Animals rely on information to make decisions. We have to integrate information from the environment, our previous knowledge, and our underlying motivation in order to make goal-directed choices. Several brain regions are recruited in this decision-making process. The mediodorsal thalamus (MD) has been shown to be necessary for cognitive tasks like working memory and goal-directed decision-making[1]. The mediodorsal thalamus (MD) takes higher order feedback and sensory information and relays it to the orbitofrontal cortex (OFC) and basal ganglia (BG). The orbitofrontal cortex (OFC) is necessary for value-based decision-making and inferring[2]. The OFC sends projections to the striatum, the input nucleus of the basal ganglia, which is needed for action performance[3].

While there is evidence that both OFC and MD project to dorsal striatum [4], how and what information is being sent or modulated through these paths is less clear. I plan to use transgenes and recombinase technologies to limit the expression of a fluorophore or a calcium indicator in a cell-type and projection-specific manner to measure the interactions between these regions during a decision-making task. *I hypothesize that distinct sensory and valuation information processing is occuring in OFC and MD*. These aims address how information in cortico-basal ganglia-thalamic (CBGT) loops is being passed on and selectively used to control decision-making.

Aim 1: *Characterize the cortico-thalamic-basal ganglia circuit using anatomical tracing.*

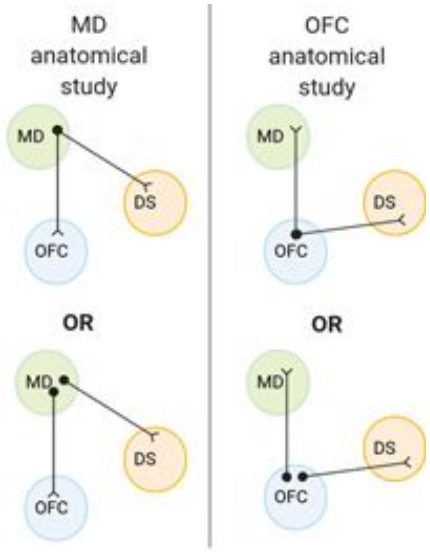

Figure 1: two potential results for each anatomical study

Previous research has focused on individual streams of information from the thalamus to prefrontal cortex[5]. However, there have been no studies examining overlapping OFC and MD collaterals in striatum. I seek to address how OFC and MD projections are overlapping. In order to understand how information is flowing through this particular CBGT loop, I will first conduct an anatomical study. I will perform stereotactic surgery in mice, which I have previously done in the Gremel lab[6]. I will inject two adeno-associated viruses into the mice: a retrograde Cre-GFP in DS and a Cre-dependent mCherry in MD. After waiting for adequate viral expression, I will visualize the neurons using fluorescence microscopy. The presence of mCherry labeled MD terminals in OFC would indicate that those MD neurons project to both OFC and DS. The same strategy will be used to look for OFC neurons that synapse onto both MD and DS. This anatomical information (*Figure 1*) will inform how to proceed with functional investigations; if the same neurons are synapsing in OFC and DS (or MD and DS), there may be an interesting mechanism controlling behavior. An undetermined portion of thalamostriatal neurons synapse onto inhibitory interneurons, so there is a possibility that they function as a clamp to perform gain control on the information coming from OFC. If I do not see overlap of collaterals in the microcircuitry of striatum, I intend to investigate how MD is contributing to holding information in a decision-making task.

Aim 2: *Examine the activity of MD and OFC neurons synapsing in striatum during a self-initiated decision-making task.*

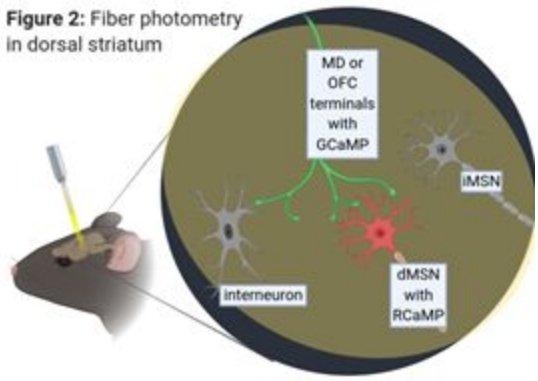

Figure 2: Fiber photometry in dorsal striatum

To examine how MD and OFC are synapsing in striatum, I will use genetically encoded calcium indicators (GCaMP and RCaMP) as a proxy for synaptic activity in behaving mice. I will perform fiber photometry to measure calcium activity in two groups of mice, one group with MD and DS, and another with OFC and DS. I will use an axon-targeting GCaMP in the MD and OFC and RCaMP in the DS so I can simultaneously record from both populations (*Figure* 2). To look at specific cell types, I will restrict RCaMP expression in DS to either indirect or direct pathway medium spiny neurons (iMSNs or dMSNs). These methods will allow me to look at how the activity in the MD or OFC is related to the two striatal output pathways. Mice will be trained to hold down a lever for a specific duration in order to earn a food reward. *I hypothesize that information may be accruing actively over the period of holding down the lever, and this information may be maintained through the MD.* Calcium transients will be examined around lever press initiation/stop and reward delivery. I will compare the transients over time (days of learning) and between MD, OFC, and DS to examine decision-making computations that may be supporting behavior. We will use regression analyses to quantify the dependency between the activity of MD and DS and OFC and DS when the animal is deciding to let go of the lever. I expect that there is more correlation in MD-DS when the animal holds down the lever long enough to earn a reward.

Intellectual Merit

This work will provide insight on circuitry underlying decision-making. The findings will also inform how neurons integrate information and use that integrated information to generate actions. Results may provide insight into circuit motifs like gain control that allow for rapid problem-solving, potentially applicable to other neural circuits and artificial intelligence.

Broader Impacts

Findings may inform the development of treatment for disorders where appropriate action selection is disrupted- OCD, mood disorders, schizophrenia, and addiction, hopefully improving well-being. Treatment for these diseases may mitigate the cost of disability in the US and help our economy grow by including more people in the workforce. Moreover, funding this project directly ensures the full participation of myself, a woman with a disability, in STEM.

Results will be shared in peer-reviewed publications and at conferences, and will also be shared with the general community by writing blog posts for NeuWriteSD[7]. I will also share my research and general scientific topics through demonstrations at K-12 schools and at community events with all ages. I am excited to have matched with a "pre-scientist" 6th grade pen pal, and we are exchanging letters about going to college, overcoming obstacles, and scientific careers. All of this outreach generates curiosity and better scientific literacy in the general public.

References

[1] Hallassa & Kastner, *Nat Neuro* (2017). [2] Gremel *et al., Nat Comm* (2013). [3] Yin, *Neuroscientist* (2017). [4] Hunnicutt *et al., eLife* (2016). [5] Parnaudeau *et al., Biol. Psychiatry* (2018). [6] Baltz *et al., eLife* (2018). [7] neuwritesd.org