Modeling the effect of differing concentrations of Norepinephrine on Working Memory in the Prefrontal Cortex through α1 and α2 Receptors

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Introduction

- **Working Memory (WM):** a type of short-term memory storage and management conducted in the brain's **Prefrontal Cortex (PFC).**
- Low levels of the neurotransmitter **norepinephrine (NE) (NT released during stress) improve** WM, but high levels **impair** WM.
- Norepinephrine affects WM function by binding to the **Alpha 1 (α1)** and **Alpha 2 (α2)** receptors in the PFC
- **Alpha 2 (α2) receptor**:
  - Activates at **lower concentrations** of NE
  - Closes HCN channels → hyperpolarizes neurons & increases neuronal response to a stimulation
  - **Improves WM**
- **Alpha 1 (α1) receptor**:
  - Activates at **higher concentrations** of NE
  - Releases intracellular Ca^{2+} → closes SK channels → depolarizes neurons and decreases neuronal response to a stimulation
  - **Worsens WM**
- This study aimed to computationally model the effects of varying levels of NE on Working Memory.

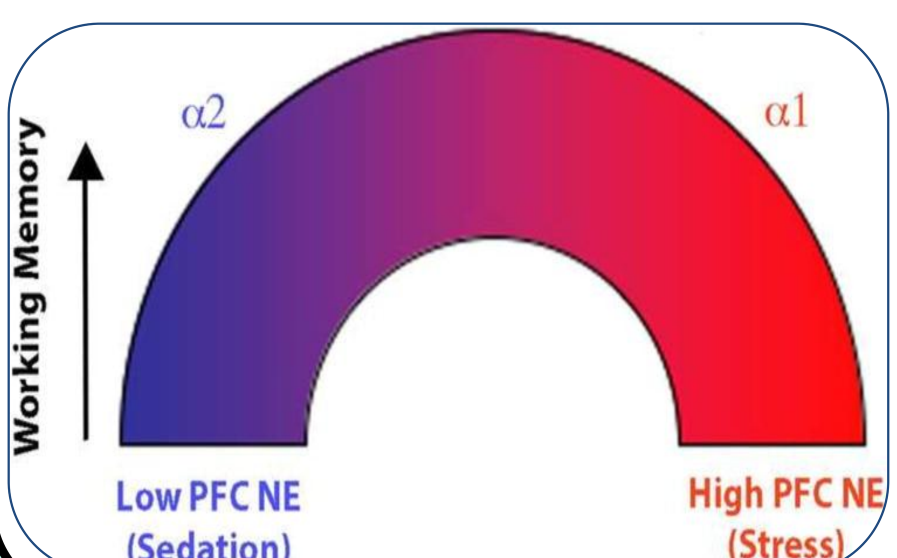

Figure 1. Relationship between NE level, Alpha receptor activation and WM performance

Results

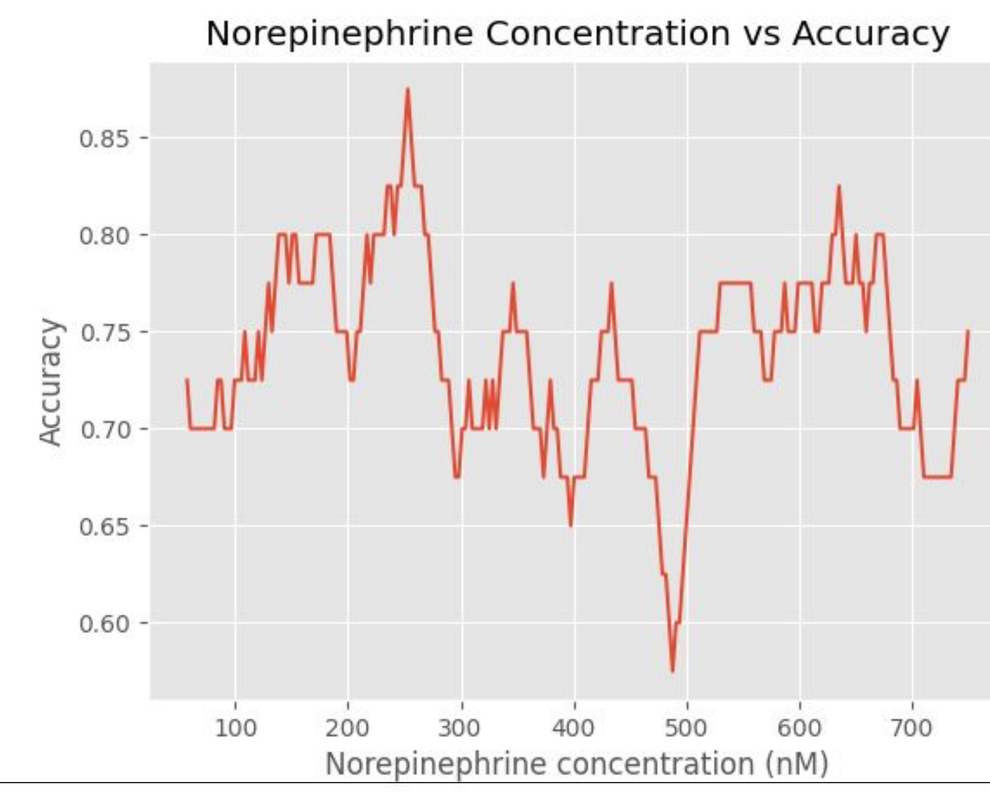

Figure 4. Graph showing the relationship between the NE concentration and the accuracy of the DFT. It should be noted that this graph includes outliers that have no statistical relevance (ex. at 500 nM)

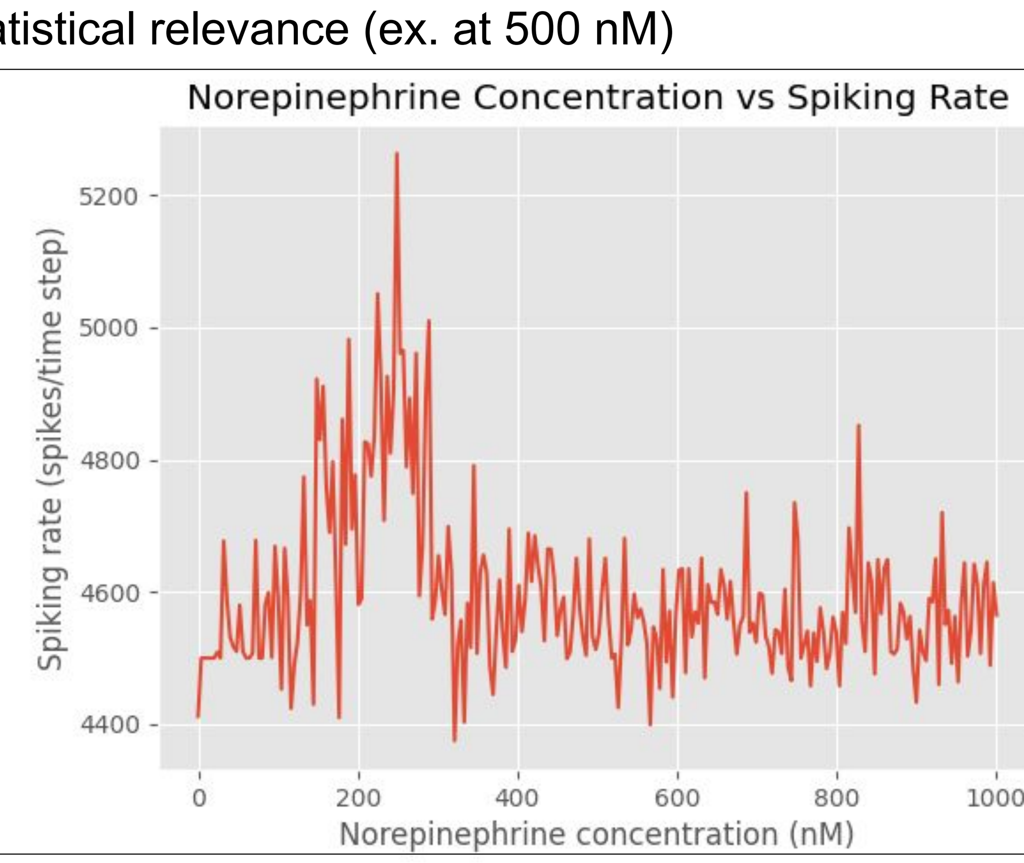

Figure 5. Graph of the relationship between the NE concentration and the average neuronal spiking rate

Discussion/Conclusions

- The relationship between NE levels and WM performance was successfully modeled.
- The graphs of both the Neuronal Firing Rates and DFT accuracy over NE concentration display an approximately **bell-shaped curve.**
  - WM performance first improves as alpha-2 receptors are activated, and then decreases as alpha-1 receptors begin to activate at higher concentrations.
  - The peak WM performance/optimal NE level was estimated to be at approximately **250 nM**.
  - These results are supported by studies that found peak WM performance to be in between Alpha-2 and Alpha-1 receptor activation.

Limitations:

- Due to a lack of specific numerical data, we were forced to make a lot of **estimations** when creating our model.
  - When more data is found in the future, it could be fed into our model to become more biologically realistic
  - More detail can also be added, such as adding **beta receptors** and other **neurotransmitters** that have been shown to affect Working Memory (ex. epinephrine and dopamine)

Potential Applications:

- This model can be used to study and **simulate the treatments of diseases** that involve dysfunction of NE levels (ex. ADHD, PTSD, Parkinson's disease, Depression, and Anxiety)
- Can also be used to gain a deeper **knowledge of the way that WM and the PFC function**

Methods

- Based on an existing model[1], we created a spiking neural network model of the PFC in Python 3 and the nengo library that could perform a **spatial delayed response task (DFT)** which analyzes Working Memory performance. A DFT is where the network must remember a cue for a certain amount of time and then output what it remembers.
  - A cue vector (input to remember) of either -1 or 1 was fed into the network for 1 second causing different spiking levels in different neurons depending on the similarity between the cue vector and each neuron's unique **preferred vector** (ex. neuron w/ PV=0.9 fires more strongly for a cue of 1 than a cue of -1)
  - After the cue was taken away, the network had to maintain this activity (remember the cue) for 8 seconds through **recurrent connections** in the network
  - At the end of each trial, the spiking activity during the presence of the cue was compared to the final spiking activity after 8 seconds to determine DRT accuracy
- **The gains (α) and biases (β)** of the neural network were multiplied by a scalar based on the **% activity of each receptor** at different NE levels to simulate the effects of NE acting on the α-2 and α-1 receptors
  - % activity was estimated using known receptor Ki values (concentrations w/ 50% total receptor activity)
    - Sigmoidal function was graphed through these values to realistically model the receptor activity at different NE levels (Figure 2)
  - We chose biologically realistic values for the scalars for the gains/biases for both receptors at 100% activity. These were then altered based on the percent of receptors active at each concentration to determine the scalar for the gain/bias in each receptor at each concentration of NE (Figure 3).
  - Ex. Gain scalar for alpha-2: **1.1 at 100%** and **1.05 (1 + 0.1*0.5) at 50%**
- Model was run for NE concentrations ranging from **0 nM to 750 nM** using **3 nM steps**
  - **3 trials** of the model were run at each concentration and the results were averaged
  - **DRT performance accuracy** and **neuronal firing** after 8 seconds for each step was recorded and graphed.

Source code is available from https://ftp.armaanb.net/research/norepinephrine_wm/

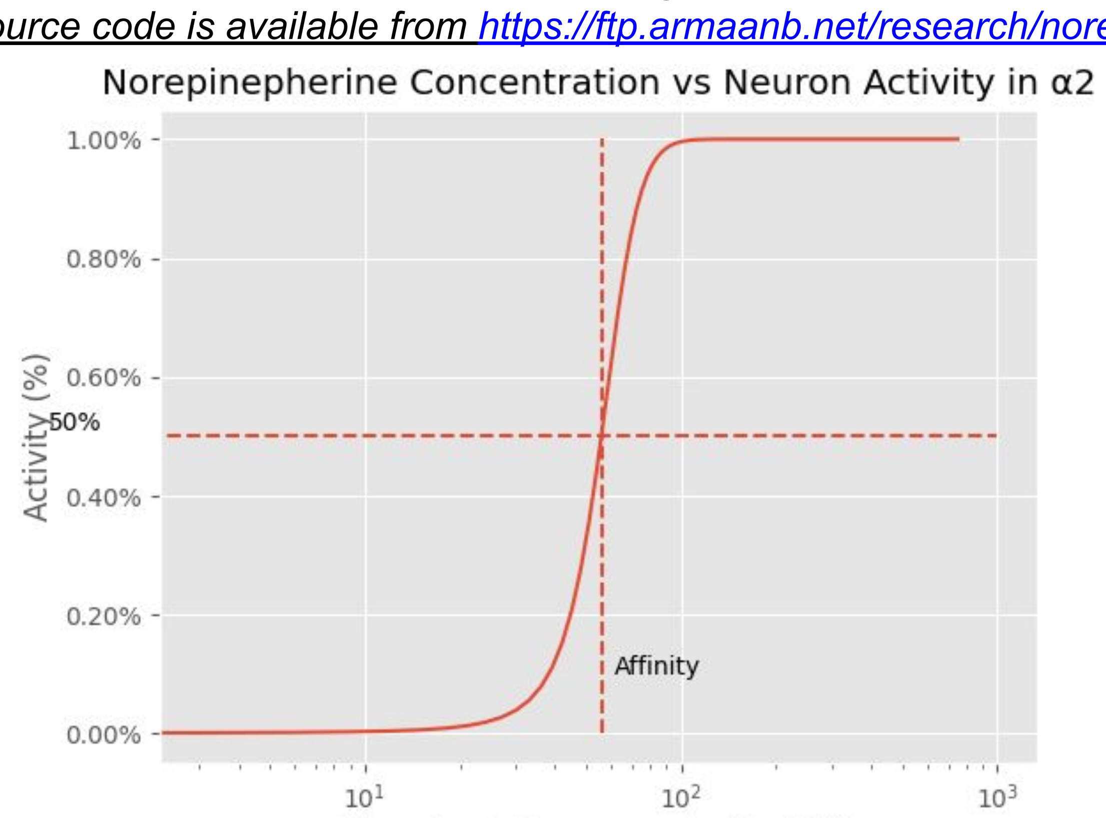

Figure 2. Sigmoidal function of NE concentration Alpha-2 receptor activity

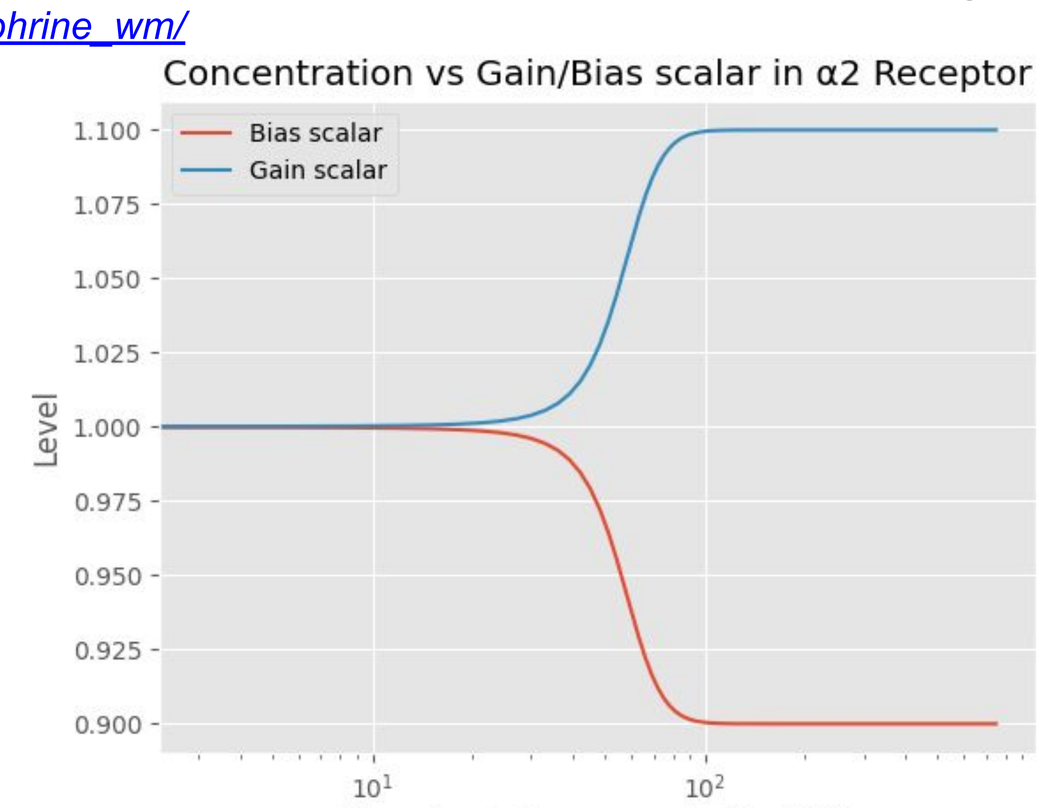

Figure 3. Graph of NE concentration vs. Gain/Bias Scalar in Alpha-2 receptor

References

Duggins, Peter, et al. "The Effects of Guanfacine and Phenylephrine on a Spiking Neuron Model of Working Memory." TOPICS 20171

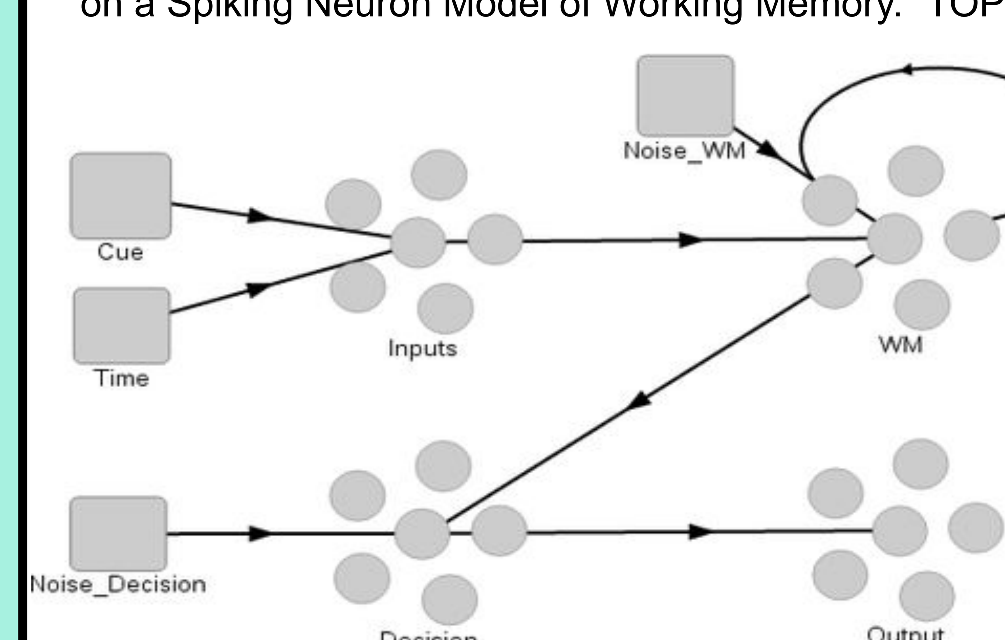

Figure 6. Diagram of the original model that the model in this study was based on

Berridge, Craig W., and Robert C. Spencer. "Differential Cognitive Actions of Norepinephrine a2 and a1 Receptor Signaling in the Prefrontal Cortex." Brain Research, special issue of New Evidence for Heterogeneous Organization and Actions of the Central Noradrenergic Transmitter System

Arnsten, Amy F., and F. M. Leslie. "Behavioral and Receptor Binding Analysis of the Alpha 2-Adrenergic Agonist, 5-Bromo-6 [2-imidazoline-2-yl amino] Quinoxaline (UK-14304): Evidence for Cognitive Enhancement at an Alpha 2-Adrenoceptor Subtype." Neuropharmacology

Arnsten, Amy F., et al. "The Contribution of α2-Noradrenergic Mechanisms to Prefrontal Cortical Cognitive Function Potential Significance for Attention-Deficit Hyperactivity Disorder." Arch Gen Psychiatry, 1996

Arnsten, Amy F. "Stress Signalling Pathways that Impair Prefrontal Cortex Structure and Function." Nature Reviews Neuroscience, 2009

Zhang, Zizhen, et al. "Norepinephrine Drives Persistent Activity in Prefrontal Cortex via Synergistic α1 and α2 Adrenoceptors." 2013

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