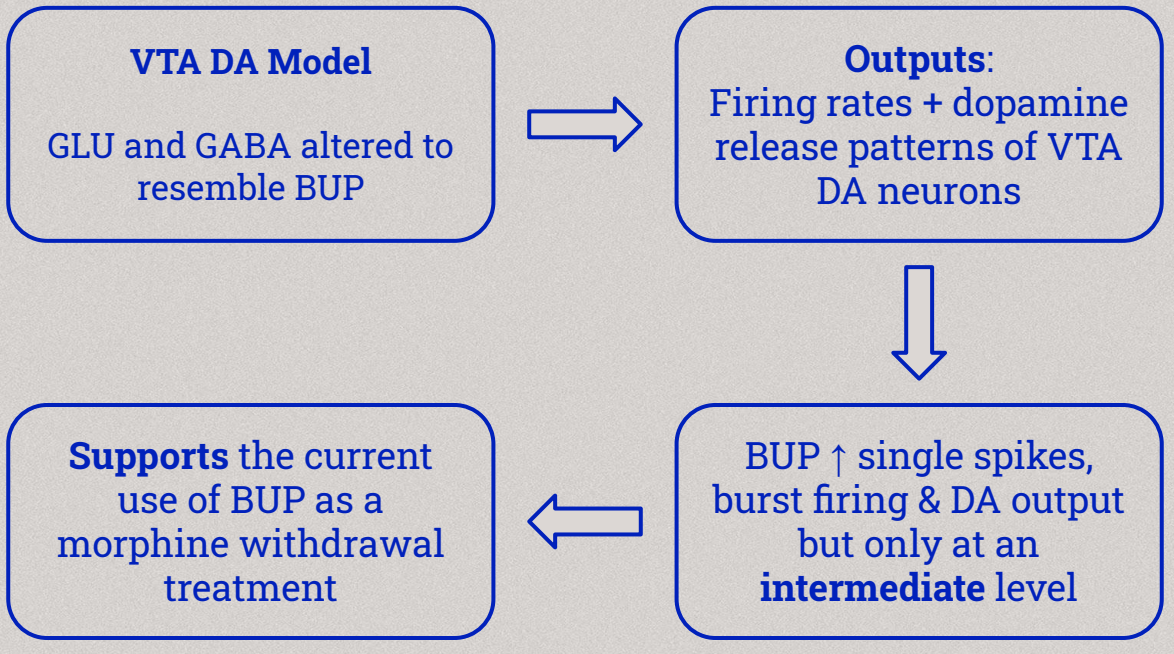
- **Although GABA and GLU have the largest effect on VTA activity, research suggests that other neurotransmitters may also have a noticeable impact**



Future Work

- **Incorporate additional neurotransmitters into the model**
- **Simulate other opioid agonists (namely methadone)**

Summary


VTA DA Model
GLU and GABA altered to resemble BUP
Outputs: Firing rates + dopamine release patterns of VTA DA neurons
BUP ↑ single spikes, burst firing & DA output but only at an **intermediate** level
Supports the current use of BUP as a morphine withdrawal treatment

Acknowledgements

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