BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

BRAIN & BEHAVIOR RESEARCH FOUNDATION
YOUNG INVESTIGATOR GRANT (YI)
2022 FACE SHEET

APPLICANT INFORMATION (***Please fill out all relevant information below***):

Principal Investigator (Full Name): Nancy Padilla Coreano

Position Title: Assistant Professor

Institution: University of Florida

For M.D. Applicants, year residency was completed: ☐

For Ph.D. Applicants, year degree was awarded: 2016

Is this your second time applying for the YI Grant? ☐ **Yes** ☑ **No**

For M.D./Ph.D. applicants please provide both years in the above designated areas.

Mentor/Institution (Please list primary mentor name first): Jennifer Bizon, University of Florida

Number of peer-reviewed papers (Total/ first authored/last authored): 11/4/1

Please identify all BBRF Scientific Council Members who will be in conflict with your application (i.e. your mentor, collaborators, same institution etc.). Completed list of members can be found here:
If no conflicts please list n/a

Kay Tye; Josh Gordon

APPLICATION INFORMATION ***(Please fill out all relevant information below):***

Research Method *(Please check all that apply):*

- ☑ Behavior
- ☑ Circuits
- ☐ Clinical Trials
- ☐ Epidemiology
- ☐ Genetics
- ☐ Molecular
- ☐ Neurostimulation
- ☐ Pharmacology
- ☑ Physiology
- ☑ Systems

Imaging *(Please check all that apply):*

- ☐ PET
- ☐ MRS
- ☐ MRI
- ☐ EEG
- ☐ fMRI
- ☐ Structural MRI

Would you classify your research as more basic or clinical?

- ☑ Basic
- ☐ Clinical

Please indicate whether you study:

- ☐ Humans
- ☑ Non-Humans
- ☐ Both

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The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. We invest in the most innovative ideas in neuroscience and psychiatric research to better understand the causes and develop new ways to treat brain and behavior disorders.

BBRF supports research for severe mental illnesses. The following list is illustrative.

Area(s) of Study
(Please select from the response that best fits your submitted application):

- ☐ Addiction
- ☐ ADHD
- ☐ Anxiety Disorders
- ☐ Bipolar Disorder
- ☐ Borderline Personality Disorder
- ☐ Depression
- ☐ Eating Disorders
- ☐ OCD
- ☐ PTSD
- ☐ Schizophrenia
- ☐ Suicide
- ☐ Other Depression and Anxiety disorde

Some disorders such as Autism, Alzheimer's Disease, and Parkinson's Disease are supported by BBRF only if primary psychiatric disorders are included in the research design. Transdiagnostic designs involving several disorders are welcome.

Below, please explain how your project and, if appropriate, the study population fit the Foundation's mission (250-word limit):

Social motivation is critical for health and survival. Many psychiatric and neurological disorders, such as Anxiety, Depression, Autism and Schizophrenia, disrupt social motivation. Research to understand the basic mechanisms of social behavior and how motivation systems modulate them is necessary for the creation of new therapeutic avenues. Most social neuroscience research focuses on studying the brain during interaction with novel individuals, which means that we do not understand how social motivation and behaviors are affected by social history. My recent work shows that the prefrontal cortex encodes social rank, an important component of social history. Moreover, the prefrontal-hypothalamic pathway modulates social competition between familiar mice. My proposed project will leverage the tools of systems neuroscience and machine learning to tackle how the ventral tegmental area modulates prefrontal-hypothalamic interactions during social interactions.

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Diversity Statement (optional)

The Brain & Behavior Research Foundation is interested in advancing the career and science for those of different backgrounds. The Foundation welcomes diversity with Grant Applications including gender, race, ethnicity and culture of the applicant and geographic location for their proposed work.

If you wish to have a diversity statement then please limit it to 50 words or less.

I seek and mentor trainees from underrepresented groups to help make science more accessible. I have mentored 15 students from diverse backgrounds. Many are co-authors in my publications and are in graduate school now. Outside of the lab, I work to increase the visibility of women in neuroscience via the project Stories of WiN (www.storiesofwin.org).

Abstract

We do not interact with our boss and mother in the same way. The ability to shift our social behavior based on the information available is known as social competence. For social animals, including humans, to thrive, they must show social competence and adjust behavior based on social history (e.g. social rank or degree of familiarity) and context. Social motivation is a critical component of social competence that is necessary for health and survival. Depression, anxiety and Autism Spectrum Disorders negatively impact social competency and social motivation yet there are limited therapies for these social deficits. Elucidating how social motivation is encoded by the brain and modulated by social history is important for understanding basic social brain function. Understanding these mechanisms may inform potential solutions for sociability changes seen in psychiatric and neurological disorders. Our recent work shows that the medial prefrontal cortex (mPFC) encodes social rank (Padilla-Coreano et al., 2022, Nature). In addition, mPFC input to the lateral hypothalamus (LH) regulates social behavior between familiar mice, suggesting a role for the mPFC-LH circuit in social history. Furthermore, the ventral tegmental area (VTA) sends dopaminergic input to LH and mPFC, and VTA-LH circuit has been found to further regulate sociability towards novel animals. However, it is unknown how the VTA interacts with the mPFC and LH as a network and how the network is modulated by social history. These previous studies only considered social interactions with novel individuals and did not account for social history. How this pro-social network works together during social interactions and how social history affects it is unknown. We propose to parameterize social history into its simplest components: familiarity and social rank. Further, we will resolve the issue of subjective human quantification of social behaviors by using novel machine learning tools to quantify behavioral differences across social history states and by using multi-site electrophysiology in vivo to record VTA, mPFC and LH simultaneously. Our central hypothesis is that dopaminergic modulation of mPFC and LH changes across social history states to enable social motivational differences. Our long-term goal is to identify the neural mechanisms of social history and how they change in disease states.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Padilla Coreano, Nancy

eRA COMMONS USER NAME (credential, e.g., agency login): npcoreano

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Puerto Rico, San Juan, PR	BS	08/2011	Molecular Biology
Columbia University, New York, NY	MA	05/2013	Neurobiology and Behavior
Columbia University, New York, NY	PhD	08/2016	Neurobiology and Behavior
Massachusetts Institute of Technology, Cambridge, MA	Postdoctoral Fellow	03/2019 11/2021	Neuroscience
The Salk Institute, La Jolla, CA and University of California San Diego	Postdoctoral Fellow		

A. Personal Statement

I am a new Assistant Professor in the Neuroscience department at the University of Florida. My goal is to understand how the brain gives rise to socially competent behaviors and how disease states disrupt social competency. Throughout my training and career, I have developed expertise in rodent models for the study of social-emotional behaviors and tools to record and disrupt brain activity, and the use machine learning tools to better understand the relationship between brain activity and behavior. In my predoctoral research I worked with Dr. Gregory Quirk where I trained in pharmacology and learning paradigms to study the neural circuits underlying fear and extinction learning. For my doctoral thesis worked in the laboratory of Dr. Joshua Gordon where I developed expertise in multi-site electrophysiology and functional connectivity to identify neural patterns associated with anxiety-like behavior. Furthermore, using optogenetics I identified that the connection between the hippocampus and prefrontal cortex is necessary for 4-12 Hz neural synchrony that emerges during anxiety and for anxiety-like behavior. My work studying how the brain encodes affective and motivated behaviors has been cited over 1,600 times. My most recent work demonstrates that the prefrontal cortex encodes social rank information and that the prefrontal connection with the hypothalamus is important to modulate social dominance behaviors (Padilla-Coreano et al., 2022). **This proposal is inspired by my recent work to understand how the dopaminergic system interacts with the prefrontal cortex and hypothalamus to modulate social motivation in a social history-dependent manner.**

B. Positions and Honors

Positions and Employment

2022-present	Assistant Professor, Department of Neuroscience, University of Florida
2016-2021	Postdoctoral Fellow, MIT and Salk Institute (advisor Dr. Kay Tye)
2011-2016	Graduate student, Columbia University (advisor Dr. Joshua Gordon)
2009-2011	MARC U*STAR undergraduate researcher (advisor Dr. Gregory Quirk)

Selected Honors and Fellowships

2021	Henry Grass Rising Star in Neuroscience Award
2020	Selected by National Academy of Sciences as Kavli Frontiers of Science Fellow
2020	L'Oreal USA For Women in Science Fellow, AAAS
2019-2020	Ford Foundation Postdoctoral Fellowship recipient, Ford Foundation
2017-2019	Simons Center for the Social Brain Postdoctoral Fellowship recipient, Simons Foundation
2016	Travel Award for the American College of Neuropsychopharmacology (ACNP) Meeting, ACNP
2015	Carl Storm Minority Fellowship Travel Award, Amygdala Gordon Conference
2013	Ford Foundation Pre-Doctoral Fellowship recipient
2013-2016	National Science Foundation Graduate Fellowship
2011-2013	Neuroscience Scholar Program (NSP) fellowship recipient, Society for Neuroscience
2010, 2014	Travel Award for University of Wisconsin (UW) Health and Emotions Conference, UW
2009-2011	MARC U*STAR fellow at the University of Puerto Rico
2008-2011	University of Puerto Rico Rio Piedras, Dean's list

C. Contribution to Science

1. *Role of medial prefrontal cortex circuits in anxiety-like behaviors*: I combined optogenetic inhibition and in vivo multi-site neurophysiology in mice to demonstrate pathway- and frequency- specific effects of the ventral hippocampal input to the medial prefrontal cortex (vHPC-mPFC) during innate anxiety. I found that the vHPC-mPFC pathway is required for normal anxiety behavior. Moreover, that anxiety-related increases in vHPC-mPFC (4-12 Hz) theta synchrony and spatial representations of aversion in the mPFC are dependent on direct vHPC input. Through several collaborations in we expanded our knowledge of the function of mPFC interneurons. Parvalbumin interneurons in mPFC mediate anxiety-like behavior changes induced by maternal immune activation and I performed the first in vivo awake recording of chandelier interneurons in mPFC.

    a. **Padilla-Coreano N**, Bolkan SS, Pierce GM, Blackman DR, Hardin WD, Garcia-Garcia AL, Spellman TJ, Gordon JA. Direct Ventral Hippocampal-Prefrontal Input Is Required for Anxiety-Related Neural Activity and Behavior. *Neuron*. 2016 Feb 17;89(4):857-66. PubMed PMID: 26853301; PubMed Central PMCID: PMC4760847.

    b. Canetta S, Bolkan S, **Padilla-Coreano N**, Song LJ, Sahn R, Harrison NL, Gordon JA, Brown A, Kellendonk C. Maternal immune activation leads to selective functional deficits in offspring parvalbumin interneurons. *Mol Psychiatry*. 2016 Jul;21(7):956-68. PubMed PMID: 26830140; PubMed Central PMCID: PMC4914410.

    c. Lu J, Tucciarone J, **Padilla-Coreano N**, He M, Gordon JA, Huang ZJ. Selective inhibitory control of pyramidal neuron ensembles and cortical subnetworks by chandelier cells. Nat Neurosci. 2017 Oct; 20(10): 1377-1388; PubMed Central PMCID: PMC5614838

    d. **Nancy Padilla-Coreano**, Sarah Canetta, Rachel M. Mikofsky, Emily Always, Johannes Passecker, Maxym V. Myroshnychenko, Alvaro L. Garcia-Garcia, Richard Warren, Eric Teboul, Dakota R. Blackman, Mitchell P. Morton, Sofiya Hupalo, Kay M. Tye, Christoph Kellendonk, David A. Kupferschmidt, Joshua A. Gordon. Hippocampal-prefrontal theta transmission regulates avoidance behavior. *Neuron.* 2019 Nov; 104(3) PMID: 31521441

    e. Sarah Canetta, Eric Teboul, Emma Holt, Scott Bolkan, **Nancy Padilla-Coreano**, Joshua Gordon, Neil Harrison, and Christoph Kellendonk (2020) Differential synaptic dynamics and circuit connectivity of hippocampal and thalamic inputs to the prefrontal cortex. *Cereb Cortex Commun*. 2020; 1(1) PMID: 33381761

2. *Neural circuits underlying social behaviors*: To understand how the mPFC is involved in social dominance I developed a new dominance assay, utilized machine learning, optogenetics and wireless electrophysiology to demonstrate that the prefrontal cortex encodes social rank and neurons that project to the hypothalamus drive social dominance behavior. In addition, in collaboration with computer vision scientists we developed a deep learning tool to track multiple animals and quantify social behaviors.

    a. **Padilla-Coreano, N**., Batra, K., *et al.* Cortical ensembles orchestrate social competition through hypothalamic outputs. *Nature* (2022). https://doi.org/10.1038/s41586-022-04507-5

b. AlphaTracker: A Multi-Animal Tracking and Behavioral Analysis Tool. Zexin Chen, Ruihan Zhang, Yu Eva Zhang, Haowen Zhou, Hao-Shu Fang, Rachel R. Rock, Aneesh Bal, **Nancy Padilla-Coreano**, Laurel Keyes, Kay M. Tye, Cewu Lu bioRxiv 2020.12.04.405159; doi: https://doi.org/10.1101/2020.12.04.405159

3. *Neural circuits of valence encoding*: In several collaborative projects we have identified subpopulations of neurons that encode valence and the neuromodulatory mechanisms that facilitate valence encoding.
    a. 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*. PMCID: PMC6645392

    b. Austin Coley, **Nancy Padilla-Coreano**, Reesha Patel, Kay M. Tye. Valence processing in the PFC: Reconciling circuit-level and systems-level views. (2021) International Review of Neurobiology. Volume 158, Pages 171-212 PMID: 33785145
    c. H Li*, P Namburi*, JM Olson*, M Borio, M Lemiuex, A Beyeler, GG Calhoon, N Hitora-Imamura, A Libster, A Bal, XS Jin, SR Choudhury, X Shi, AC Felix-Ortiz, V de la Fuente, V Page, HO King, EM Izadmehr, K Batra, L Keyes, **N Padilla-Coreano**, KM McCullogh, R Wichmann, KJ Ressler, I Fiete, F Zhang, KM Tye. Neurotensin guides valence-specific plasticity, ensemble dynamics, and behavior (in press) *Nature*

4. *Neural circuits of fear learning and extinction*: I contributed to work dissociating the role of the prelimbic and infralimbic cortices in extinction learning and retrieval using rats and pharmacology. Moreover, I led a research project that provided evidence that the dorsal medial thalamus (dMT) has a time-dependent role in the retrieval of a fear memory. Moreover, we showed evidence suggesting that within the dMT the paraventricular thalamic nucleus was recruited into the fear circuit 24 hours after fear learning, rather than early after fear learning. This was the first demonstration of a time-dependent role of the thalamus in fear behaviors.

    a. **Padilla-Coreano N**, Do-Monte FH, Quirk GJ. A time-dependent role of midline thalamic nuclei in the retrieval of fear memory. Neuropharmacology. 2012 Jan;62(1):457-63. PubMed PMID: 21903111; PubMed Central PMCID: PMC3195904.
    b. Sierra-Mercado D, **Padilla-Coreano N**, Quirk GJ. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology. 2011 Jan;36(2):529-38. PubMed PMID: 20962768; PubMed Central PMCID: PMC3005957.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1X7W9joQgeO1hu/bibliography/public/

D. Current and Past funding

Current:
BRAIN Initiative R00-MH124435

Past:
L'Oreal FWIS Postdoctoral Award
Ford Foundation Postdoctoral Award
BWF Postdoctoral Award
Ford Foundation Predoctoral Award
NSF Graduate Fellowship Award

How we interact with a stranger is very different from how we interact with a close family member. The ability to shift our social behavior based on available information (e.g., individual identities, cues, context) is known as social competence[1]. For social animals (including humans) to thrive, they must exhibit social competence. A key component of social competency is adjusting behavior based on social history. Many species, like humans, find social interactions rewarding. Brain disorders, like Autism Spectrum Disorder[2] (ASD) and Schizophrenia[3] disrupt sociability through a lack of social motivation, but there are limited therapies for these disruptions. Studying how the brain controls pro-social interactions and how neural systems modulate social motivation could lead to novel therapeutics. Dopamine has been linked to social motivation during social interactions with new individuals[4], suggesting that it may modulate social motivation across social history or in disease states. However, most neuroscience studies do not measure variables related to social history (e.g. familiarity level and social rank). Therefore, there is a large gap in studying how social history affects the neural basis of social behaviors. The status-quo approach of studying interactions with novel animals ignores the richness of naturalistic social dynamics and limits our understanding of the social brain and its relevance to potential therapeutics. By studying how dopaminergic systems could be regulating circuits that modulate social behaviors across social history we can identify potential neural mechanisms for therapeutics.

Our recent work shows that the medial prefrontal cortex (mPFC) encodes relative social rank (Padilla-Coreano, et al., 2022)[5]. Our data show that the mPFC input to the lateral hypothalamus (LH) regulates social behavior during social competition in familiar mice, suggesting a role for mPFC-LH in social history. Furthermore, the ventral tegmental area (VTA) sends dopaminergic input to LH and mPFC, and VTA-LH circuit can further regulate sociability with novel animals[4,6]. VTA dopaminergic input to LH and mPFC may serve to signal level of novelty to modulate this prefrontal-hypothalamic network based on social history state. Past studies on the neural mechanisms of pro-social behaviors targeted a single brain region or circuit connection, ignoring network interactions. However, it is unknown how the VTA interacts with the mPFC and LH as a network and how the network is modulated by social history. These studies only considered social interactions with novel individuals and did not measure or account for social history. How this pro-social network works together during social interactions and how social history affects it has not been explored. Our central hypothesis is that dopaminergic modulation of mPFC and LH changes across social history states to enable social motivational differences. Our long-term goal is to identify the neural mechanisms of social history and how they change in disease states. To close the current critical gaps towards this goal, we will 1) utilize deep learning and unsupervised clustering methods to analyze social behavior across social history states and 2) identify how social history affects the neural dynamics of the VTA-cortical-subcortical network.

Aim 1: **Use machine learning to quantify pro-social behaviors across social history states:** To understand neural mechanisms of social history, we must first understand how behavior changes across social history states. Adequately measuring behavioral differences is a challenge due to a lack of automated tracking tools and behavioral analyses that reduce human subjectivity in annotation. Measuring behavioral differences related to social history is a necessary step to study the underlying neural mechanisms. We recently developed a deep learning tool that can track multiple unmarked mice and uses hierarchical clustering to quantify behavioral motifs (**Fig 1**). Our previous data in familiar mice shows behavioral differences due to social rank while actively competing for rewards (Padilla-Coreano et al., 2022). Recent research shows that mice can perceive differences in social rank from cues in unfamiliar mice[7], suggesting that familiarity and hierarchy could be equally important for social competence. However, we have yet to explore how social behavior differs across social history states. We propose to study social history in its most basic components: familiarity and social rank, two variables we can control by treating them as binary variables and exposing the same subject to agents of varying identities (**Fig 2**). Using this design, we will record video during four types of social interactions: familiar dominant, unfamiliar dominant, familiar subordinate, and unfamiliar subordinate social agents. We will compare pro-social behavior across the four types of interactions to characterize behavioral motifs and differences that relate to social history. Importantly, we will expose animals to multiple animals of the same rank and familiarity level for identity controls. Additionally, by repeating exposure to a previously novel animal, we will have a within-animal comparison of unfamiliar vs familiar interaction (**Fig 2c**).

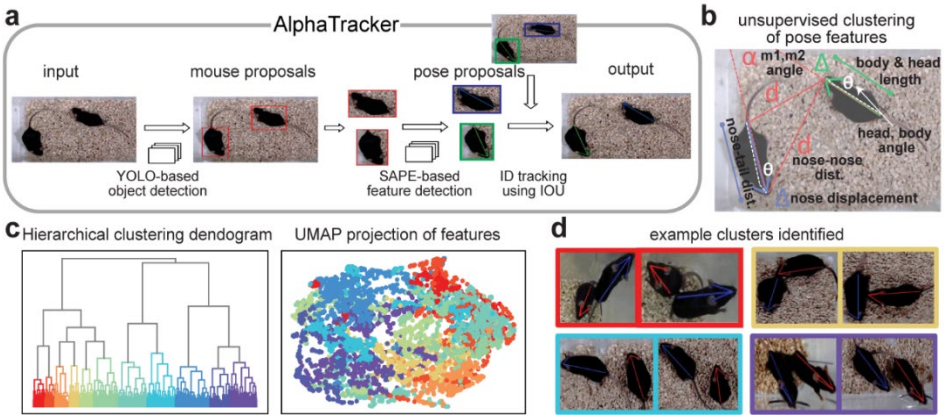

Figure 1: Machine Learning approach to quantify behavior between to identical mice. a. AlphaTracker uses multiple neural networks for multi-animal pose estimation and identity tracking. b. Based on the poses, features are calculated to do unsupervised clustering. c. Example hierarchical clustering for 4 videos of 2 mice interacting. Left, dendrogram of behavior clips color-coded per cluster;right,a lower dimensional projection of every behavior clip color-coded per cluster. d. An example frame for two clips across different clusters. Data recorded using cage mates. (from Padilla-Coreano et al. 2022)

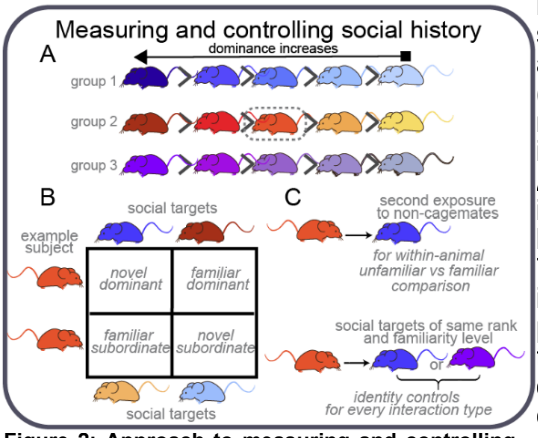

Figure 2: Approach to measuring and controlling social history. a. Mice will be group housed for at least 2 weeks to achieve social hierarchy stability. Social rank will be measure using the tube test (Padilla-Coreano et al., 2022). **b.** Subjects will be exposed to multiple freely-moving social agents: novel dominant, familiar dominant, familiar subordinate and novel subordinate individuals. **c.** Important behavioral controls will be used, such as a within-animal unfamiliar vs familiar comparison through a secondary exposure with a previously novel animal as well as varying the identity of the social target for a given interaction type.

Methods for Aims 1-2: Mice will be group-housed in groups of the same size with same-sex conspecifics for 2 weeks. Dominance will be assessed using the well-established tube test until stability is reached (**Fig 2a**). We have extensive experience using dominance assays in mice. Video will be taken during each interaction type and the order of interactions will be randomized across subjects to avoid order effects. Alphatracker (**Fig 1a**) will be used to track multiple near-identical mice in these four interaction types. Next, we will use unsupervised hierarchical clustering to cluster tracking data from all interaction types. The approach will be similar to that shown in Fig 1 except that we will include data from the four interaction types so that the algorithm will be providing a hierarchical model of social history. Thus, we will be able to see if rank or familiarity cluster together by quantifying the clustering of different interaction types to see which hierarchical relationships emerge. Using a Hidden Markov Model, we will model the behavior across social history states.

Experiment 1.1 Test the hypothesis that behavioral differences exist across social history during passive social interactions: In a clean cage, each intermediately ranking subject will be exposed to four types of social interactions with social targets of varying familiarity and social rank (**Fig 2b**). We will quantify behavioral differences based on the social history level with the agent.

Experiment 1.2 Test the hypothesis that social history modulates behavioral during active social interactions: Given that social rank greatly affects one's access to resources, it is possible that the most robust behavioral differences will be seen during a social competition for reward. We will have pairs of mice compete for signaled rewards to evoke an active social interaction. Our data shows that in familiar mice, competition outcomes and behavior are dictated by social rank (**Fig 3a**). This experiment will test, for the first time, how familiarity and social rank modulate active social interactions in mice. We expect that these experiments will reveal differences in behavioral motifs and transition probabilities that are predictive of social history state. **These experiments will be an important first step towards the discovery of the underlying neural mechanisms of social history and how they affect social motivation.**

Aim 2: Dissect the neural dynamics of the VTA-prefrontal-hypothalamic network as a function of social history: We showed that the mPFC-LH pathway modulates dominance in familiar mice, and others have shown that VTA-LH modulates sociability[6]. Our central hypothesis is that dopaminergic modulation of mPFC and LH changes across relative social history states to enable social motivational differences. Given that dopaminergic input to LH and mPFC comes from the VTA, and that VTA has prominent rhythms related to motivation states, we will record local field potentials (LFP) from mPFC, LH and VTA. **We will test the hypothesis that VTA neural functional connectivity to the cortex vs hypothalamus depends on social history.**

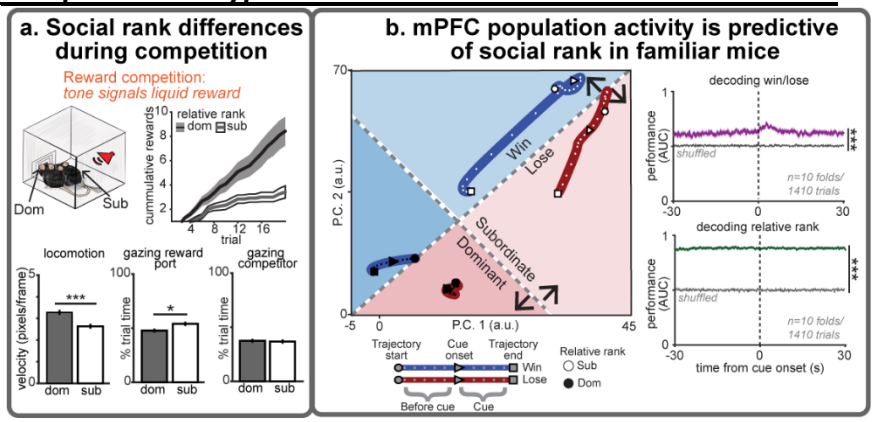

Figure 3: **mPFC encodes social rank and social competition outcomes in familiar mice**. **a**. Familiar male mice with stable hierarchy competed for a liquid reward signaled by a cue. Dominant mice obtained more rewards. Velocity and gazing were tracked using Alphatracker and showed rank differences. **b**. Left, first two principal components of mPFC population firing rate during the social competition shows separable population activity for relative rank and competition outcome (n=949 neurons). Right, a classifier predicted the outcome of the trial and the relative social rank (dominant vs subordinate). gray: shuffled data performance; Wilcoxon rank-sum p<0.001). *Data from Padilla-Coreano et al., 2022* Dominant (dom); Subordinate (sub).

My expertise in prefrontal dynamics and my collaborator's expertise in the neural dynamics of VTA during motivation behaviors makes this project feasible[8,9]. Recordings will be done during passive social interactions as described in Exp 1.1. and during active social interactions as described in Exp 1.2. Given that 4 Hz VTA rhythm increases with reduced motivation, and that the prefrontal 4-12 Hz rhythm has a role in social memory[10], we expect that VTA-mPFC and VTA-LH low frequency synchrony and directionality will be modulated by social history. Results from Aim 1 will allow us to analyze the neural activity data during the most relevant behavioral motifs and control for behavioral changes by parsing the data by each motif.

Future directions: This work will set the foundation for close-loop experiments in which we modulate the discovered neural mechanisms to alter social motivation and pro-social behaviors. Furthermore, they will guide where in the brain we will do dopamine or GABA-sensor imaging to study the role of dopamine and VTA GABA in social history and modulation of network dynamics during pro-social interactions.

e) Training/Career Plan:

My goal is to establish a research program to understand the neural mechanisms of social competence. To this end, I have opened a laboratory in January 2022 in the department of Neuroscience at the University of Florida and McKnight Brain Institute. My doctoral and postdoctoral training provided expertise in mouse models, tools for neural circuit dissection, *in vivo* electrophysiology, and machine learning applications for neuroscience. My lab is focused on using the mouse model to further our knowledge of the social brain by designing behavioral approaches, recording neural activity during behavior, and using machine learning to quantify behavior and how it relates to neural signals. I have recently hired 3 full-time staff and have several undergraduate students in the lab. Given my experience training and mentoring trainees in a large postdoctoral laboratory, I am poised to train and mentor this group to accomplish our goals. For this, my mentor and department chair Dr. Jennifer Bizon will provide practical knowledge and advice on how to lead and manage my laboratory. We meet every other week one-on-one and see each other often as our laboratories are on the same floor. Given that this NARSAD proposed work relates to dopaminergic systems and motivation, I have recruited the collaboration and expertise from Dr. Alexander Harris who will advise me on the experiments and data obtained in Aim 2.

Together, this team and the support of this NARSAD award will help launch my successful, independent research program.

Budget:

I am a new assistant professor requesting two years of funding from the BBFR NARSAD Young Investigator Grant. The data generated by this award will be critical for the generation of R01 level funding for my laboratory. We will use the funds for supplies, animals, to pay undergraduates and travel for the PI and one trainee to attend scientific conferences to present the results with relevant communities and to visit the laboratory of Dr. Alexander Harris to discuss progress in person**. Importantly, this grant will not result in duplication of funding or support.**

Category	**Year 1**	**Year 2**	**total**
Animal Costs	1,650	1,650	3,300
Hourly wages for undergraduates	8,400	8,400	16,800
Supplies	16,950	16,950	33,900
Travel	8,000	8,000	16,000
Total	**35,000**	**35,000**	**70,000**

Each Aim will require 35 animals (7 groups of 5) and will be housed for about 1 month. Each mouse costs $32 and housing is $1.20, so total costs come to: 32x70+1.20x14x30=$2744. Considering success rates with surgical experiments we will add 20% for expected off target animals or health issues for a total of $3,300

The experiments proposed include a lot of labor for behavior, electrode making and data annotation and processing for machine learning. We will support two undergraduate students to work on this project 10 hours per week at a rate of $15 per hour during the school semesters (28 weeks a year). These students will be guided and supervised by the PI and support staff of the laboratory. This amounts to $8,400 per year.

To defray the costs of surgeries supplies, electrodes (~1,000 each), chemical reagents and lab consumables to support this project we budget $16,950 per year.

The PI and one trainee will attend a yearly conference to report the findings ($5000 per year). In addition, the PI will visit the collaborating lab of Dr. Alexander Harris once a year ($3000 per year) to observe procedures and discuss progress.

UF UNIVERSITY of FLORIDA

College of Medicine
Department of Neuroscience
McKnight Brain Institute

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March 11, 2022

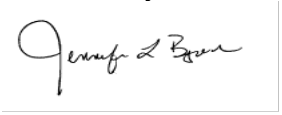
TO: BBRF Young Investigator Grant
RE: Letter of Support for Dr. Nancy Padilla-Coreano

Dear Review Committee:

I am thrilled to provide my strongest recommendation in support of **Dr. Nancy Padilla-Coreano**'s application for the BBRF Young Investigator Grant. I will serve as Dr. Padilla-Coreano's mentor and advisor through this support. As detailed below, I believe she is an absolutely stellar candidate. Dr. Padilla-Coreano is attracted to the biggest, most important questions in our field and is capable of tackling them in a rigorous, creative and quantitative manner. She is a new Assistant Professor in our department who has the goal of understanding the neural mechanisms of social competence. By every objective measure, including numerous early career grants awards, and impactful publications, Dr. Padilla-Coreano is a star who performs within the upper echelon of emerging independent scientists. We were fortunate to recruit her and I firmly believe she will build an internationally recognized research program that will produce impactful findings for years to come. Furthermore, we are fully invested in her success. As I detail below, an early investment in Dr. Padilla-Coreano is one that is sure to pay significant future dividends to her success as faculty.

Dr. Padilla-Coreano completed her doctoral thesis at Columbia University with Dr. Joshua Gordon (the current Director of the National Institute of Mental Health (NIMH)) utilizing *in vivo* electrophysiology and optogenetics to investigate an important hypothesis regarding neural oscillations and anxiety behavior. Her work resulted in several prestigious fellowships and ***two*** first-author publications in the prestigious journal *Neuron* (Impact factor 17.1). Building on her research interest in the neural circuits that mediate social and anxiety-related behaviors, Dr. Padilla-Coreano then chose Dr. Kay Tye's laboratory at MIT to pursue her postdoctoral work. As a postdoctoral fellow, she investigated the neural circuits that underlie social hierarchy. The conceptual and technical complexity of Dr. Padilla-Coreano's project is hard to overstate and involved significant grit and creativity. Her postdoctoral research required the ability to not only apply the latest technology in the neuroscience field, but also to develop new A.I. algorithms and analysis approaches. Her postdoctoral work on the neural mechanisms of social dominance is now *in press* at *Nature*. In addition, she has received numerous recognitions and prestigious fellowships, including a Brain Initiative K99-R00, a L'Oreal USA Women in Science fellowship, a Ford Foundation postdoctoral fellowship and a Burroughs-Wellcome postdoctoral enrichment fellowship (just to name a few!). Outside of the lab Dr. Padilla-Coreano leads a project to increase visibility for women in neuroscience and serves as a role model for young women aspiring to careers in science. In sum, Dr. Padilla-Coreano is an outstanding scientist, a gifted scholar and leader. I urge you to support her in this application which will allow her to expand her new research program. Please don't hesitate to contact me if I can provide any additional information.

Sincerely,



Jennifer L. Bizon, Ph.D.
Chair and Professor; Department of Neuroscience

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March 14, 2022

Nancy Padilla-Coreano, PhD
Evelyn F. & William McKnight Brain Institute
University of Florida

Dear Nancy,

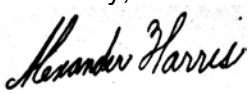
I am delighted to collaborate with you on your NARSAD project investigating the neural mechanisms underlying how social history influences social motivation. As you know, social interactions are disrupted in a variety of psychiatric disorders, including autism, schizophrenia, and anxiety, and there are presently no medications to treat these deficits. Thus, understanding the underlying neurobiology has the potential to make a large impact.

The multidisciplinary approach that you have designed to address this important question—combining advanced ethological behavior, sophisticated computational analyses, and i*n vivo* physiology—epitomizes the best utilization of currently available scientific resources and techniques. Given the excellent papers you have published with each of these of these approaches (e.g., Padilla-Coreano et al Nature (in press), Padilla-Coreano et al Neuron 2019, 2016), I am confident that you have the technical expertise to successfully execute this project. I am particularly enthusiastic about your hypothesis that prior social experiences modulates dopaminergic regulation of social motivation. In that regard, I am happy to continue to offer my expertise investigating reward circuitry. As you know, my lab focuses on understanding how stress-induced disruptions of reward circuitry (VTA dopaminergic and GABAergic projections) mediate deficits of in social interactions and reward-seeking (e.g., Harris et al 2018, Lowes et al 2021). As a result, I have over 7 years of experience designing and analyzing experiments that incorporate VTA dopamine neuron *in vivo* recordings with social behavior. Both I and my group will be happy to support you with the resources and expertise you require to carry out the proposed experiments in this grant.

This collaboration is a natural extension of our long-standing scientific relationship which started when you and I worked together in Josh Gordon's lab as graduate student and postdoc, respectively. We frequently discuss our research and I am excited that some of the ideas from those conversations now form the foundation of this collaboration. To support this project and ensure its success, I will meet with you quarterly as well as get feedback from my research group by presenting annually at lab meeting.

I look forward to working together on this exciting project!

Sincerely,



Alexander Harris, MD, PhD
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March 21, 2022

Brain & Behavior Research Foundation

RE: 2022 BBRG Young Investigator Grant Application
Dr. Nancy Padilla-Coreano

To Whom it May Concern:

The appropriate programmatic and administrative personnel at the University of Florida Academic are willing to administer the grant, acknowledge and negotiate the grant guidelines and acknowledge that the applicant is eligible for the grant because she is an Assistant Professor at the time of submission.

Sincerely,

Angela Cocchiarella

Authorized Official
University of Florida Board of Trustees