Overview/Abstract:

Parkinson's disease (PD) is among the most common neurodegenerative disorders in the world, second only to Alzheimer's disease. The motor symptoms of PD, including tremor at rest, akinesia and rigidity, are primarily caused by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), located in the midbrain. The striatum is the primary target of these midbrain dopamine neurons that die in PD, and pathological alterations in striatal circuit function following dopamine loss play a key role in the motor symptoms of Parkinsonism. The current standard of care for PD is dopamine replacement therapy with levodopa (L-DOPA; a dopamine precursor), but as the disease progresses this treatment can induce a new set of hyperkinetic symptoms known as L-DOPA-induced dyskinesias (LIDs). The striatum has a compartmental organization: about 10-15% of the striatum is made up of scattered patchy structures (called "striosomes"), with the remaining surrounding volume termed the "matrix". Importantly, we have shown that striatal neurons in striosomes and matrix respond oppositely to phasic elevations in dopamine, suggesting that the two compartments would also respond differently to loss of dopaminergic input. It has been hypothesized that imbalanced striosome vs matrix function may contribute to motor symptoms of PD and the development of LIDs, but this has not been tested due to technical limitations. We have been able to overcome these limitations by using a newly developed mouse that allows the visualization of striatal compartments in living tissue, in combination with 2-photon imaging and electrophysiological techniques. We will use these tools to directly test our ***central hypothesis*** *that compartment-specific striatal alterations resulting from dopamine depletion and replacement represent novel circuit targets for the treatment and mitigation of PD and LIDs*.

The **goal** of this SEED grant is to generate the requisite preliminary data to apply for a NIH R01 award. We have already established an experimental mouse model of Parkinsonism in our laboratory (by means of surgically lesioning midbrain dopamine neurons using the toxin 6-hydroxydopamine, the gold standard in the field). The **objectives** of the SEED grant are (i) to establish a mouse model of LIDs in our laboratory and (ii) collect preliminary data from each model condition (dopamine depletion and LIDs) highlighting key compartment-specific changes in neuronal function and structure. Once the objectives of the SEED grant are accomplished, which we anticipate will take ~12-16 months, we will submit a NIH R01 (NINDS) application. R01 will be submitted within 18 months of the award start date.

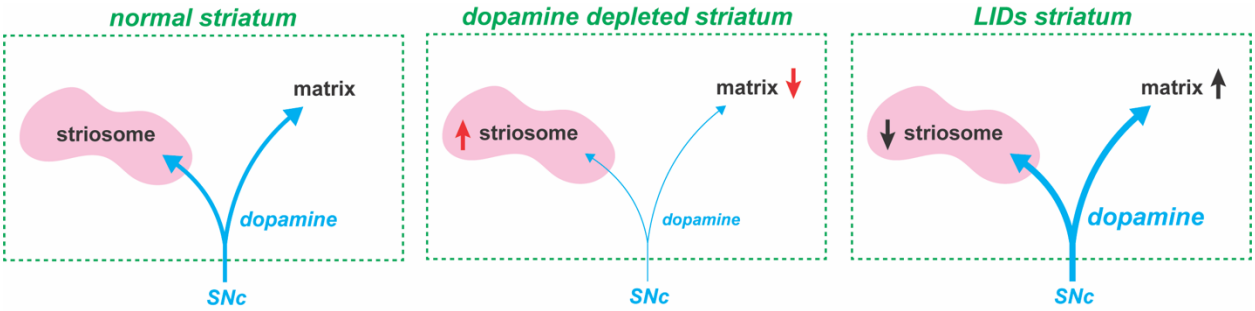

Figure 1. Simplified diagrams illustrating the compartmental organization of the striatum (dashed green boxes) and dopaminergic input to both striosome and matrix compartments from the SNc (blue). Diagrams depict the striatum under normal dopaminergic conditions (left) and the generalized changes in compartmental activity (red and black arrows) hypothesized to occur following dopamine depletion (center) and the induction of LIDs (right).