Charles Darwin was the first to hypothesize that emotions serve as an important adaptive biological mechanism to avoid pain and seek pleasure[1]. An example is anxiety, which helps organisms avoid environmental threats. However, too much anxiety becomes maladaptive and contributes to psychiatric disorders. By studying the neurobiology of anxiety behavior we can develop better treatments for anxiety disorders. Previously, neuroscientists have used lesion and pharmacological studies to identify brain structures involved in anxiety, but these manipulations lack temporal and spatial specificity. Recently developed optogenetic tools allow precise temporal and spatial control of neuronal populations. Expressing genes of light-activated proteins in neurons we can excite or inhibit neural activity with millisecond specificity. I propose to use optogenetic tools in mice to determine if communication between two brain structures that my lab (Gordon lab) has implicated in anxiety behavior is indeed required for anxiety.

A growing body of evidence, mostly from lesion and pharmacology studies, implicates the medial prefrontal cortex (mPFC) and the ventral hippocampus (vHPC) in anxiety. Interestingly, the vHPC makes strong unidirectional projections to the mPFC, suggesting that the vHPC projections to the mPFC may be part of distributed brain circuit that contributes to anxiety behavior. In support of this idea, population activity in the mPFC and the vHPC become highly correlated in the theta frequency (8-12 Hz) when mice are tested in anxiety assays[1]. Moreover, changes in anxiety behavior correlated with strong theta activity in the mPFC. Thus, anxiety behavior is correlated with multiple measures of functional connectivity between the vHPC-mPFC circuit. This correlative evidence, however, does not establish that the vHPC input to the mPFC is required for generating anxiety behavior**.**

One of the optogenetic tools is the light-sensitive protein Archaerhodopsin-3 (Arch). Arch is activated by green light and when expressed in neurons it causes neuronal activity silencing. I

1. Darwin C. *The Expression of the Emotions in Man and Animals* (1872)
2. Adhikari A., Topiwala M., Gordon J. Neuron. (2010) 65, 257-69
3. Tye K., Prakash R., Kim S. et al. Nature (2011) 471, 358-62

hypothesize that silencing vHPC projections to the mPFC will decrease anxiety behavior in mice. I will test this by expressing Arch, tagged with the fluorescent protein mCherry, in the vHPC through a viral vector. I will silence the vHPC input to the mPFC by photostimulating, with green light, the vHPC axonal terminals through a fiber optic implanted in mPFC. Optogenetic silencing axonal terminals has worked in a recent study[3] and has been successfully done in the Gordon lab. In a control group, I will inject vHPC with a viral vector containing only the inert fluorophore mCherry. I will test mice in two anxiety assays. While it is difficult to measure anxiety in mice, we can measure avoidance behavior in the presence of potential danger. I will use two well-characterized anxiety tests that allow avoidance measurements: the elevated plus maze (EPM) and the open field. Importantly, drugs that are anxiogenic and anxiolytic in humans increase and decrease, respectively, avoidance in these anxiety assays. The use of two different anxiety assays provides a robust way to confirm that the vHPC-mPFC circuit is indeed involved in anxiety behavior. I expect that during photostimulation of the mPFC avoidance will decrease in the cohort of mice injected with Arch, but not in the control cohort. If avoidance is not affected then the vHPC-mPFC circuit does not have a causal relationship in generating anxiety behavior. Alternatively, it is possible that projections from the amygdala, another brain structure involved in emotions, to both the vHPC and the mPFC has a causal role in generating anxiety behavior. Using the same optogenetic tools I have described, I can test the role of the amygdala in anxiety behavior. Understanding the circuitry of anxiety brings us one step closer to understanding the mechanisms of emotional regulation. Moreover, knowledge of the circuitry of anxiety will help develop novel, more effective treatments for anxiety disorders.

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My first research experience was in Dr. Gregory J. Quirk's laboratory. The Quirk Lab studies how the brain regulates emotions using fear learning in rats as a model system. Fear learning is induced by pairing a tone with a shock such that the tone elicits freezing (immobility), an innate fear response in rodents. On the other hand, fear extinguishes with repetitive presentation of the tone without a shock. I was determining the roles of two medial prefrontal cortex (mPFC) subregions, as well as the ventral hippocampus in fear memory and extinction. I was trained by a graduate student, but quickly became independent. Using pharmacological methods to locally disrupt neural activity, we found that the prelimbic region of the mPFC is necessary for fear memory recall, whereas the neighboring infralimbic region is necessary for fear extinction. This project turned into my first publication[1]. How are these brain regions encoding fear memory? This question led me to become interested in electrophysiology.

My interest in using electrophysiology led me to work with Dr. Christopher Moore at the Massachusetts Institute of Technology during an internship. I worked with a graduate student to determine how sensory perception is altered by artificially inducing gamma oscillations in the somatosensory cortex in behaving mice. Gamma oscillations emerge in states of attention and correlate with increased perception in behavioral tasks, but no one has tested if gamma is sufficient to increased perception. Using optogenetic tools to manipulate neural activity, and induce gamma oscillations we tested this idea. By expressing the light sensitive channel ChR2 in neurons, gamma oscillations can be generated by shining light in the somatosensory cortex in a temporally controlled manner. I presented this work in a national conference.

Working in the Moore lab I learned about sensory neuroscience, specifically the thalamo-cortical interactions during sensory perception. Although much is known about the interactions of the thalamus with the sensory cortex, little is known about how the thalamus interacts with

[1] Sierra-Mercado D., **Padilla-Coreano N.** and Quirk G.J. *Dissociable roles of prelimbic, infralimbic, ventral hippocampal, and basolateral amygdala areas in fear expression and extinction memory.* Neuropsychopharmacology, January 2011.

[2] **Padilla-Coreano N.,** Do Monte F.H. and Quirk G.J. *A time-dependent role of midline thalamic nuclei in the retrieval of fear memory.* Neuropharmacology, August 2011.

higher order cortices such as mPFC. I returned to the Quirk lab and started my thesis on the role of the thalamus in fear and extinction. The dorsal midline thalamus (dMt) projects strongly to mPFC and to other brain regions involved in fear: vHPC and the amygdala. I hypothesized that dMt could be regulating fear through inputs to any of these regions. Indeed, pharmacological silencing of dMt 24 h after the fear learning, but not earlier, impaired recall of the fear memory. This suggests that dMt becomes part of the fear circuitry slowly after learning occurs. Moreover, dMt affected neuronal activity in the amygdala during fear memory recall. This work became my first publication as a first author[2].

In graduate school, I have focused on learning electrophysiology techniques. During a rotation in the laboratory of Dr. Randy Bruno, I studied the role of spike synchrony in sensory stimuli encoding across the cortical layers. Previous work showed that activity of thalamic pairs becomes correlated when stimuli is present, suggesting that timing of spikes is important for encoding stimuli. I predicted that neuronal pairs that receive thalamic input might also become correlated with stimuli presentation in order to propagate the signal from thalamus to cortex. This project was essential for learning how to perform and analyze electrophysiological recordings. Under Dr. Joshua Gordon's guidance, I am using optogenetic tools, and electrophysiological recordings of single neurons and population activity during anxiety assays (see proposal). Similar to fear learning, which I studied in the Quirk lab, anxiety is dependent on mPFC and the hippocampus. Furthermore, my training in the Moore lab prepared me to using optogenetic tools in behaving mice. With these set of research experiences I hope to employ the knowledge I have acquired towards increasing the present understanding of the neural mechanism underlying anxiety behavior.

[1] Sierra-Mercado D., **Padilla-Coreano N.** and Quirk G.J. *Dissociable roles of prelimbic, infralimbic, ventral hippocampal, and basolateral amygdala areas in fear expression and extinction memory.* Neuropsychopharmacology, January 2011.

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It was in front of my piano where I was first mesmerized by the brain. Ever since I was a child, I have experienced music's magical effects. Chopin's nocturnes made me cry and Mozart's sonatas were exhilarating. During high school, while reading excerpts of a biology textbook, I discovered that the music's magical effects come from the brain, and not the 'heart'. This awoke my scientific curiosity. How do we perceive sounds? How does music evoke such strong emotions? I started a quest to understand how the brain works, and regulates emotions. During this quest, I developed my career goal: to become a leader of the research community in Puerto Rico, as well as a professor.

As an undergraduate, I joined Dr. Gregory Quirk's laboratory at the University of Puerto Rico (UPR). The Quirk lab focuses on understanding how two brain regions, the medial prefrontal cortex (mPFC) and the amygdala, interact during fear regulation. While working on my undergraduate thesis, I frequently stood in front of the white board in my mentor's office drawing diagrams and debating potential experimental outcomes. As my research experience expanded through conferences and internships, I realized that my institution lacked a rigorous research community, and part of my goals is to improve the research community at UPR. I was one of the few students fortunate enough to receive research training thanks to the commitment of Dr. Gregory Quirk[1]. I often encouraged my peers to seek research experiences, and told them about my research to motivate them. The mentoring I received, and challenges I faced as an undergraduate shaped my passion for research and my desire to mentor students with limited access to training opportunities.

As a socially conscious scientist, every year during Brain Awareness Week, I visited multiple public schools in PR. I used interactive methods to teach students about the brain and discussed career opportunities available within science. Giving advice to students interested in pursuing a

1. http://www.md.rcm.upr.edu/quirk/Home.html
2. http://blogs.cuit.columbia.edu/cuno/

science career was very fulfilling. It was especially meaningful because I never received such advice, nor had I met a scientist prior to entering college. Even though I am no longer at UPR, my involvement with the UPR continues. I recently visited the UPR, together with Columbia University's Dean, to offer workshops about applying to graduate school and research internships.

At Columbia University, I am the vice-president of a group known as Columbia University Outreach Program (CUNO)[2]. We are committed to bring research into classrooms to improve science in local schools and foster excitement for science. Using neuroscience lessons prepared with the help of schoolteachers, we have reached out to over 1,000 K-12 students during the past two years. New York City has a lot of Hispanic children and some public schools have classrooms for students who have difficulties with English. For these classrooms, I have developed neuroscience lessons in Spanish since science is more intuitive and engaging to students when presented in their native language. By improving the science opportunities in public schools, we are helping to build the next generation of scientists. Teaching undergraduates is another way I am helping build the next generation of scientists. Columbia University allows graduate students to design special courses for undergraduates. I designed a course that explores how art is perceived in the brain, and how art evokes pleasure and emotions. Students will learn techniques used in neuroscience research and discuss current research in cognitive neuroscience. Moreover, we will discuss how human and animal research findings overlap regarding emotional regulation and pleasure. At the end of my graduate, and eventually post-doctoral, training I plan to return to Puerto Rico in order to establish my own research laboratory. In Puerto Rico, I will continue college level teaching and will continue studying emotional regulation using animal models. I hope to inspire students to pursue research careers, the same way I was inspired.

1. http://www.md.rcm.upr.edu/quirk/Home.html
2. http://blogs.cuit.columbia.edu/cuno/