BOSTON UNIVERSITY

MODELING THE EFFECTS OF PROPRANOLOL ON MEMORY RECONSOLIDATION FOR PTSD IN THE LATERAL AMYGDALA

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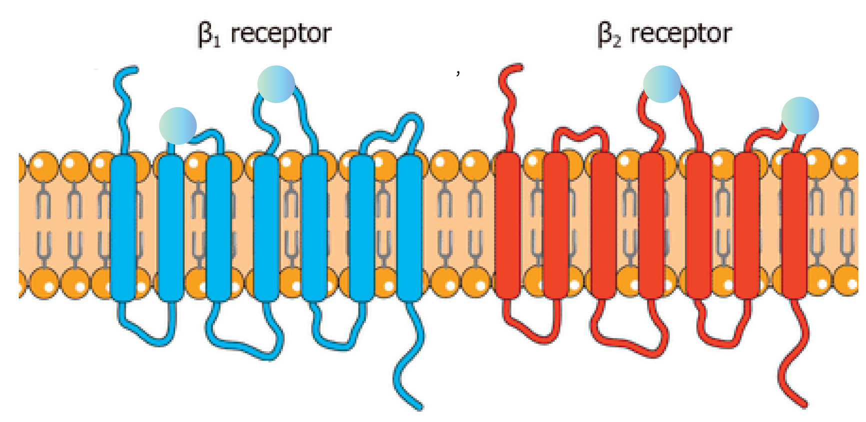
INTRODUCTION

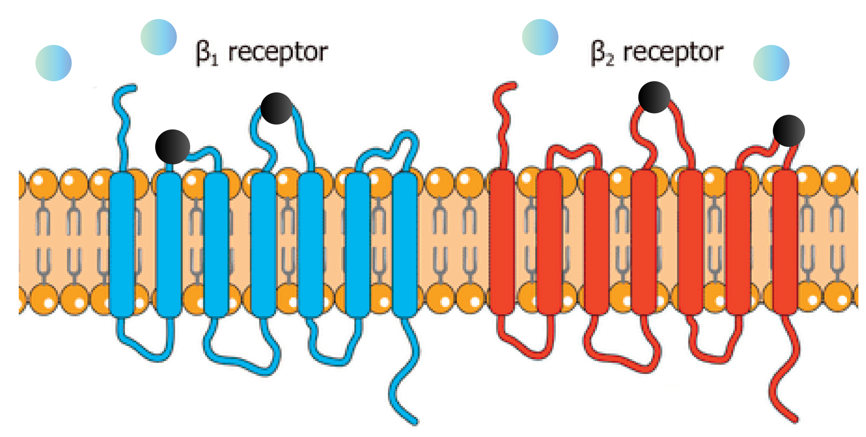
- **Post Traumatic Stress Disorder (PTSD)**
  - Result of experiencing a traumatic event.
  - Induces anxiety and stress in non-threatening environments.
- **Propranolol**
  - Beta blocker prescribed to patients with heart problems and high blood pressure.
  - Blocks **norepinephrine (NE),** a fight or flight neurotransmitter, from binding to beta-adrenergic receptors. **(Fig. 1)**
- **Beta-Adrenergic Receptors**
  - Activation inhibits **slow afterhyperpolarization (sAHP)**-period when neuron resets.
  - Allows cells to fire trains of action potentials, enhancing synaptic connectivity- neurons that fire together wire together.
- **Focus**
  - To model the combination of **propranolol** and **memory reconsolidation** as it has the potential to diminish negative emotions linked to memories in patients with **PTSD**.

Figure 1. *Before and After Propranolol is Administered* (Borovac, Josip Anđelo, et al., 2020, World Journal of Cardiology)

1. Beta Receptors Before Propranolol is Administered



2. Beta Receptors After Propranolol is Administered

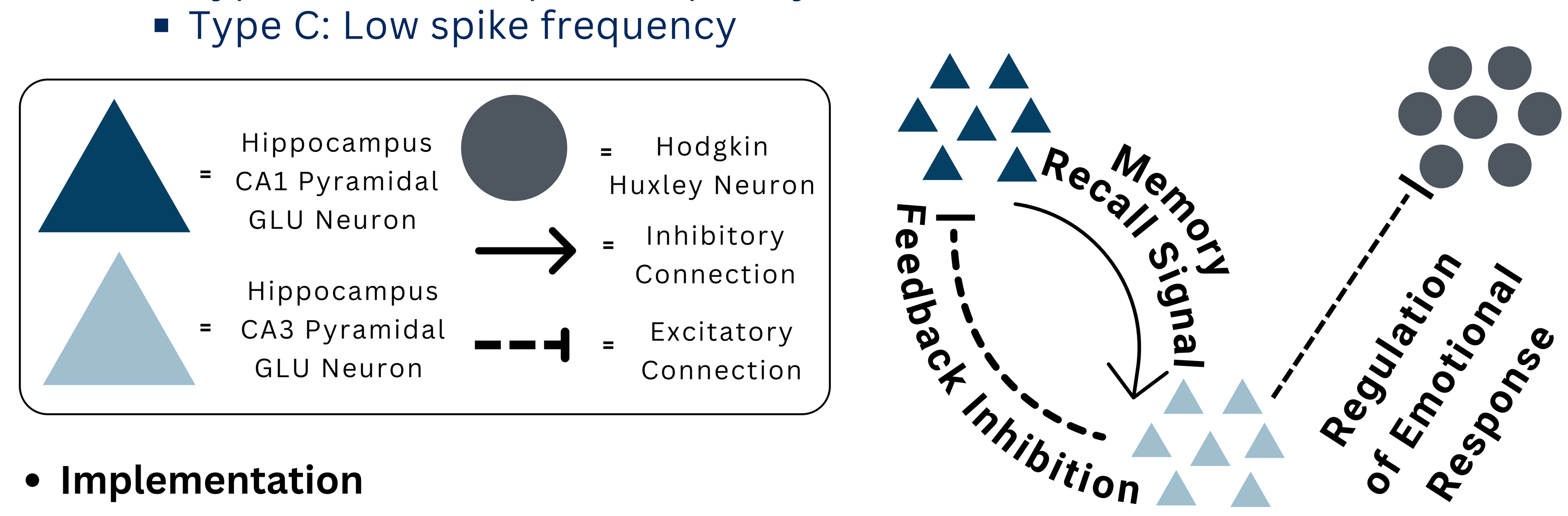


Propranolol ●
Norepinephrine ●

METHODOLOGY

- **Development**
  - Adapted model of Principal CA1, CA3, Hodgkin-Huxley neurons **(Fig. 2)** which were all split in 50:30:20 ratio of:
    - Type A: High spike frequency
    - Type B: Medium spike frequency
    - Type C: Low spike frequency

Figure 2. *Interconnected Neural Network Model*



- **Implementation**
  - Simulated Propranolol
    - Increased conductance of sAHP in model
  - Step by step process:
    1. Propranolol inhibits beta receptors
    2. Increases activation of sAHP
    3. Decreases firing rates of neurons
    4. Decreases synaptic connectivity
    5. Memories become more vulnerable to manipulation
- **Graphing/Analysis**
  - Firing rates of type A, B, & C and neurons graphed with raster plot.
  - Graphed over time to represent each section of Pavlovian conditioning.
    - Pavlovian conditioning is the associative learning through repeated pairing of stimuli and response.

RESULTS

KEY
Red = Type A
Green = Type B
Blue = Type C
Grey = Interneurons

Control:

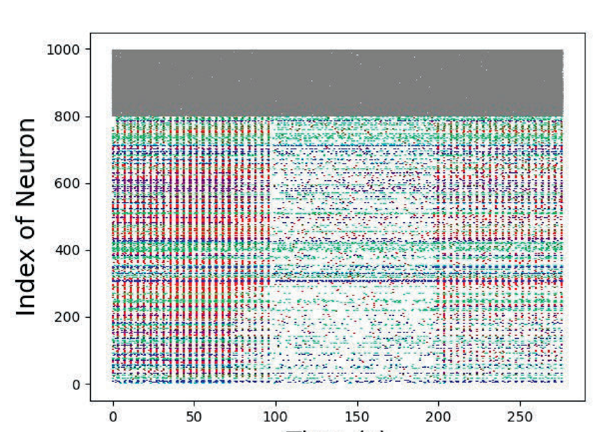


Figure 3.
Neurons firing, 0mg (0%) Propranolol

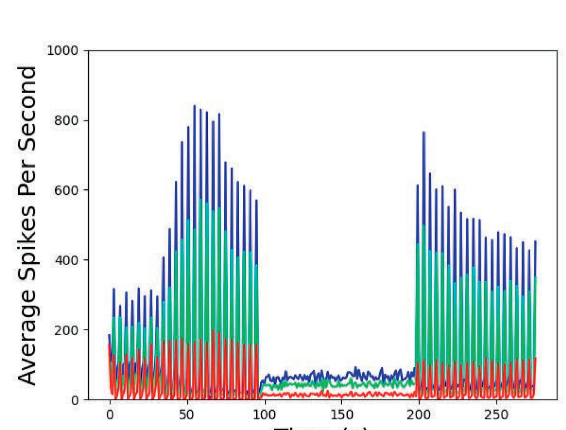


Figure 4.
Average neuron firing rate, 0mg (0%) Propranolol

With Propranolol:

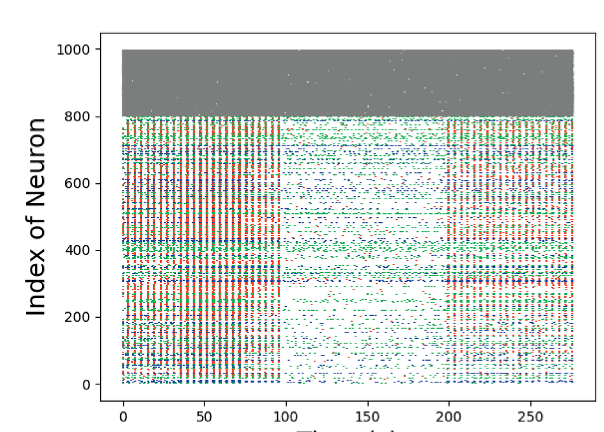


Figure 5.
Neurons firing, 20mg (25%) Propranolol

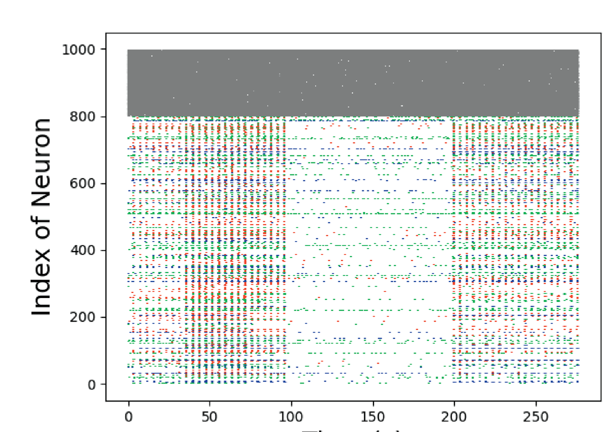


Figure 7.
Neurons firing, 40mg (50%) Propranolol

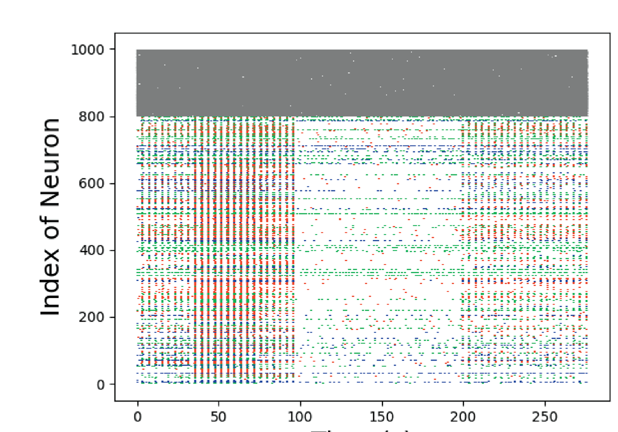


Figure 9.
Neurons firing, 60mg (75%) Propranolol

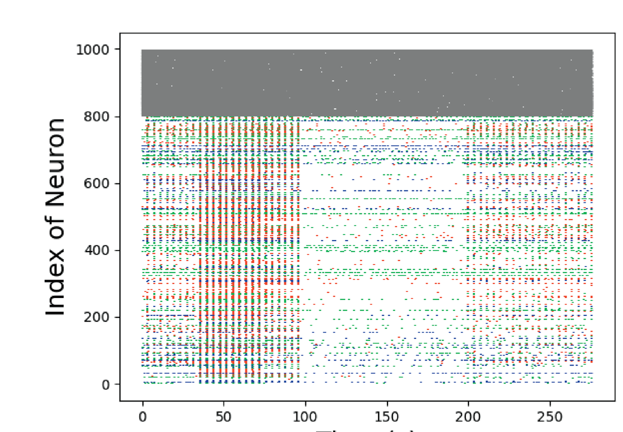


Figure 11.
Neurons firing, 80mg (100%) Propranolol

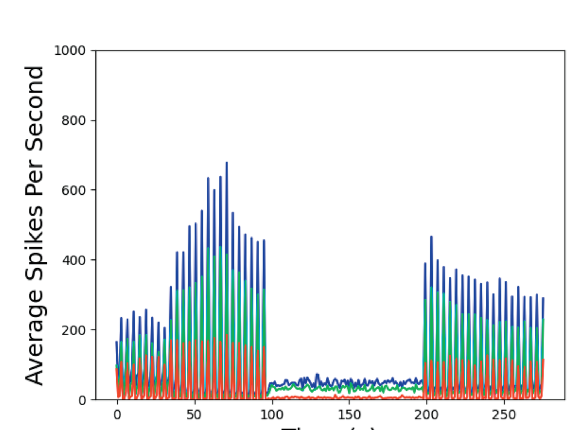


Figure 6.
Average neuron firing rate, 20mg (25%) Propranolol

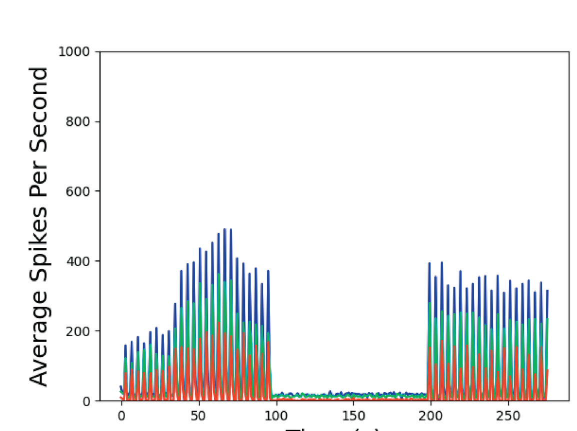


Figure 8.
Average neuron firing rate, 40mg (50%) Propranolol

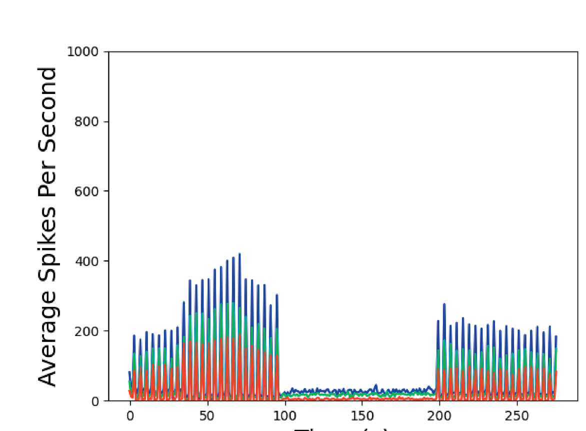


Figure 10.
Average neuron firing rate, 60mg (75%) Propranolol

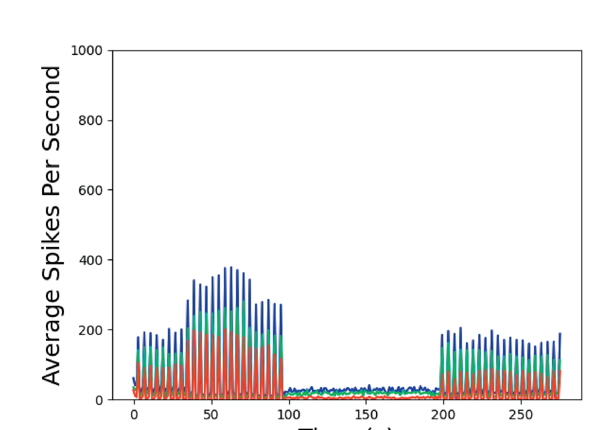


Figure 12.
Average neuron firing rate, 80mg (100%) Propranolol

DISCUSSION

- **Conclusions**
  - Model demonstrates increase of sAHP and beta receptor inhibition decreases neuron firing rates throughout Pavlovian conditioning.
    - As propranolol dosage increases, the raster plots display a decrease in neuron firing rates.
  - Synaptic connectivity decreases as neurons fire together less frequently.
  - Memories are more vulnerable to being altered as pre-existing connections are weakened.
  - *Thus, our model suggests propranolol has the ability to alter fear-inducing memories.*
- **Limitations**
  - Assumed propranolol only affects the binding of NE and not dopamine
  - Measured NE only, despite epinephrine having similar behavior in memory reconsolidation.
- **Future**
  - Expand model to include the Ventromedial Prefrontal Cortex and Hippocampus - parts of the brain heavily involved in fear memories
  - Explore model to further justify the usage of propranolol and increase personalization of medication treatments in PTSD patients

REFERENCES

Borovac, Josip Anđelo, et al. “Sympathetic Nervous System Activation and Heart Failure: Current State of Evidence and the Pathophysiology in the Light of Novel Biomarkers.” World Journal of Cardiology, vol. 12, no. 8, 2020, pp. 373–408, https://doi.org/10.4330/wjc.v12.i8.373.

Church, T. W.; Brown, J. T.; Marrion, N. V. B3-Adrenergic Receptor-Dependent Modulation of the Medium Afterhyperpolarization in Rat Hippocampal CA1 Pyramidal Neurons. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6520626/ (accessed 2023-08-07).

Johnson, L. R.; Hou, M.; Prager, E. M.; Ledoux, J. E. Regulation of the Fear Network by Mediators of Stress: Norepinephrine Alters the Balance between Cortical and Subcortical Afferent Excitation of the Lateral Amygdala. https://pubmed.ncbi.nlm.nih.gov/21647395/ (accessed 2023-08-06).

Kim, D.; Paré, D.; Nair, S. S. Mechanisms Contributing to the Induction and Storage of Pavlovian Fear Memories in the Lateral Amygdala. Learning & Memory 2013, 20 (8), 421–430. DOI:10.1101/lm.030262.113.

Kindt, M.; Soeter, M.; Vervliet, B. Beyond Extinction: Erasing Human Fear Responses and Preventing the Return of Fear. https://www.nature.com/articles/nn.2271 (accessed 2023-08-07).

McDonald, A. J.; Augustine, J. R. Localization of GABA-like Immunoreactivity in the Monkey Amygdala. Neuroscience 1993, 52 (2), 281–294. DOI:10.1016/0306-4522(93)90156-a.

Muravieva, E. V.; Alberini, C. M. Limited Efficacy of Propranolol on the Reconsolidation of Fear Memories. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2884288/ (accessed 2023-08-07).

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