Background Info:

My WIN submission this week is the Specific Aims portion of an NRSA (F31) that I will be resubmitting in either December or April, depending on the reviewer comments I receive. This portion of the F31 must not exceed 1 page, so feedback on balancing clarity and brevity would be great.

**Specific Aims**

Cognitive dysfunction is a core feature of schizophrenia as it is often present prior to diagnosis and is a strong predictor for quality of life1–3. Dysfunctional neuronal activity in the prefrontal cortex has been associated with impaired cognitive functions (e.g., attention, working memory, thought coordination) commonly observed in this disease4–6. However, current treatments do not improve cognitive symptoms in schizophrenia. Therefore, to develop new therapies for these deficits, there is a critical need to investigate the neural circuitry underlying cognitive symptoms of schizophrenia.

The cerebellum is largely associated with coordinating motor functions, however, relayed cerebellar projections to cortical areas like the prefrontal cortex are instrumental in a variety of cognitive and executive functions7,8. In line with these observations, one neuronal pathway implicated in the cognitive symptoms of schizophrenia is a cerebello-thalamo-cortico- cerebellar loop9. Decreased structural and functional connectivity within this pathway and dysfunction of its nodes has been observed in patients with schizophrenia10–12. It is hypothesized that the role of the cerebellum in this circuit is to coordinate cognitive processing through modulation of areas like the prefrontal cortex13,14. The dentate nuclei, or lateral cerebellar nuclei (LCN) in rodents, send the majority of cerebellar input to the prefrontal cortex15,16. A population of inhibitory D1 dopamine receptor (D1DR)-expressing neurons in the LCN has been recently implicated in pre-frontal dependent cognitive tasks 17. However, precisely how D1DR-expressing cells of the LCN contribute to cognitive function and modulation of the frontal cortex is unclear.

To address this, we will evaluate the role of LCN D1DR-expressing neurons in performance of an interval timing task. In interval timing tasks, subjects are presented with a cue that signals them to respond after a certain duration elapses (e.g., press a lever after 12 seconds). Interval timing performance is impaired in schizophrenia patients18–21, depends on multiple nodes in our circuit of interest22,23, and is impacted by manipulations of dopaminergic signaling24–26. Successful interval timing performance requires recruitment and coordination of several different executive functions such as working memory, attention, and decision making. Importantly, interval timing task measures can be readily compared across animal models, neuropsychiatric patients, and healthy human comparisons. Therefore, it is an ideal type of task with which to probe our circuit and neuronal population of interest in rodent models. Specifically, we will investigate how LCN D1DR-expressing neurons contribute to performance in a peak interval timing task, and how performance correlates with population activity in the LCN and prelimbic cortex (PL), the rodent medial frontal cortex. Based on our prior work and the primary literature, our **overall hypothesis** is that inhibitory D1DR-expressing cells of the LCN are necessary for successful interval timing through modulation of activity in the PL.

**Aim 1. Determine if LCN D1DR-expressing neurons are necessary for interval timing**

The cerebellum and LCN specifically have been implicated in both sub-second and supra-second interval timing23,27–30. Dopaminergic signaling is crucial for timing behavior and is one of several abnormal neurotransmitter systems in schizophrenia4,21. The role of inhibitory D1DR-expressing neurons in the LCN is presently unknown. We will determine if LCN D1DR-expressing neurons are necessary for interval timing performance using optogenetically driven inactivation during the task. Additionally, synchronization of cortical pyramidal cell activity by inhibitory interneurons is associated with cognitive processing31,32. Therefore, we will record local field potentials (LFPs) and single neurons during optogenetic inactivation to assess whether LCN D1DR-expressing neurons contribute to synchronized activity in the LCN and PL. Combining optogenetic and electrophysiological methods will allow us to test the hypothesis that inactivation of LCN D1DR-expressing neurons results in interval timing deficits and decreased synchronized neuronal activity in the LCN and PL.

**Aim 2. Determine if stimulating LCN D1DR-expressing neurons compensates for PL dysfunction**

Cerebellar stimulation may reduce cognitive symptoms in schizophrenia33 but it is unknown to what extent and by which mechanisms. We can pharmacologically mimic frontal cortex dysfunction, allowing us to determine whether optogenetic stimulation of LCN D1DR-expressing neurons rescues interval timing performance and impacts neuronal activity in the PL. This design will allow us to test the hypothesis that stimulation of LCN D1DR-expressing neurons can compensate for aberrant activity in the PL and improve interval timing performance. Here we will measure ‘compensation’ based on improvement in interval timing task performance precision and increased frontal cortex single unit synchronization and LFP 1-4Hz power.

The proposed project will provide extensive training in vital techniques for my future research such as, focal drug infusion, optogenetic stimulation, electrophysiological recording, and conducting associated data analyses. Additionally, our results will provide further insight into cerebellar modulation of the frontal cortex during cognitive processing at baseline and in pharmacologically altered states. Therefore, our findings could better define therapeutic targets for treatment of cognitive symptoms of schizophrenia.