Overview/Abstract. We seek Seed Grant funds to support a new collaboration between the Maffei and Kritzer labs and to pilot two innovative, high risk, high impact initiatives that require their collective expertise. These studies are integral to a larger translational research effort also involving the labs of Drs. Carine Mauer (SBU Dept Neurology) and Chuan Huang (SBU Depts. Radiology and Psychiatry) that investigate the causes and novel treatments for cognitive and memory dysfunction in Parkinson's disease (PD). In addition to significantly interfering with patients' quality and activities of daily life[1,2], cognitive and memory deficits in PD predict a more rapid course of cognitive and motor decline, greater risk for freezing and falls and higher risk for developing PD-related dementia which is a major cause of institutionalization and death in PD patients[3-5]. At present, these disabling outcomes are also unavoidable. This is because unlike the plurality of treatments available for managing PD's motor signs, there are few therapeutic options available for mitigating the cognitive and memory deficits of PD. However, recent work in across the Kritzer, Huang and Maurer labs suggest that therapeutic stimulation targeting the ventromedial division of the subthalamic nucleus (STN) could be important, untapped means of improving cognition and memory in PD patients. While deep brain stimulation (DBS) in the STN is a mainstay of effective treatment for PD's motor signs, until now this treatment has offered either no benefit or produced unwanted stimulation-induced impairments in cognition and memory[6]. In investigating the basis for this, studies combining tractography imaging with STN DBS have localized the ability of DBS to alleviate PD's motor signs to stimulation of the dorsolateral division of the STN and identified current spread into its ventromedial division as contributing to the negative impacts of stimulation on cognition and memory[7]. This fits with the functional parcellation of the STN based on its topographic inputs from associative/limbic vs. sensorimotor areas of the cerebral cortex[8]. It also aligns with emerging preclinical data from our labs suggesting that anatomically discrete, functional domains of the STN have unique physiological signatures that are differentially dysregulated in PD. It follows that functional STN domains could also be valuable as therapeutic targets for site-specific DBS that could benefit patients' cognition and memory as well as motor function. We currently have data in hand from dopamine lesioned rat models of PD that support these hypotheses. Specifically, we have data that link activation of the ventromedial, limbic/associational division of the STN (vmSTN) to cognition and memory function; that correlate decreased activation in the vmSTN to cognitive and memory deficits in PD model rats; and that show that the same hormone manipulations that restore rats' cognitive and memory function also selectively restore vmSTN activation. We have secured pilot funding (Hartman Award to Maurer, Kritzer and Huang) to launch clinical studies based on these findings. These use multimodal imaging including tractography of cortex-to-STN projections to identify functional subdomains of the human STN and correlate regional patterns of STN activity with cognition, memory and motor function in male and female PD patients. Here we seek Seed Grant support to pilot related high risk/high impact preclinical studies that similarly leverage the hyper-direct cortical projections that divide the STN into discrete functional subdomains and will allow us to dig deeper into the mechanisms that shape them in health and disease. Using male and female control and PD model rats as models, we will introduce novel viral vectors engineered to be transported anterogradely, transsynaptically and/or to carry the light-gated channel, channelrhodopsin, to generate pilot/feasibility data for studies that:

1. Define the electrophysiological signatures that differentiate neurons in different functionally specialized STN domains and determine how they are dysregulated in PD.
2. Define the impacts of DBS that is regionally targeted and tailored to discrete STN domains on motor, cognitive and memory function in awake, behaving animals.

At present little is available to mitigate the relentless cognitive and memory decline in PD. Our goals are to fill these therapeutic gaps. Here, the expertise of the Maffei and Kritzer labs will be combined for the first time to generate pilot data for innovative preclinical aims that will dovetail with planned translational research proposals and elevate them to meet NIH demands for feasibility, private foundation demands for patient value and the demands of both for innovation.