

Recently, a card from my student read “Nancy: Dreamer, Scientist and Mentor”. To me, this meant that the hard work and sleepless nights had been worth it. I had been overwhelmed five months earlier with conflicts amongst my mentees that constantly interrupted my research, largely because I had little experience leading research teams. Each of them had tremendous potential and passion for science, yet we struggled. For example, two of my students, were struggling to work together because they perceived body language differently based on their cultural backgrounds. To improve our communication, I implemented weekly meetings and established an open and democratic culture. I learned to identify our values and strengths, and aligned them to our scientific goals. We turned the team into a productive and happy scientific family. As my student wrote in the card, my life has been a journey of becoming a dreamer, a scientist and most recently a mentor.

The Dreamer: I value creativity in science as much as I value rigor. I find inspiration for experiments in the most uncommon places, from people watching to my own dreams. Coming from a family of musicians, music drove me to neuroscience. As a child, I wondered how music triggered emotions and why some sounds were noise but others melodies. This curiosity drove me to study biology with the hopes of understanding the brain. Nowadays, my curiosity continues. I dream of creating a ‘neuro-biodome’, a place where experiments have no beginning nor an end by integrating neurotechnology to monitor neural activity and behavior 24/7. I also use creativity to solve problems in my research. For example, I study social dominance and the established assays to study it lack the trial structure we need for statistical power and manipulations. Inspired by pushing boundaries, I designed a social dominance assay that has both trial structure and ethological validity. The BWF grant will allow me to get additional training to track and quantify social behaviors more deeply and push the boundaries of my project and the field.

The Scientist: Growing up, I never met a scientist, so I started college with no clear path to satisfy my curiosity for the brain. Once I joined a neuroscience research lab I found a path for intellectual satisfaction. As an undergrad, I completed a research project, from beginning to end, which resulted in two peer-reviewed publications. At Columbia University, where I pursued my PhD, I prioritized learning electrophysiology and novel techniques to manipulate neuronal activity to study circuits underlying behaviors in mice. I also published several papers and collaborated with other groups. I took quantitative classes to improve my scientific rigor, and presented my work and international conferences. Now, I am using electrophysiology and optogenetics to investigate how the brain controls social behaviors. With the BWF grant I will be able to establish several collaborations that will improve the scope of my project and to continue presenting my research at international conferences. My goal is to become a professor who conducts research that goes beyond existing paradigms and impacts society beyond the bench. I have actively participated in educational outreach activities during the past 7 years. Moreover, I started a collaborative project that increases visibility of women neuroscientists by creating online profiles that highlight their scientific contributions.

The Mentor: I had mentors who taught me that science *can* transform lives and society. Certainly, science transformed my life and created opportunities for me. I now pay it forward by mentoring others. My journey of mentoring has only begun, as I am still learning how to best teach, instill scientific purpose and guide mentees, but my commitment drives me to become a better scientist every day. During graduate school, I also experienced women and minority in STEM experience often, but this drove me to work even harder and become a role model and mentor to the next generation. This BWF grant will help me acquire skills, network, present my research and become a successful professor that does impactful research and is deeply committed to mentoring.

Layman Summary:

Many psychiatric disorders include debilitating social deficits. Although research has provided insights linking genes to social deficits in animal models, there has been little progress in elucidating the neural circuits that underlie normal social behaviors. Identifying these circuits is crucial for identifying potential therapies for psychiatric disorders. Dominance hierarchies have a profound impact on animals' well-being and on their subjective experience during social interactions. Especially, access to important resources, such as food, is determined by social rank. Moreover, by acting according to their social rank, animals decrease unnecessary aggression and save energy. Although dominance hierarchies are central to successful group dynamics and social interactions, the neural basis of dominance behaviors remains unknown. Mice, like humans in modern societies, have flexible hierarchies in which social rank is not inherited, but earned. These similarities –combined with the vast number of tools for circuit dissection–make mice a good model to investigate the neural dynamics of social hierarchy. Cross-species evidence suggests that the medial prefrontal cortex (mPFC) is crucial for social dominance behaviors. Given the role of the lateral hypothalamus (LH) in innate behaviors, and its connectivity with the mPFC, it is well positioned to modulate social behaviors in a rank-dependent manner. In order to study the role of the mPFC-LH pathway in social dominance, I have developed a trial-based reward competition assay that measures dominance. This assay offers the benefit of statistical power for studying neural dynamics and of repetition for reversible manipulations, such as optogenetics. To minimally the effects of tethers in social interactions while recording, I will use wireless electrophysiology to characterize the mPFC-LH neural dynamics of dominance. By combining, optogenetic manipulations, wireless electrophysiology and novel social assays, I will investigate the role of the mPFC-to-LH in the expression of dominance behavior. First, in mice with identified social rank, I will record mPFC LH projectors during social dominance assays to characterize the encoding properties of this subpopulation and how they differ across ranks (Aim 1). Then, I will use optogenetics to selectively manipulate mPFC LH projector cells during social interactions and survey the behavioral consequences using novel computer vision technology for in depth behavioral tracking (Aim 2). Using an innovative approach, this work will provide a comprehensive understanding of how mPFC to LH pathway regulates social dominance behaviors in mice. Moreover, this work will further our understanding of how social rank influences mPFC-hypothalamic neural dynamics during social behaviors.

Nancy Padilla-Coreano PhD

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EDUCATION

2011-2016* Columbia University

PhD in Neurobiology and Behavior, Department of Neuroscience.
Thesis: Dissecting the role of the prefrontal hippocampal circuit in anxiety
* Defended in June and Degree conferred in October 2016

2007-2011 University of Puerto Rico

BS in Molecular Biology, Magna Cum Laude Department of Biology, Rio Piedras
Thesis: Brain regions involved in fear extinction learning and consolidation

RESEARCH EXPERIENCE/POSITIONS

2016- Massachusetts Institute of Technology

Postdoctoral Fellow, Dept. of Brain and Cognitive Sciences
Topics: Neural representations of hierarchy in the brain during social behaviors;
Development of social behavior methods for mice
Advisor: Kay Tye PhD

Highlights: During my time as a postdoc, I have pioneered several social hierarchy behavioral paradigms, set-up wireless electrophysiology technology and supervised a diverse team of students. Moreover, I have already been a coauthor in publications from the laboratory.

2012-2016 Columbia University

Graduate Thesis Research, Dept. of Integrative Neuroscience
Topics: Functional connectivity in hippocampal-prefrontal pathway during anxiety behavior; Collaborations on the role of interneurons in the prefrontal cortex during cognition
Advisor: Joshua A. Gordon MD, PhD

Highlights: Besides two first author papers, I collaborated in two studies that resulted in publications. In addition, I trained successfully several undergraduates and graduate students.

2012 Columbia University

Graduate Rotation Research, Dept. of Neuroscience, Columbia University
Topic: Synchrony of neuronal spiking across cortical layers during stimulus

decoding
 Advisor: Randy Bruno PhD

2008-2011 University of Puerto Rico

Undergraduate Thesis Research, Dept. of Psychiatry, Medical Campus
 Topic: Brain regions involved in fear extinction learning and consolidation
 Advisor: Gregory J. Quirk PhD

Highlights: My research resulted in two publications, one of which has been cited >600 times.

2010 Massachusetts Institute of Technology

Summer Internship, Dept. of Brain & Cognitive Sciences
 Topic: Neural responses in the barrel cortex during artificial gamma oscillations in behaving mice
 Advisor: Christopher Moore PhD

PEER-REVIEWED PUBLICATIONS

Padilla-Coreano N., Canetta S., Garcia-Garcia A., Warren R., Teboul E., Blackman D., Morton M, Kellendonk C., and Gordon J.A. (2018) Hippocampal-prefrontal theta transmission regulates anxiety-like behavior. *Neuron* (pending revisions).

C.M. Vander Weele, C.A. Siciliano, G.A. Matthews, P Nambury, E.M. Izadmehr, I.C. Espinel, E.H. Nieh, E.H.S. Schut, **N. Padilla-Coreano**, A. Burgos-Robles, C. Chang, E. Kimchi, A. Beyeler, R. Wichmann, C.P. Wildes, K.M. Tye. (2018) Dopamine enhances signal-to-noise ratio in cortical-brainstem encoding of aversive stimuli. *Nature*.

Jiangteng Lu*, Jason Tucciarone*, **Nancy Padilla-Coreano**, Miao He, Joshua A. Gordon, Z. Josh Huang. (2017) Selective inhibitory control of pyramidal neuron ensembles and cortical subnetworks by chandelier cells. *Nature Neuroscience*.

Padilla-Coreano N., Bolkan S., Pierce G., Blackman D., Spellman T. and Gordon J.A. (2016) Direct hippocampal-prefrontal input is required for anxiety-related neural activity and behavior. *Neuron*, 89, 857-866.

Canetta S., Bolkan S., **Padilla-Coreano N.**, Song L., Sahn R., Harrison N., Gordon J.A., Brown A. and Kellendonk C. (2016) Prenatal Maternal Immune Activation Leads to Selective Functional Deficits in Adult PV Interneurons. *Molecular Psychiatry*, 1-13

Padilla-Coreano N., Do Monte F.H. and Quirk G.J. (2012) A time-dependent role of midline thalamic nuclei in the retrieval of fear memory. *Neuropharmacology*, 62(1):457-63.

Sierra-Mercado D., **Padilla-Coreano N.** and Quirk G.J. (2011) Dissociable roles of prelimbic, Infralimbic, ventral hippocampal, and basolateral amygdala areas in fear expression and extinction memory. *Neuropsychopharmacology*, 36(2):529-38.

ABSTRACTS IN SCIENTIFIC CONFERENCES

Padilla-Coreano N., Canetta S., Hardin W., Blackman D., Warren R., Kellendonk C., Gordon JA. Theta frequency oscillatory stimulation of vHPC inputs to the mPFC increases anxiety-like behavior. Annual Meeting of the Society for Neuroscience. San Diego, CA. November 2016 and ACNP Annual Meeting December 2016.

Canetta S., Bolkan S., **Padilla-Coreano N.**, Gordon J., Kellenkdonk C. Mechanisms by which prefrontal cortex distinguishes ventral hippocampal from mediodorsal thalamic inputs. ACNP Annual Meeting. December 2016.

Padilla N., Bolkan S., Pierce G., Blackman D., Spellman T, Gordon JA. Direct hippocampal-prefrontal input is required for anxiety-related neural synchrony and behavior. Annual Meeting of the Society for Neuroscience. Chicago, IL October 2015

Canetta S., Bolkan S., **Padilla N.**, Song L., Sahn R., Harrison N., Gordon J.A., Brown A. and Kellendonk C. Maternal immune activation leads to a selective deficit in the functioning of offspring parvalbumin interneurons. Annual Meeting for the American College of Neuropsychopharmacology. December 2015

Padilla N., Pierce G., Blackman D., Spellman T, Gordon JA. Ventral hippocampal input to medial prefrontal cortex is necessary for anxiety behavior and anxiety-induced theta synchrony. Annual Meeting of the Society for Neuroscience. Washington D.C., November 2014

Do Monte F.H., **Padilla-Coreano N.**, Quirk G. "Midline thalamic nuclei are required for maintenance of remote fear memory" Federation of European Neuroscience Societies Meeting. Barcelona, Spain July 2012.

Do Monte F.H., **Padilla-Coreano N.**, Quirk G. "A time-dependent role of midline thalamic nuclei in the retrieval of fear memory." Annual Meeting of the Society for Neuroscience. Washington D.C., October 2011.

Padilla N., Pritchett D., Siegle J. and Moore C. "Neuronal responses during artificial gamma oscillations in behaving mice" 10th Annual Biomedical Research Conference for Minority Students. Charlotte, NC. November 2010.

Padilla N., Sierra-Mercado D., Quirk G. "The roles of the ventral hippocampus and mediodorsal thalamus in fear expression and extinction" Annual Society for Neuroscience Meeting. San Diego, CA. November 2010.

Padilla-Coreano N., Sierra-Mercado D. and Quirk G.J. "Neural circuits of fear: is the ventral hippocampus involved" 21st Annual Biomedical Research Conference for Minority Students. Phoenix, AR. November 2009. (Excellence Award for oral presentation)

Sierra-Mercado D., **Padilla-Coreano N.** and Quirk G.J. "Dissociable roles of the

basolateral amygdala, prelimbic and infralimbic cortices in fear expression and extinction.” Annual Meeting of the Society for Neuroscience. Chicago, IL, USA. October 2009

RESEARCH TALKS

- 2016** Winter Brain Conference invited panelist
- 2015** Department Student Series talks
- 2013** Department of Psychiatry, University of Puerto Rico
- 2011** Centro Internacional de Restauracion Neurologica, Habana Cuba

HONORS, AWARDS & FELLOWSHIPS

- 2017-pres** Simons Social Brain Center Postdoctoral Fellowship
- 2016** American College of Neuropharmacology (ACNP) travel award recipient
- 2015** Carl Storm Fellowship Travel Award for the Amygdala Gordon Conference
- 2014** Travel Award for University of Wisconsin Health and Emotions 2014 Conference
- 2013-2016** National Science Foundation Graduate Research Fellowship
- 2013** Ford Foundation Predoctoral Fellowship recipient
- 2011-2013** SfN Neuroscience Scholar Program (NSP) recipient
- 2010** Travel Award for University of Wisconsin Health and Emotions 2010 Conference
- 2010** MIT research program research oral presentation award
- 2009** ABRCMS Best oral presentation award
- 2009-2011** Minority Access to Research Careers (MARC) Research Fellowship
- 2008-2011** Natural Sciences School UPR-RP Honor Roll and Dean’s list

PROFESSIONAL AND COMMUNITY SERVICE

- 2018-pres.** Member of Minority Task Advisory Committee for the American College of Neuropharmacology
- 2017-2018** Postdoctoral representative seminar selection committee at the Brain and Cognitive department at MIT
- 2016-pres.** Member of Trainee advisory committee for the Society of Neuroscience (SfN)
- 2014** Member of Committee for departmental retreat program
- 2012-2015** President of Columbia University Neuroscience outreach (CUNO) program
- 2012** Organizer of the neuroscience bootcamp for incoming graduate students

TEACHING EXPERIENCE

- 2013-2015** Instructor for Brain Research Apprenticeships in New York at Columbia (BRAINYAC) Program for high school students to work in research laboratories at Columbia University
- 2015** Designed and proposed graduate course “Quantitative approaches for

2016-2017 experimental neuroscientists”
Invited Lecturer for Neuromodulation and Neuroendocrine Systems course at
Massachusetts Institute of Technology

Social hierarchies are ubiquitous and organize interactions in most species, including humans¹. They are highly important for survival in any social species^{1,2} – yet this is a severely understudied area in neuroscience. Studying the circuits and neural mechanisms that govern social behaviors and hierarchies could inform the development of treatments for psychiatric disorders that feature social deficits, such as the inability to follow social rank or rules. The medial prefrontal cortex (mPFC) is implicated in dominance behaviors in humans, other primates³, and in mice⁴. My goal is to identify mPFC downstream projections that encode social rank and modulate dominance behaviors. The hypothalamus is well positioned to modulate social dominance since it is critically involved in innate social behaviors⁵ and regulates hormones that modulate social behaviors⁶. Specifically, out of all hypothalamic nuclei, the lateral hypothalamus (LH) receives the strongest projection from the mPFC. Moreover, LH subpopulations can drive social investigation⁷. I will combine the use of novel behavioral paradigms, optogenetic circuit dissection and wireless electrophysiology to identify how mPFC→LH neural dynamics encode social rank. I hypothesize that the mPFC-hypothalamic pathway provides social rank information that guides dominance behaviors (Aim 1). To establish a causal relationship between mPFC→LH activity and social rank expression, I will optogenetically modulate mPFC→LH activity during social dominance assays. I hypothesize that modulation of mPFC→LH activity will disrupt the appropriate social rank expression (Aim 2).

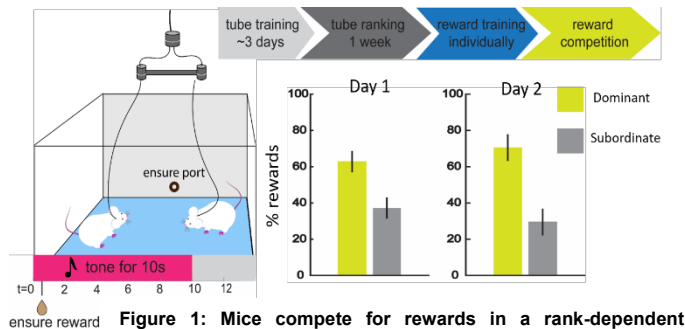


Figure 1: Mice compete for rewards in a rank-dependent manner. Top, schematic of experiment showing order of behavioral testing. Left, cartoon showing two mice competing for a reward that is predicted by a tone. Right, dominant mice, as defined by tube test (green=wins tube test; gray=loses tube test), win most rewards during competition.

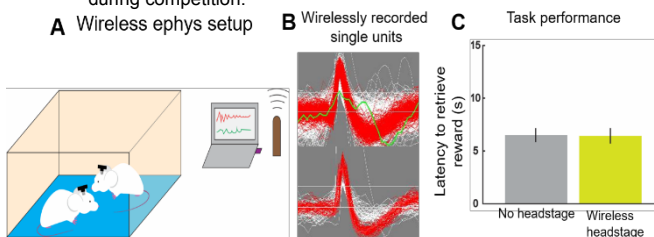


Figure 2: Preliminary data showing feasibility of wireless electrophysiology during reward competition. A. A cartoon showing wireless setup for recording ephys from both mice simultaneously. B. In red, representative single units recorded using the wireless ephys. C. Latency to retrieve reward with and without wireless headstage (n=4).

Aim 1: Characterize the mPFC→LH neural dynamics during social dominance

I will target mPFC-to-LH projectors by virally expressing channelrhodopsin 2.0 (ChR2)⁷ in this subpopulation which renders neurons identifiable by light response latencies, an approach known as phototagging⁸. I will inject a Cre-dependent ChR2 virus into the mPFC and the retrogradely traveling viral vector canine adenovirus carrying Cre (CAV-Cre) into the LH. In addition, I will implant an electrode with an optical fiber into the mPFC. I will record neural activity during social interactions in the home cage and in two social dominance assays: the tube test and a reward competition. The tube test is an easy and well-characterized dominance assay where the dominant mouse pushes the subordinate out of a narrow tube^{4,9}. Trial structure enables statistical power for neuronal analyses and facilitates controlled manipulations, thus I developed a trial-based

reward competition to measure dominance behaviors. First mice learn to associate a tone with a small palatable liquid reward and once trained they are tested in the presence of a cagemate, thus creating competition for the reward. On average, dominant mice consumed more rewards than subordinates did, and this is consistent across days (Figure 1). Across assays, I will record the same mouse against a dominant and subordinate within the same

session, thus providing a same cell comparison across social rank and conditions. Using linear or nonlinear regressions, and neural population analyses, I will characterize mPFC→LH activity across social dominance and conditions. To dissociate rank and mouse identity, I will repeat the assays under pharmacological blockage of testosterone of the conspecific, which disrupts social rank¹⁰. During subordination vs. dominance conditions, I expect differences in the identity, activity level, size or activity patterns of the mPFC→LH neurons that show task-related activity and that mPFC→LH activity patterns will be predictive of social rank using regression methods. Finally, Aim 1 results will inform how I will manipulate this pathway during social dominance behaviors in Aim 2 experiments. Overall, these experiments will provide a model of how the medial prefrontal-hypothalamic neurons encodes social rank.

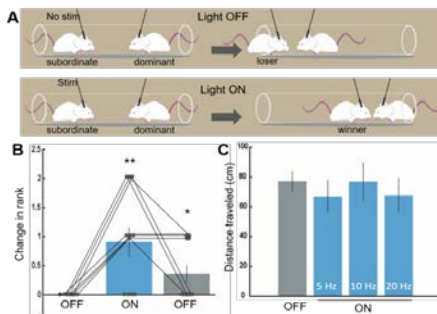


Figure 3: mPFC to LH optogenetic stimulation increases social dominance in the tube test. A. Tube test paradigm used for optogenetic stimulation. The subordinate mouse was stimulated during the tube trials of light OFF and light ON. B. Average changes in tube rank during the light OFF and ON trials (n=11 pairs of mice; paired t-test compared to first trial OFF period **p<.01 *p<.05). Increase in rank indicates more winning in tube test. C. Locomotion in the open field across counterbalanced frequencies of stimulation (n=7).

Aim 2: Manipulate optogenetically mPFC-to-LH activity during social dominance behaviors.

In order to selectively inhibit or excite mPFC→LH projectors I will use the dual virus approach described above to express the light-activated chloride pump halorhodopsin (eNpHR3.0) for inhibition⁷, ChR2 for excitation or a fluorophore control, and implant optical fibers into the mPFC for localized light delivery. After viral expression and behavioral training, mice will be tested in the tube test, the reward competition and in their homecage with alternating light off and on periods. My preliminary data show that mPFC→LH optogenetic activation in subordinate mice increases dominance expression in the tube test without affecting locomotion (Figure 3). Next, I will test if activation of mPFC→LH affects dominance behavior in the reward competition. Importantly, I will use a triple commutator (Figure 4) in order to do optogenetic

manipulations during the reward competition without tethers affecting the behavioral outcome. In addition, I will investigate how mPFC→LH manipulations during homecage interactions using wireless optogenetics to ensure we can look at interactions of all four cagemates simultaneously. Moreover, I will use 3D pose sub-second analysis¹¹ to assess how behavior in homecage changes with mPFC→LH manipulations in an unbiased manner. Based on the neural activity differences observed in Aim 1, I can make predictions of what will happen with dominance behavior during mPFC→LH optogenetic manipulations. For example, if the neuronal ensemble during dominance expression is larger in size or more active, then I expect that mPFC→LH inhibition will decrease dominant behavior while mPFC→LH activation could increase dominant behavior. Indeed our preliminary data shows that mPFC→LH activation results in increased dominance in the tube test, which supports outcomes A and B (Fig. 5).

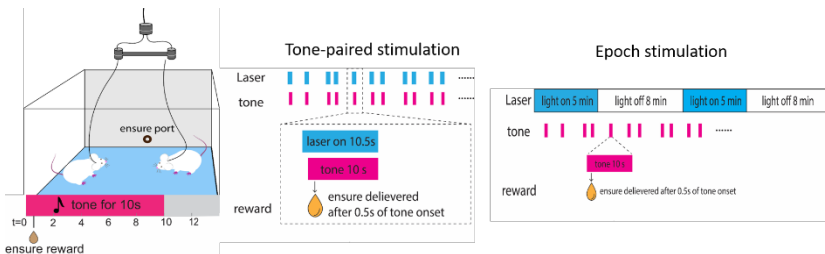


Figure 4: Reward competition assay modification for optogenetics and stimulation parameters. Left, schematic showing the reward assay and two mice tethered by a triple commutator. This tethering successfully prevents tangling during the task (data not shown). Optogenetic manipulations during the reward competition will be done paired with each tone or in an epoch manner.

Figure 5 has several other predicted outcomes and interpretations for the optogenetic inhibition experiments. In summary, these two aims combine innovative techniques, such as wireless electrophysiology and novel behavioral paradigms to advance our knowledge of how the prefrontal

BURROUGHS WELLCOME FUND
Postdoctoral Enrichment Program for Underrepresented Minorities

Applicant Name (Last, First, Middle)	Padilla Coreano, Nancy
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DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

EQUIPMENT <i>(Itemize)</i> Wireless Optogenetics system: Neurolux \$7,500	
	7,500
SUPPLIES <i>(Itemize by category)</i> wireless implantable LEDs \$500 Computer with GPU \$3,000	
	3,500
TRAVEL Society for Neuroscience Annual Meeting 2019, Chicago, IL \$2000 New Frontiers in the Study of Animal Behaviour Konstanz, Germany August 2019 \$2500	
	4,500
OTHER EXPENSES <i>(Itemize by category)</i> Professional societies membership fees \$300	
	300
TRAINING ACTIVITIES Python class at UCSD \$695 Visiting collaborator James Curley's laboratory \$1700 Visiting collaborator Bob Datta's laboratory \$1805	
	4,200
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	\$ 20,000

BURROUGHS WELLCOME FUND
Postdoctoral Enrichment Program for Underrepresented Minorities

Applicant Name (Last, First, Middle): Padilla Coreano, Nancy

Equipment:

My research requires specialized equipment to study social behaviors in the most naturalistic ways possible. In order to do optogenetic manipulations without tethers that affect the behavior of the mice, I will purchase a wireless optogenetic system called NeuroLux. I will also purchase a computer with a graphic processing unit (GPU) in order to use computer vision technologies to track multiple mice automatically and analyze their behavior without the need of handscoring. Regular desktop computers do not have the computational power necessary for video analyses, thus my project requires acquiring a more specialized computer.

Supplies:

The wireless optogenetic system requires implant microLEDs, so we will purchase a supply of microLEDs to implant.

Other:

I will use some of my funds to become a member of several professional societies, such as Society for Neuroscience and Society for Social Neuroscience.

Training:

In order to use computer vision tools for mouse tracking, such as DeepLabCut and Datta's lab 3D mouse pose analysis, I need to learn python. I will use part of my training funds to take a python class.

In order to get training for how to work with our behavior dataset I will visit several labs. James Curley is an expert in the study of social dominance behaviors in mice. His lab also has expertise in applying statistical techniques for social network analysis. Datta's lab has developed an unsupervised subsecond behavioral analysis that takes video depth into consideration. Visiting his lab will allow me to maximize the use of their analysis tool.

Travel:

I will travel to two meetings to share my scientific findings, learn, and receive feedback from field experts. Society for Neuroscience Annual Meeting and New Frontiers in the Study of Animal Behaviour. In addition, Society for Social Neuroscience is a satellite meeting that is highly relevant for my work and it occurs one day prior to SfN's Annual Meeting.