RESEARCH STATEMENT

Overview

We make decisions every day. These decisions rely on current information – what we see, hear, and feel. Our decisions also rely on our past experiences, or memories. Even something as trivial as deciding to turn at a traffic light depends attention to the "now" (i.e., the light is "green") and memory of where we are going (i.e., the grocery store is on this road). Yet, we don't understand how our brains integrate this information to inform our decisions. Our lack of understanding is particularly troubling given that patients with devastating mental health disorders, such as schizophrenia, attention deficit-hyperactivity disorder (ADHD), and major depressive disorder, all have dramatic impairments in attention and memory. Thus, my research goal is **to understand how our brains coordinate attention to the present, and memories of the past, to guide our future actions**. My research program will accomplish this goal by focusing on three fundamental questions about brain function during decision making:

1. Are attention and memory networks in the brain distinct, or overlapping?
2. How does sex affect attention and memory networks during decision making?
3. Do cells in these networks share common gene expression programs that differentiate them from other cells in the brain?

Which neurons support attention, and which support memory?

A striking principle of brain organization is that it has modularity. Damage to anatomically discrete brain areas often results in specific cognitive deficits – for example, hippocampal damage impairs episodic memory, while damage to the basal ganglia impairs habit formation (**Squire, 2004**). At the same time, many brain areas also support multiple cognitive functions – for example, the prefrontal cortex (PFC) plays a role in both attention (**Knight, Grabowecky, & Scabini, 1995**) and memory (**Curtis & D'Esposito, 2003**). How can the architecture of the brain be both modular and distributed?

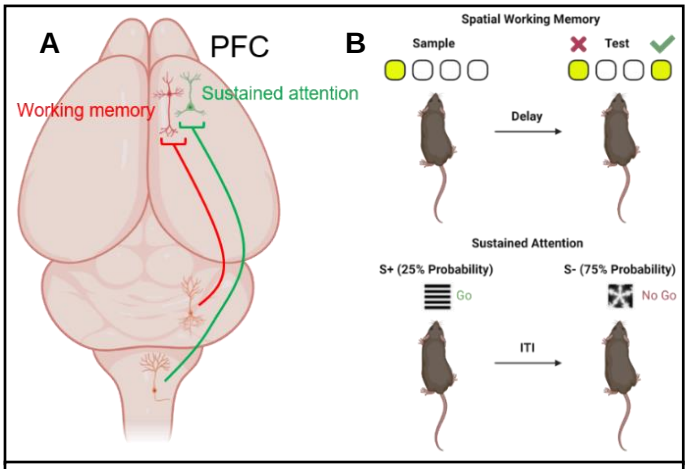

Fig. 1: *(A)* Distinct PFC circuits may control different aspects of decision-making. *(B)* Schematic of touchscreen tasks designed to test working memory (top panel) and attention (bottom panel).

As a graduate student, I used *in vivo* electrophysiology and optogenetics to show that the PFC is one part of a larger network that supports working memory (**Hallock et al., 2013a; Hallock et al., 2013b; Hallock et al., 2016**). Using computational tools, such as supervised machine learning, I found that patterns of neural activity in multiple, connected brain regions could decode working memory-specific behavior with high accuracy. The major conclusion from these studies was that connections *between* brain areas are what drive specific cognitive functions, like attention and memory. The PFC receives contact from both attention and memory "centers" in other parts of the brain. These findings set up an important research question with opposing, testable hypotheses. One hypothesis is that different groups of neurons with different connections in the PFC support attention and memory. The alternative hypothesis is that the same groups of PFC neurons can support both attention and memory, regardless of their connections. To test these hypotheses, my research program will use a mixture of viral tools, immunohistochemistry for proteins related to cellular activation (i.e., c-Fos, Arc), and DREADD receptors for synthetic activation/inhibition of these PFC neuron sub-types during touchscreen-guided decision making in mice (**Fig. 1**). The touchscreen chambers used for this testing are funded by a NARSAD Young Investigator Award through the Brain and Behavior Research Foundation. The touchscreen chambers are fully automated, and can be used in collaboration with other members of the department, as well as during courses such as Learning (PSYC 321), Perception (PSYC 322), or a seminar course on the Neurobiology of Learning and Memory.

How does sex affect attention and memory during decision making?

Biological sex influences both attention and memory in complex ways. For example, adolescent males often show higher levels of impulsivity than females during attention tasks, while the opposite is true during adulthood (**Newcorn et al., 2001**). During working memory tasks, females often rely more heavily on spatial information (e.g., the *location* of testing cues), while males often rely more heavily on information about the testing cues themselves (**Voyer et al., 2017**). These results parallel sex differences in onset and severity of cognitive symptoms in neuropsychiatric disorders such as ADHD and schizophrenia (**McGrath et al., 2004; Morgan et al., 2013**). What is the neurobiology underlying these sex differences?

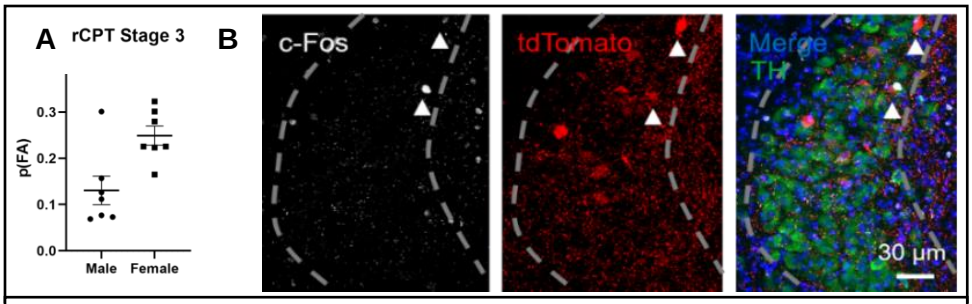

Fig. 2: *(A)* Female mice show a higher rate of false alarms (increased impulsivity) during a sustained attention task, as compared to males. *(B)* Activation of locus coeruleus neurons (quantified by presence of c-Fos protein in white) is seen following completion of a sustained attention task in male mice (TH = tyrosine hydroxylase in green, used to identify neurons in the locus coeruleus).

As a post-doc, I found that adult female mice showed higher levels of impulsivity during a touchscreen-based sustained attention task (**Fig. 2a**). In male mice, completion of this task was associated with activation of cells in the locus coeruleus (**Fig. 2b**), a brainstem nucleus that is important for attention and arousal (**Sara & Bouret, 2012**). How might biological sex influence how locus coeruleus neurons respond during sustained attention? Additionally, how might biological sex influence how other brain areas, like the hippocampus and PFC, respond during attention and working memory? To answer these questions, my research program will test both male and female animals on attention and working memory tasks. We will use computational tools for the identification and classification of unique behavioral characteristics related to task performance (an avenue that I am currently pursuing for working memory-related deliberation in rats; **Stout, Hallock, et al., *submitted***). We will then use a comparative approach to examine differences in both behavior and regionally-specific neuronal activity between sexes. This research will be critically important for a thorough understanding of how sex differences lead to differences in decision making deficits in mental illness. This research will also lead to many avenues of exploration for undergraduate and graduate students in the laboratory. In the classroom, data on sex differences in cognitive domains affected in neuropsychiatric disorders can be used for interactive projects in Abnormal Psychology (PSYC 232).

Do PFC cells in distinct circuits share common transcriptomes?

Unique behavioral experiences induce patterns of gene expression in a number of brain regions (**Mukherjee et al., 2018**), indicating that an animal's behavioral state can be predicted by molecular signatures in the brain. Additionally, much recent research has shown that cell populations in many brain areas are genetically heterogeneous (**Gray & Spiegel, 2019**), suggesting that anatomically-localized cells may be identified and accessed by targeting molecules selectively expressed in those cells.

My postdoctoral research (**Hallock et al., 2019; Hallock et al., 2020**), funded by a National Research Service Award (NRSA) from the National Institutes of Mental Health (NIMH), showed that stimulation of either hippocampal or locus coeruleus inputs to the PFC caused distinct transcript expression patterns in bulk PFC tissue (**Fig. 3**). To understand how these gene expression patterns influence cellular function in the PFC, it will be necessary to know in which cell types these genes are regulated. To address this problem, I will use a combination of techniques, including viral labeling and single-molecule *in situ* hybridization (RNAscope), to identify marker genes that are expressed in PFC neurons after touchscreen-based working memory or attention-guided behavioral testing. The use of RNAscope will be invaluable for assessing whether specific cell types in the PFC co-express enriched genes in the RNA-sequencing datasets that I generated as a postdoc. Uncovering these gene expression patterns will be a critical first step toward providing novel markers for the possible

diagnosis and treatment of cognitive symptoms in diseases such as schizophrenia, ADHD, and major depressive disorder. Results from these experiments will also be used as teaching tools in courses such as Molecular Genetics (BIOL 255), or Computational Methods (CM 151).

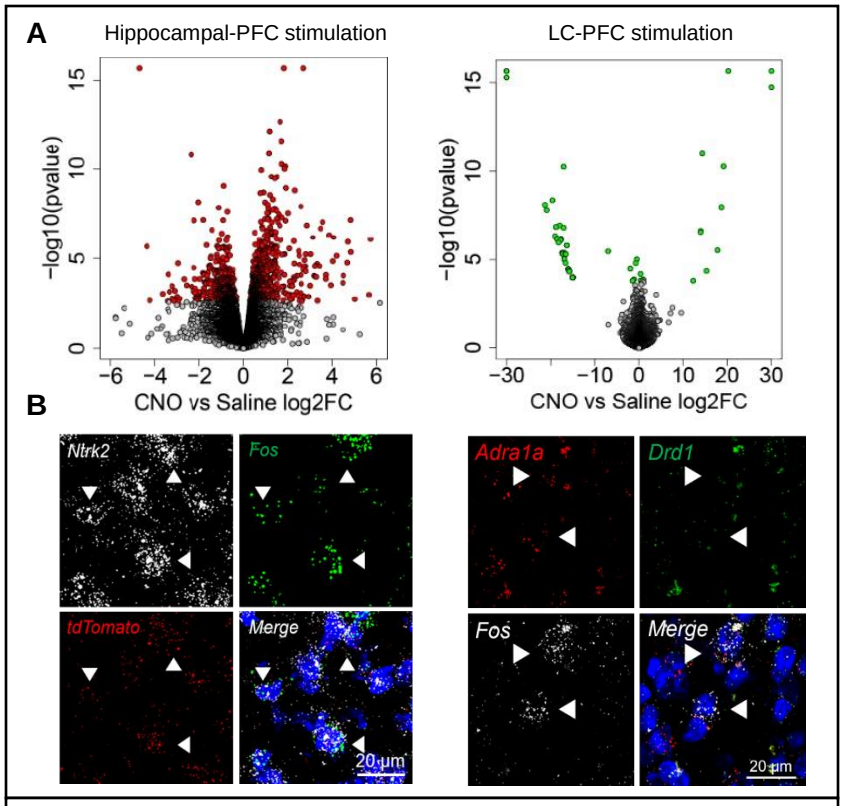

Fig. 3: Gene expression in PFC after stimulation of hippocampal or LC inputs. *(A)* Volcano plots showing enriched and depleted genes in PFC tissue following hippocampal (left panel) or LC (right panel) stimulation. *(B)* Validation of RNA enrichment in specific PFC cell types following hippocampal (left panel) or LC (right panel) stimulation using single-molecule *in situ* hybridization.

Conclusions

My work to date has shown the power of studying the connections between brain structures, and how this connectivity might support the integration of both attention and memory during decision making. Moving forward, I am excited about continuing to engage students in neuroscience research. As a graduate student and post-doc, I have worked with over 20 undergraduate, post-baccalaureate, and graduate students in the laboratory. During this time period, I have supervised undergraduate honors theses, trained students to independently perform a variety of lab techniques, empowered my mentees to present posters at local and national conferences, supervised students as they prepared and submitted scientific manuscripts as first or co-author, and assisted undergraduate students and post-bacs as they applied for grants, awards, and graduate school. My approach to mentoring students in research is all-encompassing – I have designed my research program so that undergraduates will be able to participate in every aspect of the scientific process, including data collection, analysis, and dissemination of results. I am also strongly committed to making my research program accessible to students from diverse backgrounds. Actionable plans to maintain diversity in my research laboratory include 1) actively recruiting underrepresented minorities (URMs), both through the classroom and Lafayette's Association of Black Collegians, 2) standardizing the application process for becoming a researcher in my lab, and 3) working closely with each individual undergraduate researcher to understand how I can be a supportive mentor to them. My research requires little background and minimal special techniques, and is well-suited for students who are interested in advanced topics in neuroscience, cognitive psychology, and systems and molecular neurobiology. I cannot imagine anything more rewarding than creating new knowledge in neuroscience with young scientists-to-be, and look forward to fulfilling that dream at Lafayette College.

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