Investigating the Role of the VTA and PVN in Social Motivation

by

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ABSTRACT

Social motivation is often disrupted in neuropsychiatric conditions, and two brain regions, the ventral tegmental area (VTA) and the paraventricular nucleus (PVN), are thought to play key roles through their dopamine- and oxytocin-related pathways. However, little is known about how activating these regions directly affects social behavior, especially when effort is required. This study used optogenetics to selectively stimulate neurons in either the VTA or the PVN of adult mice and examined how this influenced a range of social and effort-based behaviors.

Across tasks, stimulation of the VTA produced clear sex-dependent effects. Male mice showed increases in exploration, social approach, novelty preference, and performance on effortful tasks like climbing and pushing a weighted door. In contrast, females often showed reduced motivation under the same stimulation, suggesting that dopamine-related circuits may respond differently across sexes.

Stimulation of the PVN led to more subtle effects that depended on the specific context. PVN activation influenced social behavior in certain situations, such as familiarity preference or low-effort social exploration, but did not consistently increase motivated behavior when effort demands were high.

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CHAPTER I

INTRODUCTION

Social interaction is a fundamental aspect of human life, yet so many individuals with neuropsychiatric disorders experience persistent difficulties in navigating social relationships. These difficulties are not merely the result of disinterest or lack of opportunity but often stem from impaired social motivation and the heightened cognitive and emotional effort required to engage in prosocial behavior. Engaging in prosocial interactions often requires conscious effort, which is particularly challenging for individuals with certain clinical conditions. These challenges are observed in conditions such as schizophrenia, major depressive disorder (MDD), anxiety, substance abuse, and autism spectrum disorder (ASD) (Correll & Schooler, 2020; Daley, 2013; Frye, 2018; Kupferberg & Hasler, 2023; Pomrenze et al., 2022; Tse & Bond, 2004). Given human beings' inherently social nature, these difficulties can place additional psychological stress on those affected (Cacioppo & Patrick, 2008; Tomova et al., 2020).

These conditions share many of the same symptoms. For instance, schizophrenia and ASD exhibit genetic and phenomenological similarities, with both conditions marked by flat affect, disrupted social cognition, and social disengagement (Chisholm et al., 2015). Major depressive disorders have been shown to significantly increase the risk and severity of drug abuse (Arnaud et al., 2022). Anxiety is a prominent symptom across all of these disorders (Bergmann et al., 2021; Chen, 2022; Compton et al., 2007; Mutluer et al., 2022; Ryan et al., 2023). The same is also true with depression in connection to schizophrenia, substance abuse, and autism (Lanyi et al., 2022; Onaemo et al., 2022; Shnayder et al., 2022). The comorbidity between depression and anxiety is especially well-documented, with evidence indicating that the two conditions are frequently present simultaneously (Platona et al., 2024; Saha et al., 2021).

Although these disorders are clinically distinct and individuals may experience one in the absence of others, disruptions in social interaction are a common and significant factor across all of them.

Social Interaction in Schizophrenia

Social difficulties have been known to be a prominent symptom in schizophrenia, especially in patients who have a flat affect (Aghevli et al., 2003). Research has turned to a social cognitive impairment view of understanding and treating schizophrenia (Billeke & Aboitiz, 2013). The lack of social interaction could be thought to be because of social disinterest; however, people with schizophrenia report interest in social activity, the same as people without schizophrenia (Billeke & Aboitiz, 2013; Kirkpatrick et al., 2006; McCann, 2010). Although individuals with schizophrenia express a desire for social engagement, motivational impairments can make the effort required to initiate and maintain interaction feel overwhelming. A study done by Sündermann and colleagues (2014) investigated the connection between first-episode psychosis in schizophrenia and loneliness: 34% of the participants diagnosed with schizophrenia reported not having a confidant. These participants also reported elevated levels of loneliness, anxiety, and paranoia due to poor social support, highlighting the importance of social interaction. It is also believed that lack of social support has a significant effect on depression (Kirsch et al., 2019; Magnuson & Constantino, 2012).

Disrupted Sociability in Depression

Similarly, individuals with depression often exhibit disrupted nonverbal social behaviors. Depression can blunt the perceived rewards of social engagement, making the act of initiating interaction feel disproportionately effortful. While individuals with depression can recognize

basic emotions, they typically exhibit disrupted nonverbal social behaviors, such as reduced eye contact, prolonged silence, and diminished attentiveness (Akinci et al., 2022). This inactive behavior can hinder relationship formation and reinforce social withdrawal and loneliness (Kupferberg et al., 2016; Warth et al., 2020). Beyond these interpersonal difficulties, depression has also been shown to be socially contagious (Paz et al., 2022). Through the mirror neuron system-activated during both performing an action and observing it-emotional contagion can occur via automatic mimicry. In this process, individuals unconsciously mirror other's expressions or moods. If unaddressed, depression can lead to suicidal ideation or behavior, which itself has shown to follow a contagion pattern (Muniz et al., 2021; Shaman et al., 2024; T. White, 2021). Positive, supportive relationships are therefore critical for mental health, potentially acting as a buffer against depressive symptoms (Filia et al., 2021). This is reflected in findings from the COVID-19 lockdown, where individuals with greater social contact and support experienced fewer depressive symptoms than those who had less. (Sommerlad et al., 2022).

Anxiety in Social Interaction

Anxiety disorders, particularly social anxiety, further compound social impairments. According to the influential model by Clark and Wells (1995), negative beliefs and heightened self-focus drive anxiety, leading to patterns of avoidance behavior. The mental labor associated with anticipating social threat or rejection can make even simple interactions feel mentally exhausting, leading to avoidance. In this framework, avoidance functions as a means for a protective mechanism, aimed at reducing anticipated negative evaluation or failure. Anxiety in this context is linked to demand avoidance—an extreme reluctance to comply with requests or expectations (O'Nions et al., 2018). Demand avoidance should not be thought of as opposition; rather, it is increasingly understood as a maladaptive coping strategy used to regulate

overwhelming anxiety triggered by perceived social or performance-related threats (R. White et al., 2023). The stressful stimulus in this case is wrongly attributed to a negative perception of threat. Research shows that anticipating a threat activates the body's innate defense system, as evidenced by heart rate deceleration, a marker for "freezing" response, which prepares one for potential danger (Murakami et al., 2010; Roelofs, 2017). What may appear as social noncompliance or social disengagement is often rooted in deeply ingrained fear responses and cognitive distortions associated with anxiety (Cook et al., 2023; Rubin & Burgess, 2001).

Difficulties in Social Interaction and Autism

Individuals on the autism spectrum frequently self-report difficulty initiating, maintaining, and seeking out interpersonal relationships (Bennett et al., 2018; Soares et al., 2021). In 2025, approximately one in 31 children was diagnosed with ASD (Shaw et al., 2025). Contrary to the misconception that individuals with ASD are indifferent to social relationships, research indicates that they may desire connection but lack the internal drive to pursue it (Chan et al., 2023). In ASD, challenges in processing and interpreting emotional and social cues increase the cognitive effort of interaction, often discouraging engagement despite underlying interest. One area of research hypothesizes this to be due to interpreting expressions and stimuli differently. A study done by Unruh (2020) expanded on this, finding that autistic adults recognized negative facial expressions quicker than positive facial expressions. Such findings align with the emotional valence theory of ASD, which proposes that individuals with ASD have difficulty correctly recognizing a preferred stimulus (happy faces), recognize quicker an aversive stimulus (sad faces) (Beaurenaut et al., 2024; Saraiva et al., 2013). Furthering this finding, it has also been found that ASD youth showed an increase in parasympathetic arousal to aversive stimuli. (Bradley & Lang, 2000; Bradley et al., 2008 Jung et al., 2021; Lang et al., 1993).

Diminished social motivation, coupled with frequent experiences of social rejection due to miscommunications, can reinforce avoidance behaviors and contribute to the elevated rates of loneliness, anxiety, and depression observed in this population.

Loneliness and Isolation

For many individuals with neuropsychiatric disorders, chronic loneliness arises not from apathy but from the taxing nature of social interaction, a combination of low motivation, high perceived effort, and frequent social failures. Across these clinical populations, social isolation and loneliness are linked to psychological distress and poorer physical health. Social isolation and loneliness can have profound and damaging effects on individuals' well-being. A systematic review and meta-analysis revealed that both loneliness and social isolation are significantly correlated with increased risks of coronary heart disease and stroke (Valtorta et al., 2016; Holt-Lunstad et al., 2015; Simard & Volicer, 2020). The COVID-19 pandemic made these vulnerabilities especially visible. During lockdowns, restrictions on social interaction led to substantial rises in loneliness, emotional distress, and behavioral symptoms, particularly among older adults and individuals in long-term care settings (Simard & Volicer, 2020). The economic cost of loneliness is even more poorly understood. Some research indicates that more socially isolated people are more likely to seek medical assistance to get social interaction (Gerst-Emerson & Jayawardhana, 2015; Valtorta et al., 2018). To reduce this, Pitkala and colleagues (2009) suggested an increase in therapeutic group therapy and found increased quality of life and decreased health care utilization and costs. In another study by Bryan and researchers (2024), it was suggested that early loneliness can predict socioeconomic challenges; individuals with higher loneliness ratings at the age of 12 also reported reduced employability by age 18.

Oxytocin

Oxytocin (OXT), a neuropeptide synthesized in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus, is implicated in a wide range of physiological functions (Jurek & Neumann, 2018; Kerem & Lawson, 2021). Although traditionally recognized for its peripheral roles in lactation and maternal behavior, OXT also impacts processes that manipulate social behaviors (Carter, 2014; Matsushita & Nishiki, 2025). While some studies suggest that oxytocin can effectively treat social impairments in certain populations, the results have been inconsistent, highlighting the need for further research to better understand its translational potential as a therapeutic agent for addressing social deficits in humans (Alvares et al., 2017; Yamasue, 2016; Yin et al., 2024).

Effect of Elevated Oxytocin Levels in Humans and Rodents

Intranasal oxytocin has been used to test the effectiveness of psychotherapy for people diagnosed with MDD (Ellenbogen et al., 2024). Participants who received intranasal OXT showed a significant reduction in depressive symptoms over time compared to the placebo group, as well as a self-reported therapeutic alliance with their therapist, but these effects did not persist throughout the subsequent sessions. Comparable patterns have been observed in patients with generalized anxiety disorder and in volunteers undergoing social stress tasks, where intranasal OXT administration improved stress regulation and enhanced positive social engagement, but did not have lasting effects. (Alvares et al., 2012; Heinrichs et al., 2003; Myers et al., 2014). Variable results also appear in individuals with autism receiving OXT treatment. A study done by Moerkerke and colleagues (2024), chronic intranasal OXT administration in children with ASD significantly elevated salivary OXT concentrations, confirmed that the treatment successfully increased peripheral OXT levels. However, only a subset of children showed increased social responsiveness and reduced repetitive behaviors.

Animal studies have shown that administering OXT increased social contact and affiliative approach behaviors (Amini-Khoei et al., 2017; Eapen et al., 2014; Joushi et al., 2021). Administering an OXT agonist in male prairie voles has been found to increase partner preference rather than stranger preference (Johnson, M. et al., 2024). These findings indicate OXT's impact on social bonding is highly time dependent. Administering OXT before the initial bonding enhanced partner preference but giving it after different cohabitation periods produced no difference. A similar emphasis on timing appears in Pantouli et al. (2024), who tested whether acute versus chronic OXT administration affected social behavior in Oprm1 knockout mice. Only the mice given OXT five minutes before testing showed improved social interactions, the other time conditions had no effect. Together, these studies demonstrate that OXT's behavioral effects are not only context-dependent but also highly sensitive to the precise timing of administration.

Effect of Decreased Oxytocin Levels in Rodents and Humans

Conversely, the inhibition of OXT receptor signaling has been linked to disruptions in social behavior. For instance, pharmacological blockade of OXT receptors in prairie voles has been associated with decreased social interaction, highlighting the pivotal role of oxytocin in maintaining affiliative behaviors (Johnson, Z. et al., 2016). Similarly, acute stress restraint in rats, a commonly used method to induce psychological stress, has been shown to enhance prosocial behavior, suggesting a stress-induced activation of the oxytocinergic. However, this prosocial effect is significantly attenuated when an oxytocin receptor antagonist is administered before testing, further underscoring the importance of oxytocin signaling in modulating social responses under stress system (Wang et al., 2024). Subchronic treatment with phencyclidine (PCP), an NMDA-receptor antagonist, reliably reduces social interaction in rodents (Sapp et al.,

2025) .Notably, chronic PCP exposure also decreases OXT mRNA expression in the hypothalamus, indicating a suppression of OXT production and release within circuits that support social behavior (Lee et al., 2005).These findings collectively illustrate the critical involvement of oxytocin signaling in promoting social interaction and its vulnerability to both pharmacological and stress-related disruptions.

In humans, reduced plasma OXT levels are consistently associated with impairments in social functioning, suggesting that endogenous oxytocin contributes directly to socioemotional regulation. For instance, Scantamburlo et al. (2007) found that lower circulating OXT was linked to greater depressive and anxiety symptoms, conditions characterized in part by social withdrawal and diminished social engagement. Similar patterns emerge in schizophrenia: decreased OXT levels are associated with more severe global impairment (Goldman et al., 2008; Rubin et al., 2010), and, notably, Strauss et al. (2015) reported that reduced plasma OXT significantly predicted the severity of negative symptoms, including social withdrawal, reduced social drive, and blunted affect. Collectively, these findings suggest that endogenous oxytocin is closely tied to the integrity of social behavior across psychiatric conditions. At the same time, inconsistent outcomes from OXT-based clinical interventions indicate that oxytocin's influence on social behavior is likely shaped by additional biological and contextual factors, such as individual differences in neural circuitry, receptor distribution, and the social environment in which OXT is released.

Dopamine

A growing body of research implicates the ventral tegmental area (VTA) in social behavior, suggesting that disruptions in VTA-mediated DA signaling may contribute to the social impairments observed in individuals with neuropsychiatric disorders (Becker-Krail et al., 2022;

Fitzgerald & Day, 2025). Dopamine (DA) is a catecholamine neurotransmitter and hormone that plays a crucial role in multiple physiological processes, including motor control, motivation, reward, and mood regulation. It is synthesized in the brain from the amino acid tyrosine and is primarily active in brain regions such as the nucleus accumbens (NAc), hypothalamus, and VTA (Carlsson et al., 1958; Yamamoto & Vernier, 2011). DA release in the mesolimbic pathway, which runs from the VTA to the NAc, is prominently known for its vital role in substance abuse (Al-Hasani et al., 2021; Ebrahimi et al., 2024; Nestler & Carlezon, 2006). This pathway plays a key role in the brain's reward system, governing reward processing, motivation, and the reinforcing effects of substance abuse (Plaisance et al., 2024). Substance use seems to hijack the brain's motivational systems, studies finding that it decreases the perceived value of social connection and replacing it with immediate substance-related rewards (Beard et al., 2022; Pomrenze et al., 2022).

Dopamine in Social Behavior

The VTA plays a crucial role in modulating reward processing, motivation, and emotional regulation, particularly in social contexts (Lowes & Harris, 2022). In rodent models, Ioanas et al. (2022) combined optogenetic stimulation with fMRI to generate a whole-brain-opto-fMRI map of dopaminergic activity in mice, demonstrating that the function of the VTA dopaminergic system aligns with its structural projections. Further connecting to sociability, Solié et al. (2022) demonstrated that VTA DA neurons scale activity with social interaction. This pattern is also observed in humans, where self-induced VTA activation following fMRI-based neurofeedback training increased connectivity within the mesolimbic network (MacInnes et al., 2016). Collectively, these findings highlight the connecting role of the VTA in supporting motivation and sharing a pathway within the mesolimbic network.

Dopamine and Oxytocin Pathways

Oxytocin and dopamine share many of the same systems and have been found to have a modulating effect on each other (Rappeneau & Castillo Díaz, 2024). Mentioned previously, oxytocin is primarily produced in the PVN and SON, while dopamine arises from the VTA and SN. While produced in different nuclei, each area shares receptors with each neuron. The PVN innervates DA-containing regions like the VTA and NAc and expresses DA receptors and receives dopaminergic innervations (Melis et al., 2007; Roeling et al., 1993). OXT has also been found to exert precise control over DA neurons (Xiao et al., 2017). The hypothalamus, where the PVN and SON are located, contains a high number of dopamine terminals as well (Rodrigues et al., 2025). The NAc receives converging input from both the VTA and PVN, resulting in dopaminergic and oxytocinergic signaling (Borland, 2025). This further reinforces their role in regulating reward, motivation, and social behavior.

Dopamine and Oxytocin Interaction in Social Behavior

Growing evidence indicates that OXT exerts powerful modulatory effects on dopaminergic circuits involved in motivation and reward. In rats, DA activity has been shown to increase in several brain regions, including the VTA, in response to OXT signaling (Petersson & Uvnäs-Moberg, 2024). Within the context of sexual motivation, intracerebral administration of oxytocin has been found to elevate dopamine levels not only in the NAc, a critical component of the mesolimbic reward system, but also in the PVN, a major site of oxytocin synthesis (Argiolas & Melis, 2005; Geert et al., 1992; Martino et al., 2005). Supporting the idea of dopaminergic modulation in this region, Ran et al. (2019) used immunofluorescence labeling to map the expression of D1 and D2 dopamine receptors in the PVN, demonstrating their co-localization with oxytocin-producing neurons. Hung et al. (2017) used a combination of optogenetic and

chemogenetic techniques to demonstrate that oxytocin increases excitatory input onto VTA dopaminergic neurons, further supporting a role for oxytocin in enhancing dopaminergic signaling in reward-related brain circuits.

Evidence for an oxytocin–dopamine interaction extends to human neuroimaging research. Groppe et al. (2013) demonstrated that intranasal oxytocin increases activity in the VTA, a dopamine-rich midbrain region, during reward anticipation. Scheele et al. (2013) similarly reported heightened VTA activation in heterosexual men when viewing images of their romantic partner after oxytocin administration compared to unfamiliar women. Although this effect may reflect romantic or sexual reward processing rather than purely social motivation, it nonetheless indicates that oxytocin enhances the motivational salience of socially and emotionally significant cues by engaging dopaminergic circuits

Neurobiological Regulation of Social Salience

Building on this understanding, researchers have turned their attention to the salience network, how certain social cues stand out as important or attention-grabbing. Evidence has been presented that DA neurons respond to a broad range of salient and arousing stimuli, irrespective of their association with reward (Horvitz, 2000). Using DA amperometry in hamsters, Cross and researchers (2025) found that projections from the VTA to the NAc core code salience of social stimuli through phasic release of DA in response to rewarding and aversive social stimuli. OXT within the VTA also plays a role in salience (Grieb et al., 2024). In hamsters, OXT administered in the VTA acted to decrease social avoidance after exposure to social defeat.

Proposed by Shamay-Tsoory and colleagues (2009), the salience network in connection to OXT primarily consists of the anterior insula and dorsal anterior cingulate cortex is essential

for integrating sensory inputs with cognitive processes (Li et al., 2024). For example, the insular cortex processes sensory input and language (Augustine, 1996), influencing how strongly sensations are perceived. Dysfunction in this network can impair regulation of both internal and external stimuli, leading to atypical cognitive processing and contributing to social impairments (Green et al., 2016). Clinical fMRI studies have also demonstrated that the anterior insula is activated in response to both positive and negative emotional expressions (Kober et al., 2008).

It has been shown that administration of OXT enhances memory of faces, especially faces associated with positive social interactions, and recognizing and correctly responding to others' emotional states (Hurlemann et al., 2010; Kober et al., 2008). Increasing how positive social interactions are perceived has a pronounced effect on promoting prosocial behavior. In social anxiety disorder, OXT reduces activity in the amygdala, pointing to the use of OXT having a potential role in reducing social threat perception (Labuschagne et al., 2010).

Oxytocin and Dopamine Modulate Emotional Valence and Motivational Response

Emotional valence refers to whether a stimulus evokes an approach (positive valence) or withdrawal (negative valence) response (Lynne Lane, 1999). This concept traces back to foundational Theory of Mind research, which investigated how individuals recognize and attribute mental states to themselves and others, a key predictor of social functioning (Premack & Woodruff, 1978). Gamer and Büchel (2012) demonstrated that oxytocin modulates autonomic responses to emotional faces in a valence-dependent manner. Specifically, OXT enhanced heart-rate deceleration to negatively valanced facial expressions (fear, anger), which reflects increased attentional engagement with socially relevant threat cues. In contrast, OXT reduced heart-rate responses to positively valanced faces (happiness), suggesting a dampened physiological arousal to affiliative signals. Notably, these effects were specific to parasympathetic cardiac responses,

OXT did not alter electrodermal activity, indicating that sympathetic arousal remained unchanged. Together, these findings show that oxytocin biases the motivational evaluation of social stimuli by selectively modulating physiological responses based on the emotional valence of the cue This suggests that OXT plays a role in assigning motivational value to social stimuli by modulating parasympathetic responses. Building on this, it has been explored how OXT affects brain responses to emotional faces. They found that OXT reduced amygdala activity regardless of whether the facial expression was positive or negative. This suggests that lower amygdala activity may reduce uncertainty about the social significance of stimuli, facilitating social approach behaviors (Domes et al., 2007; Domes et al., 2007).

Depletion of dopamine reliably reduces motivation to work for rewards, impairing effortful and goal-directed behavior (Lex & Hauber, 2008; Palmiter, 2008; Salamone & Correa, 2012). However, dopamine's function extends far beyond reward. Dopaminergic populations also contribute to action inhibition and aversive processing, with several studies showing that DA neurons respond robustly to punishing or threatening conditions. For instance, Darvas et al. (2011) demonstrated that optogenetic stimulation of VTA dopamine neurons can act as an aversive signal, producing conditioned place avoidance rather than approach. Likewise, Zweifel et al. (2011) showed that midbrain DA neurons disrupt aversive conditioning, indicating that dopamine signaling is required for learning about negative outcomes. Supporting this, McCutcheon et al. (2012) and Oleson et al. (2012) found that dopamine release in the NAc increases during anticipated punishment and during successful active-avoidance responses. Together, these findings reveal that dopamine encodes more than reward value; it also signals aversive prediction, supports avoidance learning, and shapes behavioral inhibition when negative outcomes must be anticipated. Consistent with this, positive stimuli increase DA release across

striatal regions, whereas negative stimuli produce DA decreases reflecting a valence-dependent prediction system (Bornhoft et al., 2025). Such prediction-error signals, where DA activity increases in response to unexpected rewards and decreases when expected rewards are omitted, have also been observed within limbic regions, including the NAc. This aligns with evidence that subsets of NAc neurons promote reward-seeking behavior, while others mediate aversive responses, illustrating DA's central role in computing motivational value along both positive and negative manners (Reynolds & Berridge, 2002).

Motivation for Social Interaction

Several areas of research suggest evidence that explains why individuals with ASD are less intrinsically motivated to engage in social interactions. Neuroimaging studies show that social cues elicit reduced activation in core reward regions such as the ventral striatum and nucleus accumbens, indicating that social stimuli are experienced as less rewarding (Kohls et al., 2012; Schultz et al., 2012). Developmental work similarly finds diminished early orientation to social signals, reflecting lower innate interest in social engagement (Mundy, 1995). Together, these findings support the social motivation theory of autism, which proposes that reduced social reward processing leads to decreased intrinsic motivation for social interaction (Chevallier et al., 2012).

This is related to the changes that occur in the dopaminergic reward system (Pavăl, 2017; Pavăl & Micluția, 2021). This further explains two core features of ASD discussed earlier: reduced social approach and diminished social engagement (Clements et al., 2018). DA is thought to mediate the motivational, or 'wanting; component of reward rather than the hedonic, liking', response, a distinction captured by the incentive salience model (Berridge & Robinson, 1998). Mentioned previously, dopaminergic neurons respond to not only rewarding stimuli but

also to aversive events, again highlighting DA's brother role in signaling motivationally salient information regardless of valence (Bromberg-Martin et al., 2010; Matsumoto & Hikosaka, 2009)

This theory complements earlier frameworks and offers a useful lens for thinking about impaired social motivation, while also highlighting potential directions for future research. It aligns with previously mentioned emerging evidence suggesting interactions between dopaminergic and oxytocinergic systems in shaping social behavior. Although more work is needed, this integrated perspective may help clarify the neurobiological mechanisms that contribute to differences in social motivation. It also raises the possibility that targeting these pathways could eventually inform therapeutic approaches aimed at supporting social engagement. While such applications remain largely speculative, considering both neurochemical systems together may guide the development of more nuanced strategies to help individuals navigate social environments and maintain social relationships.

Research Aims

The central aim of this research is to determine the modulatory effects of dopaminergic and oxytocinergic nuclei activation on social motivation, particularly when effort and context shape the decision to engage with social partners. With this goal in mind, I proposed two complementary hypotheses grounded in the functional roles of the VTA and PVN in coordinating dopaminergic and oxytocinergic signaling during social behavior using a rodent model.

First, I hypothesized that targeted optogenetic excitation of the VTA will increase social interaction and affiliative interest in a peer-to-peer context, further enhancing social motivation when effort is required to access a social partner. The VTA was selected for fiber optic implantation and targeted stimulation due to its central role in processing reward, motivation, and

the salience of social cues. Critically, the VTA contains both dopaminergic and oxytocin-sensitive neurons, which are involved in encoding the value and drive associated with social engagement. Dopaminergic signaling from the VTA has been extensively linked to effort-based decision-making and reinforcement learning, while oxytocin signaling within this region has been shown to modulate social salience and reduce avoidance behavior in socially stressful contexts.

Second, I hypothesized that targeted optogenetic excitation of the PVN of the hypothalamus will increase sociability in mice during peer-to-peer social interactions, but only in contexts where access to a social partner does not require additional effort. The PVN was selected for study due to its critical role in regulating social behavior, particularly through its oxytocinergic projections to key reward and salience-processing regions. Although the PVN contains multiple neurochemical cell types, the stimulation parameters in this study predominantly engage oxytocinergic neurons. Oxytocin neurons within the PVN have been shown to modulate the encoding of social salience and affiliative behavior, making this region a prime candidate for investigating the neurobiological basis of social motivation. Prior work has demonstrated that PVN activation enhances social exploration and reduces social avoidance, particularly in low-stress or non-threatening environments. This suggests that PVN activity may be more effective in promoting sociability when external barriers are minimized.

Benefits of Using Mice as a Translational Model

Investigating neurochemical activity necessitates an invasive approach that may broadly impact brain function and elevate the risk of harm in clinical work. Using rodents as an alternative animal model circumvents these ethical and practical issues, as they share similar neuroanatomical structures and high genetic similarity with humans, while also having shorter

lifespans, ranging from two to five years, depending on the species (Dennis et al., 2021). Rodent models offer a valuable opportunity to look deeper into behavioral and neural circuits that share similarities with humans to offer a greater understanding. Using laboratory animals allows us to control the environment and enact specific genetic modifications to mimic the scenario that is needed. Mouse models are commonly selected models as their genome has been sequenced, they are inexpensive to maintain and breed, and they have high homology with human brain anatomy and genetics (Wong et al., 2023). Overall, mice provide a great advantage of decreasing external factors that could influence the outcome of research while also giving comparable behavioral outcomes.

Usage of Optogenetics for Behavioral Manipulations

In our laboratory, preliminary findings suggest a modulatory interaction between OXT and DA that diverges from traditionally understood mechanisms, specifically, in the context of effort-based social motivation (Wells et al., 2024, Wells et al., 2025). While OXT is well-documented to enhance sociability in rodents, our early data indicates that this effect diminishes significantly when an effort-related obstacle is introduced. Under these conditions, mice demonstrate a marked decrease in motivation to engage socially, despite the presence of OXT. Conversely, administration of L-dopa, a precursor to DA, appears to sustain motivated behavior even in the face of effort-related challenges, suggesting a dopaminergic contribution to the persistence of social pursuit (Wells et al., 2024). Notably, previous investigations of OXT and DA in this behavioral context have primarily relied on pharmacological methods, such as intracranial, intraperitoneal, and intranasal administration. While these approaches have provided valuable insights into behavioral outcomes, they lack the spatial and temporal resolution to directly assess neural activity or establish causal relationships.

To overcome these limitations, this study employed optogenetics, a powerful technique that enables cell-type-specific activation or inhibition of neuronal populations with high precision. This is accomplished using adeno-associated viruses (AAV) as vectors for gene delivery. AAVs are widely used in neuroscience due to their safety profile, ability to infect non-dividing cells, and stable transgene expression. By introducing light-sensitive proteins, called opsins, into targeted cells, we can precisely activate these cells using light. This is through channelrhodopsin proteins depolarizing neurons upon illumination, which activates the cell. Optical fibers were implanted within the desired brain region, and the light was delivered. From there, wavelength, intensity, and duration of the light can manipulate the neuronal activity (Deisseroth, 2010; LaLumiere, 2011; Zhang et al., 2006). It opens a door to a more causal effect, in that stimulating this brain area increases this activity, which causes this behavioral change. There are many different AAVs that one can use, each targeting different cells, creating different neuronal activity, or tagging cells with a different color. For this experiment, I will be using these AAVs: AAV1-hSyn-hChR2(H134R)-EYFP and AAV-hSyn-EYFP as a control. AAV1 is especially efficient at infecting neurons, and hSyn ensures the gene being delivered will only be turned on in neuronal cells. Channelrhodopsin-2 is the protein that will be light-activated; H134R is a variant that increases light sensitivity. Lastly, EYFP stands for enhanced yellow fluorescent protein, the tagging agent that will color the cells (Issa et al., 2023; Naso et al., 2017).

CHAPTER II

METHODOLOGY

Subjects

A total of 22 C57Bl/6 mice bred in the MTSU vivarium were used.

- PVN – CHR2/Male N = 3 EYFP/Male N = 3
- PVN – CHR2/Female N = 4 EYFP/Female N = 3
- VTA – CHR2/Male N = 2 EYFP/Male N = 2
- VTA – CHR2/Female N = 3 EYFP/Female N = 2

All animals were housed in the vivarium at Middle Tennessee State University. To limit cage mates interfering with each other's probes, mice were group-housed in 2-3 mice per cage in a temperature- and humidity-controlled environment under a 12:12 hour light/dark cycle (lights on at 07:00). Food and water was provided *ad libitum* throughout the study. Nesting materials were included to support animal welfare.

All procedures involving animals have been reviewed and approved by the Middle Tennessee State University Institutional Animal Care and Use Committee (IACUC Protocol #22-3011) and were conducted per the National Institutes of Health guidelines for the care and use of laboratory animals. Animals were monitored daily for health and well-being, including signs of pain, distress, or anhedonia, with veterinary oversight available as needed. Any animal exhibiting abnormal behavior or adverse reactions would have been immediately evaluated and, if necessary, removed from the study following humane criteria.

Materials

The Social and Affective Neuroscience lab conducted this experiment, led by Dr. Rogers at Middle Tennessee State University within the science building. All behavioral tasks were recorded via a GoPro camera, which was then transferred onto an SD card and put onto the lab computer within the Academic Classroom Building. Noldus Ethovision XT was used to visualize and code various behaviors and times spent in a specific area, as well as hand-coding approach

and avoidance behaviors by a blind observer. Specific behaviors of importance will be discussed further during behavioral assays.

General Stereotaxic Surgery

All surgery tools were placed in a GERMINATOR 500 sterilizer (Braintree Scientific) to ensure a clean and sterile environment. Anesthesia was induced with isoflurane within an induction chamber (3–5% isoflurane, 1–2% O_2). The mice's heads were shaved and then placed in a stereotaxic frame (Kopf Instruments). The mice then had continuous anesthesia through a nose cone (1–2% isoflurane, 1–2% O_2). The body temperature was maintained through a heating pad. Betadine was applied to the scalp to sterilize prior to incision as a sterilizer. Then, a subcutaneous injection of 0.1–0.2 ml of bupivacaine was administered, and a sterile cotton swab was used to spread the anesthetic throughout under the skull and left for two minutes to allow a strong numbing effect. An incision was made down the midline of the skull, ensuring bregma, the most used origin point for stereotaxic surgeries, was visible (De Vloo & Nuttin, 2019; Paxinos et al., 1980). Cotton swabs were used to gently brush away the remaining tissue and membrane on the skull. A scalpel was used to score the skull, creating a place for stronger adhesion when securing the probes. A 32-gauge syringe (Hamilton) was attached to an arm of the stereotaxic instrument, in which the arm was moved in the different axes of the skull (anterior/posterior [AP], medial/lateral [ML], dorsal/ventral [DV]). This arm was placed at a 90-degree angle so all measurements would stay consistent unless the needle itself was moved. If the needle was incorrectly moved, the bregma was found again, and the new zero coordinates were written down. The arm was moved until the needle point was directly above the bregma, which was recorded as the zero point. These coordinates were written down in our lab notebook. From here, the needle was moved to the VTA (AP: –3.1 mm, ML: ±0.5 mm, DV: –4.0 mm) or to

the PVN (AP: –0.6, ML: ±0.3, DV: –4.8) from bregma (Liu et al., 2025; Paxinos & Franklin, 2019; Solié et al., 2022). Two dots marking the location on each hemisphere of the skull were made using a fine-point Sharpie. The needle was moved out of the way, and a stereotaxic drill was used to drill through the dots barely past the surface of the skull, and a drop in resistance was felt, roughly at 3 mm ventral. The syringe arm was used again to move to the previously stated coordinates. AAV1-hSyn-hChR2(H134R)-EYFP or AAV-hSyn-EYFP (UNC GTC Vector Core) for control was injected at both sites at a rate of 0.1 µl/min using the 32-gauge syringe. For AAV injection into the VTA, it was a total of 1.0 µl, 0.5 µl at each site. For AAV injections into the PVN, it was a total of 0.6 µl, 0.3 µl at each site. The syringe remained in both sites for five minutes to ensure the virus did not backflow. A bilateral LED probe (Amuza Inc.) was inserted in the VTA and sealed using acrylic. A unilateral probe was used for PVN groups. Immediately after surgery, 5–10 mg/kg of Carprofen was administered subcutaneously in the scruff of the mouse to assist with pain relief. The skin that was cut was glued back together using VetBond. Another 5–10 mg/kg of Carprofen was administered 24 hours later in the same location and was administered as needed.

Brain Extraction

Prior to brain extractions, mice underwent one more run of an effortful social motivation task. 90 minutes after, mice were euthanized and underwent brain extractions. The mouse was euthanized via CO_2, and perfusions were performed. An incision was made to expose the xiphoid. The xiphoid was grabbed, and a lateral incision beneath the ribcage was made to expose the diaphragm and liver. Incisions were made along the entire length of the rib cage. Tissues covering the heart were carefully removed to provide a clear view of the heart and vessels. A trimmed needle was inserted from the tip of the left ventricle. A small incision on the right atrium

was then made. Ten percent Neutral Buffered Formalin was perfused at a constant rate of ~1 ml/5 s for a total of 50 ml of 10% Neutral Buffered Formalin.

The mouse was decapitated, and an incision was made along the midline from the neck to the nose. The skin was pulled laterally to expose the skull. One blade of the scissors was slid into the foramen magnum, and a lateral cut was made. This was repeated on the contralateral side. The skull covering the cerebellum was carefully removed. The tip of the scissors was then inserted between the foramen magnum and the brain. A cut along the mid-sagittal suture was made. The skull was further removed to expose the brain. A micro spatula was used to sever the nerve bundle on the ventral surface of the brain and scoop the brain out. It was then transferred into a container containing 10% Neutral Buffered Formalin. 48 hours later, brains were transferred into a container containing a 30% sucrose in phosphate buffered saline in a 4° C fridge for long term storage. Brains then went through site validation to ensure the correct brain area was targeted. This was done by taking brain slices of the VTA and brain slices of the PVN and locating the lesion site, using the Paxinos and Franklin Brain Atlas to confirm the correct location.

Histology

Prior to imaging, brain slices must be dehydrated to fit onto a microscope slide for microscopy. The dehydration process is shown in Table 1. After the dehydration processes, tissue was then embedded in paraffin. Coronal brain sections (8 μm thickness) were cut using a rotary microtome and floated onto a 56°C water bath before being mounted onto gelatin-coated slides and dried overnight at 37°C.

Dehydration		
Chemical Reagent	**Wash Amount**	**Wash Time**
70% ethanol alcohol	3 times	30 minutes
90% ethanol alcohol	2 times	30 minutes
100% ethanol alcohol	3 times	30 minutes
Xylene	2 times	20 minutes

Table 1: Dehydration of the Brain Tissue Shown in Order

Behavioral Assays

Experiments were conducted one-to-two weeks after viral injections to allow for proper recovery and desired expression. Behavioral assays were performed over 7 days in the following order shown in Table 2.

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Tube test	Tube test	Tube test	Tube test	Tube test	Tube test	Weighted door – Trial 3
Rotarod	FDSI	Weighted door	SiCPP – Isolation	SiCPP – Grouped	SiCPP – Task	
EPM	Three chamber	Ladder task				

Table 2: Outline of How Behavioral Assays were Performed

For the VTA group, optical stimulation was delivered using a 473 nm wavelength laser, employing a patterned burst of 5 pulses at 20 Hz, each burst lasting 50 ms and followed by a 100 ms interburst interval. This stimulation protocol is designed to closely mimic phasic dopaminergic firing, which has been implicated in reward prediction, motivation, and goal-directed behavior (Dreyer et al., 2010; Grace & Bunney, 1984; Tsai et al., 2009). This specific pattern was selected based on a comprehensive review of existing optogenetic literature

examining dopaminergic neuron activity within the VTA (Hung et al., 2017; Kayama et al., 2022; Kim et al., 2012).

For the PVN group, we used a stimulation pattern also employing a 473 nm wavelength, but with single pulses delivered at 30 Hz, each with a 10 ms duration. This protocol is modeled on studies that have successfully mimicked endogenous OXT neuron firing patterns to evoke social behavioral changes (Marlin et al., 2015). By employing discrete stimulation profiles tailored to the physiological characteristics of each neuromodulator, we aimed to investigate their distinct and potentially synergistic roles in modulating social motivation, especially under varying effort-related conditions.

All behavioral data was recorded via a GoPro camera and analyzed using Noldus EthoVision XT, a platform for automated behavioral tracking and analysis. Unless specified otherwise, this software was used for all behavioral assays, ensuring consistency in data acquisition across experimental conditions. For assays involving repeated trials or multiple subjects, the testing arena was cleaned thoroughly with 70% ethanol between trials to eliminate residual olfactory cues. In social interaction tasks requiring a stimulus mouse, a novel conspecific was introduced for each trial to avoid confounding familiarity effects. At the conclusion of each behavioral testing day, all arenas were hand-washed using unscented soap, rinsed thoroughly, and air-dried to preserve the integrity of subsequent testing environments.

Rotarod Test

The rotarod test (Med Associates) was used to evaluate motor coordination, balance, and general locomotor ability, which are critical for interpreting results in effort-based tasks. Mice were placed on an accelerating rotating rod that begins at 4 RPM and steadily increased to 30

RPM over five minutes. The ability to remain on the rotating rod without falling was interpreted as an index of neuromuscular function and balance. Latency to fall was automatically recorded by the Med-PC software. This test serves as a control for ensuring that observed behavioral differences in other assays are not due to motor deficits.

Elevated Plus Maze

The Elevated Plus Maze (EPM) is a widely validated assay for assessing anxiety-like behavior in rodents (Hogg, 1996; Rodgers & Dalvi, 1997; Walf & Frye, 2007). The plus-shaped apparatus consists of two open arms and two closed arms elevated above the floor, capitalizing on rodents' innate aversion to open spaces and exploratory drive. Increased time in closed arms is indicative of anxiety-like behavior, while more time in the open arms suggests reduced anxiety or increased risk-taking. This task served to examine anxiety-like behavior in each of the mice.

Stimulation was administered continuously till the task ended. The task was recorded using Noldus Ethovision, with the primary outcome measure being time spent in open arms. The task ended after five minutes.

Three-Chamber Sociability and Social Novelty Test

The three-chamber test evaluates both sociability and preference for familiarity or novelty. The arena consists of a central compartment and two side chambers connected by open doorways. Stimulation was administered continuously till the task ended. The task was divided into three phases:

1. Habituation (5 minutes): The mouse freely explores the empty three-chambered arena.
2. Sociability phase (10 minutes): One side chamber contains a social stimulus mouse enclosed under an inverted wire pencil cup, while the other contains a plastic mouse.

3. Social novelty phase (10 minutes): The original stimulus mouse remains in the same cup, and a novel conspecific is introduced under the cup in the opposite chamber.

Figure 1: Depiction of Three-Chamber Task Created in Biorender.com

Free Dyadic Social Interaction

This test assesses natural, unstructured social behavior without barriers or artificial constraints. Following a five-minute habituation period in the testing arena, a novel, sex- and age-matched mouse is introduced. The pair was then allowed to interact freely for another five minutes. Time spent in approach (moving toward target/interacting) and avoidance (moving away from target) was hand-coded by a blind observer. Stimulation was administered continuously until the task ended. The task ended after five minutes.

Ladder Task

The ladder task was previously developed and validated by our lab to assess effort-based decision-making in the context of social motivation. The apparatus is 24x12 inches, featuring a ladder connecting the starting zone to a raised platform containing a social stimulus mouse underneath an inverted pencil cup. The task consists of five trials, with the ladder angle increasing in steepness across trials to progressively raise the effort required. After each trial, the mice are given a 2–5-minute break to clean the arena. In trial 1, the ladder lies flat to assess baseline social approach without physical effort. Each subsequent trial increases the angle of

elevation, challenging the mouse's willingness to expend effort for social reward. The task can last for a total of three minutes, but if the mouse successfully climbs the ladder to the social platform on the highest setting, the task will end. Stimulation was administered until the task ended.

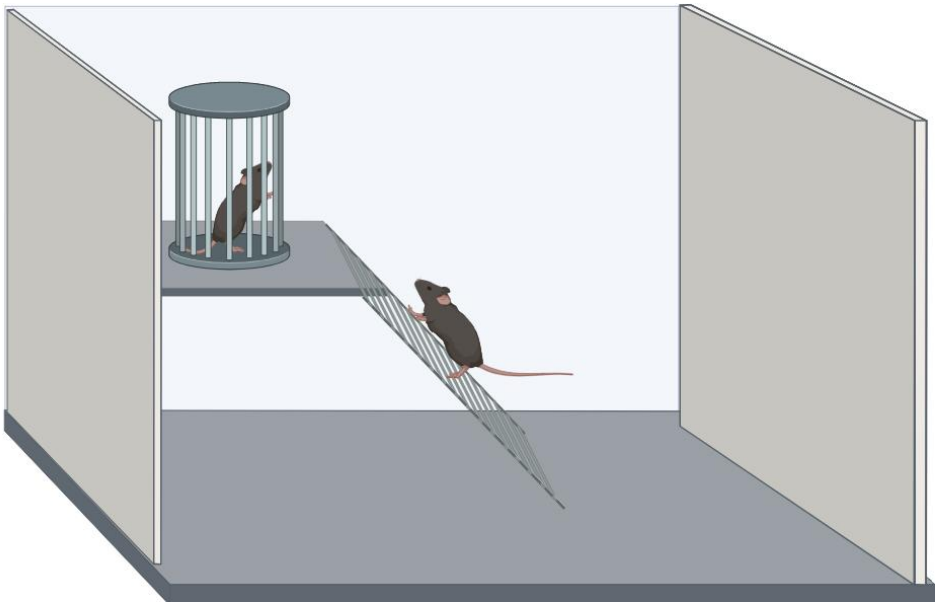

Figure 2: Depiction of the Ladder Task Created with Biorender.com

Weighted Door

The weighted door task is conceptually like the ladder task in that it assesses effort-based decision-making in a social context. However, instead of climbing, mice are required to physically push open a weighted door to access the chamber containing a social peer. The arena used for this assay is 17x6 inches, with a clear partition separating the start zone from the social chamber, which houses a same-sex, age-matched mouse underneath a pencil cup. Prior to the start of the test, all mice were habituated and trained for the weighted door, in that they go through the door multiple times and therefore know that there is something on the other side of the door. The task consisted of five consecutive trials. In trial 1, the door is unweighted (0 oz),

allowing baseline assessment of exploratory and social behavior. With each subsequent trial, the door's weight was increased by 1/3 oz, culminating in trial 5 with a final weight of 1 1/3 oz. After each trial, the mice were given a 2–5-minute break to clean the arena. This gradual increase in effort demand enables assessment of effort discounting behavior, whether motivation to obtain social interaction diminishes as the cost increases.

The task can last for a total of three minutes; however, if the mouse successfully opens the door at the greatest weight and enters the social chamber, the task ended. Stimulation was administered continuously until the task ended. Behavioral outcomes include time spent pushing the door and latency to enter the social chamber. This task, therefore, serves as a measure of social motivation under increasing physical cost, capturing a dynamic interplay between effort, reward valuation, and social drive.

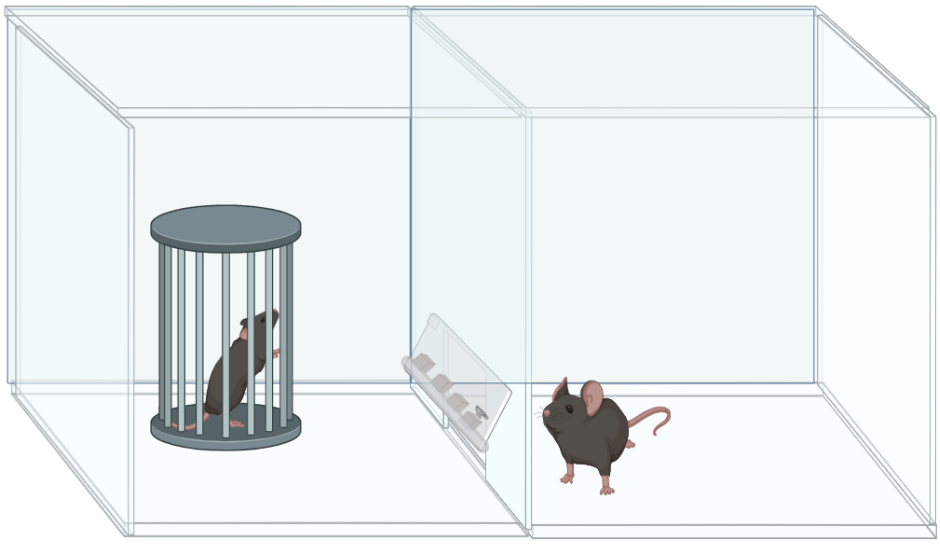

Figure 3: Depiction of the Weighted Door Task Created with Biorender.com

Social Interaction Conditioned Placement Preference

This paradigm examines conditioned social reward learning over 72 hours. On the first day, each mouse was isolated in either aspen or paper bedding. The isolation bedding will be counterbalanced to account for individual differences in preference. On the second day, mice were grouped back together with their cage mates in the opposite bedding from where they were just isolated. The task will then take place after the final 24-hour period. The test arena consists of two conditioning chambers, one with aspen and the other with paper, connected by a neutral bedding-free middle zone. Stimulation was continuously administered until the task ended. The task ended after five minutes. The primary measure was the time spent in each chamber that contains the social conditioned bedding.

CHAPTER III

RESULTS

Elevated Plus Maze

A univariate ANOVA tested whether sex, opsin condition, or injection site influenced open-arm exploration. Descriptive statistics showed considerable variability across groups, particularly among CHR2-expressing mice. Male CHR2 mice exhibited a wide range of open-arm behavior, with VTA-injected males spending an average of $M = 86.43$ seconds ($SD = 17.54$) in the open arms and PVN-injected males averaging $M = 128.89$ seconds ($SD = 14.69$), yielding a combined mean of $M = 107.66$ seconds ($SD = 27.84$). Male EYFP controls showed substantially reduced open-arm engagement, with VTA males averaging $M = 29.63$ seconds ($SD = 23.52$) and PVN males averaging $M = 34.30$ seconds ($SD = 10.61$). Female mice displayed similarly broad but generally higher levels of open-arm exploration, with CHR2–VTA females averaging $M = 86.42$ seconds ($SD = 33.60$) and CHR2–PVN females averaging $M = 69.35$

seconds (*SD* = 75.82). EYFP females also showed relatively high exploration (VTA: *M* = 109.17, *SD* = 8.49; PVN: *M* = 124.10, *SD* = 23.94). When collapsed across site, females averaged *M* = 93.94 seconds, compared to *M* = 69.81 seconds in males.

Inferential analyses revealed that the overall model was not significant and there were no significant main effects of sex, condition, or site on open-arm exploration. However, a significant sex x condition interaction emerged, $F(1, 12) = 8.40$, $p = .013$, driven primarily by a pronounced difference between male and female EYFP controls. Follow-up comparisons indicated that EYFP females spent significantly more time in the open arms than EYFP males ($p = .013$; mean difference = 84.67 seconds), whereas no sex difference was detected within CHR2 groups. Additionally, simple-effects testing identified a localized effect within male PVN mice, where EYFP males spent significantly less time in the open arms than CHR2 males ($p = .040$), though this pattern did not generalize to females or to the VTA site.

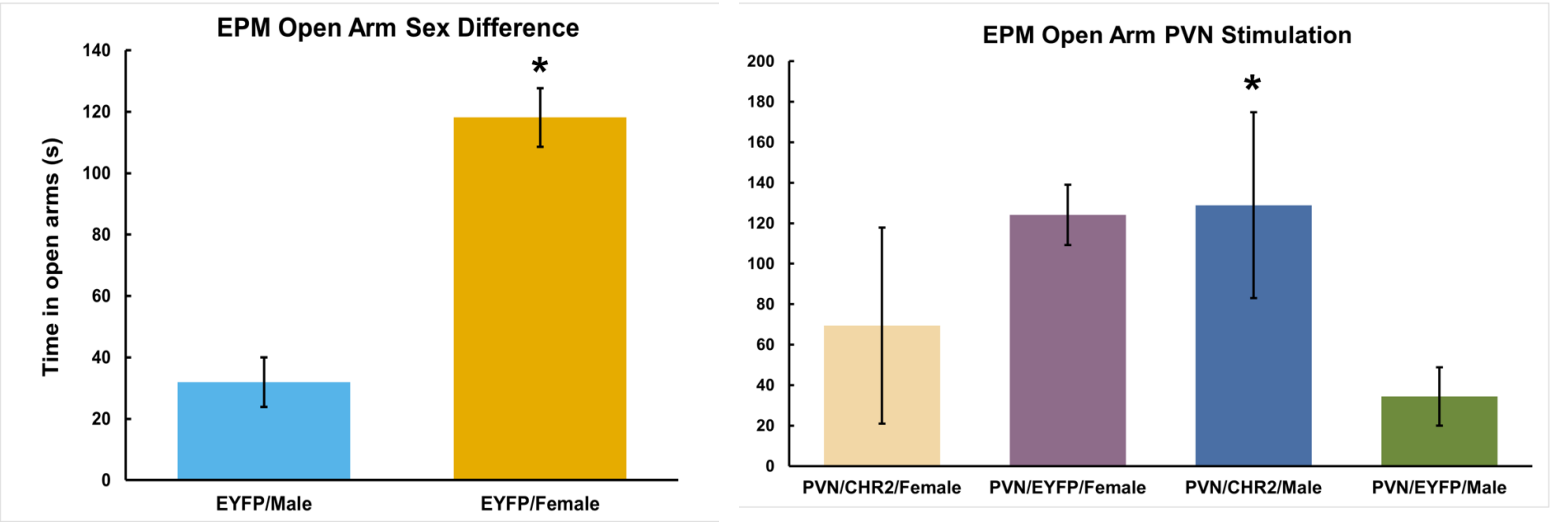

Figure 4: EYFP Females Spent More Time in Open Arms than EYFP Males. PVN/CHR2 Males Spent More Time in Open Arms than other PVN Groups

Three Chamber

Sociability preference

Sociability scores varied widely across sex, opsin condition, and injection site. A multivariate analysis found no significant main effects of sex, condition, or site on Phase 2 sociability. However, a significant condition x site interaction emerged, $F(1,11) = 7.92$, $p = .017$, indicating that the effect of CHR2 stimulation differed between VTA and PVN groups. Pairwise comparisons showed that VTA–CHR2 mice spent more time in the social chamber than PVN–CHR2 mice, suggesting a site-specific facilitation of sociability under optogenetic stimulation. Mean patterns further suggested elevated social exploration among male VTA–CHR2 mice ($M \approx$ 327 seconds) relative to females ($M \approx 217$), whereas PVN–CHR2 mice showed the opposite pattern; however, the three-way interaction did not reach significance.

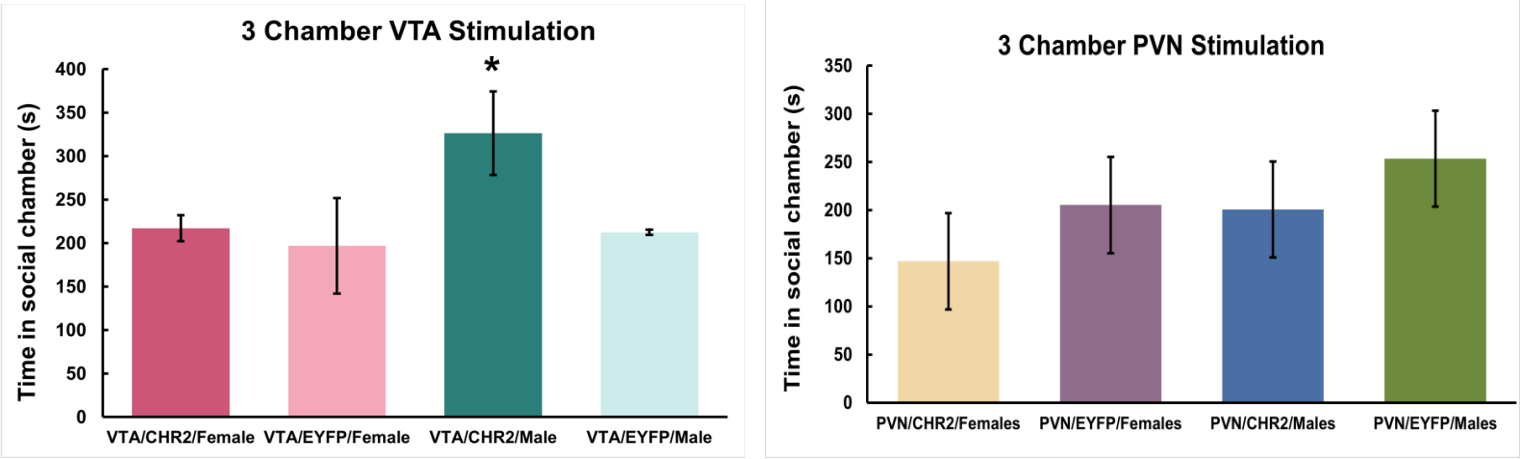

Figure 5: VTA Stimulation Increased Social Chamber Time for Males, but not for Females or for PVN Groups

Familiar/Novelty Preference

The multivariate ANOVA revealed a significant condition × site interaction, $F(1,11) = 10.44$, $p = .008$, demonstrating that CHR2 stimulation influenced novelty preference differently in the VTA versus the PVN. Within the PVN–CHR2 group, females spent more time with the

familiar mouse than males ($p = .015$). In contrast, male VTA–CHR2 mice spent significantly more time in the novel chamber than female VTA–CHR2 mice ($p < .05$). No sex differences were observed within PVN–CHR2 or EYFP controls. These patterns suggest that PVN stimulation biases females toward familiar stimuli, whereas VTA stimulation enhances novelty-driven social motivation, particularly for males.

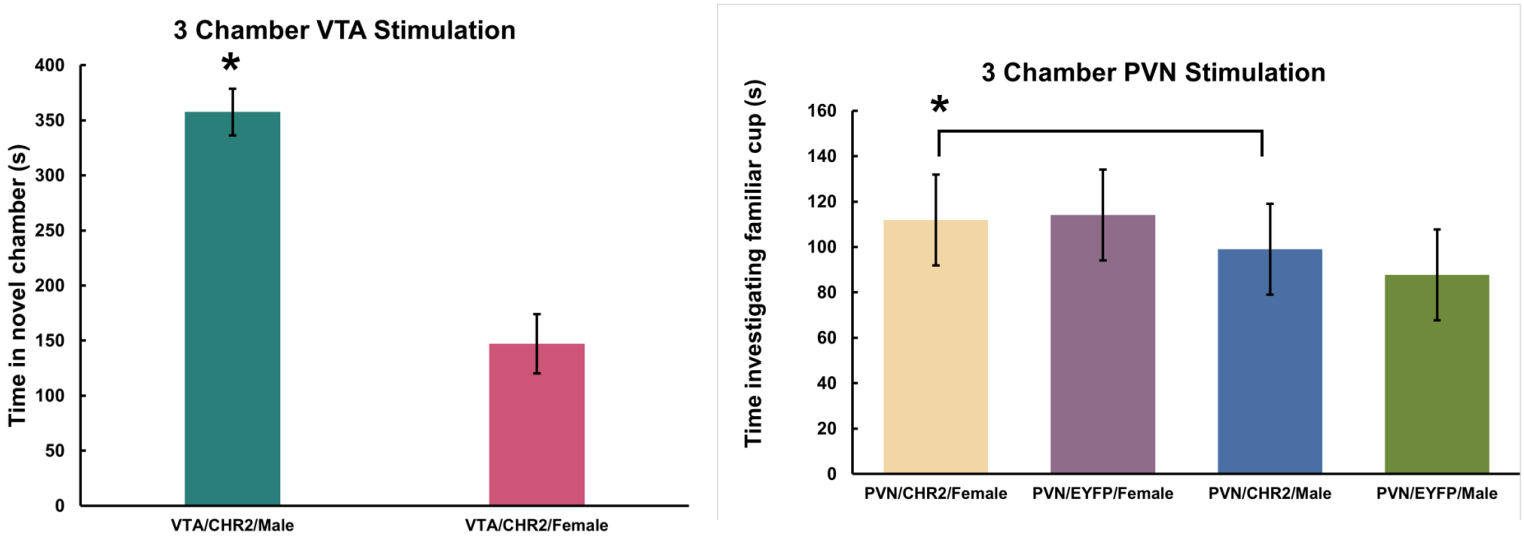

Figure 6: VTA Stimulation Increased Novel Chamber Time for Males. Stimulation in the PVN Increased Investigation of Familiar Mouse in Females.

FDSI

A multivariate ANOVA assessed effects of sex, opsin condition, and site across social interaction measures (approach/avoidance). Descriptively, males generally displayed higher investigatory behavior than females. Although approach did not yield a significant overall main effect, the sex × condition × site interaction contained a meaningful simple effect: VTA–CHR2 males ($M = 153.00$, $SD = 50.91$) showed significantly higher approach behavior than VTA–CHR2 females ($M = 52.33$, $SD = 25.70$; $p < .05$). No corresponding sex differences appeared in PVN–CHR2 or EYFP groups.

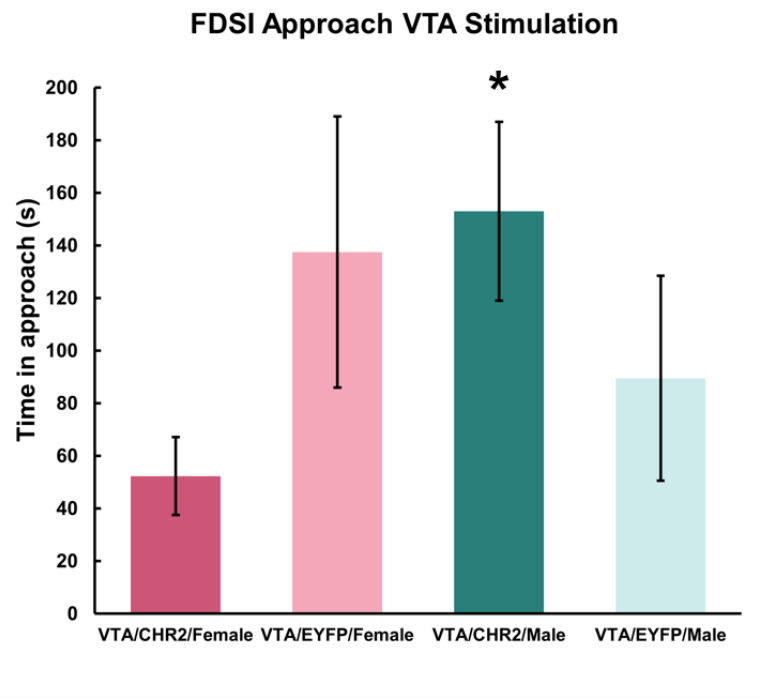

Figure 7: VTA Stimulation Increases Approach in Males. While not Significant, VTA Stimulation Seems to Drive Down Approach in Females.

Ladder Task

Performance was assessed using two dependent variables: latency to climb and climb success, each analyzed with a mixed repeated-measures general linear model including trial steepness and peer condition as within-subjects factors and sex, opsin condition, and injection site as between-subjects factors.

Latency

Latency increased reliably with ladder steepness, producing a significant main effect, $F(4,36) = 18.48$, $p < .001$. Mice climbed faster during social compared to nonsocial trials, $F(1,9) = 8.23$, $p = .019$, indicating social facilitation. Several localized effects emerged: male CHR2–VTA mice showed significant social-condition differences at Trials 2–4 (mean difference =

129.02, *SE* = 50.81, *p* = .032), and male CHR2–PVN mice showed a similar effect at Trial 4 (mean difference = 137.87, *SE* = 41.48, *p* = .009).

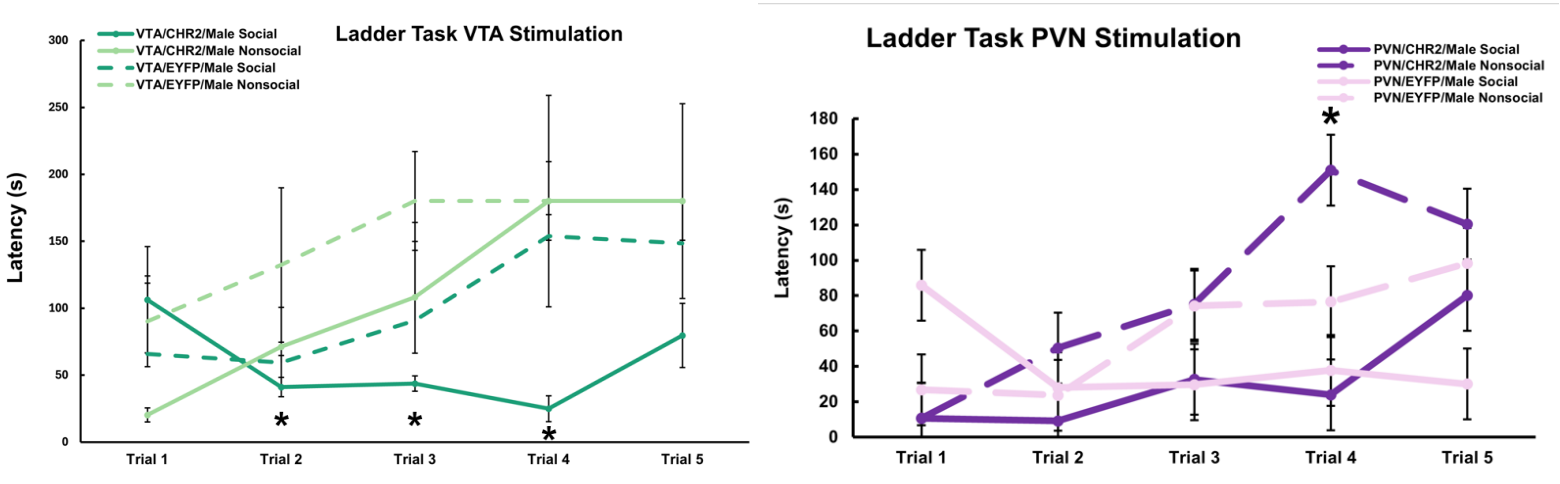

Figure 8: CHR2-VTA Males in the Social Condition have the Lowest Latency in Trials 2, 3, and 4. CHR2-PVN Males have the Highest Latency in the Nonsocial Condition

Climb Time

Climb performance decreased with increasing difficulty, $F(4,36) = 7.20$, $p < .001$. Significant interactions, including steepness x condition, steepness x site, and the three-way steepness x condition x site interaction, indicated that CHR2 stimulation modulated performance differently across sites. CHR2–VTA mice outperformed CHR2–PVN mice at moderate difficulty levels (Trials 2–4). Sex differences emerged only within the CHR2–VTA subgroup, where females outperformed males at Trial 2, but males surpassed females at Trials 4 and 5. No sex differences were observed in PVN or EYFP groups.

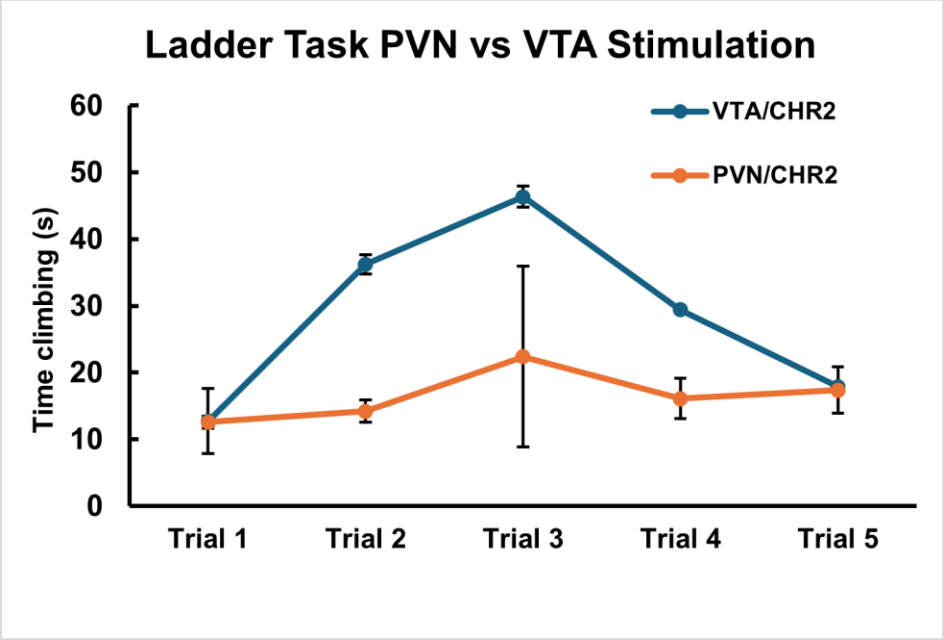

Figure 9: VTA stimulation increased climb time until trial 3, then declined. PVN stimulation kept a relatively similar trend throughout trials.

Weighted Door

Performance in the Weighted Door Task was analyzed using a mixed repeated-measures general linear model with weight and peer condition as within-subject factors, and sex, opsin condition, and injection site as between-subject factors. Push duration did not differ across weight levels, $F(4,44) = 0.47$, $p = .76$, and no weight-related interactions were significant. However, several meaningful simple effects emerged. CHR2–VTA males pushed significantly longer than females in the nonsocial condition across multiple early trials (Trial 1: mean difference = 69.07, $p = .004$; Trial 2: mean difference = 83.83, $p = .002$; Trial 3: mean difference = 46.40, $p = .024$). In contrast, CHR2–PVN females pushed longer during social trials than nonsocial trials ($p = .026$). No significant sex effects were found in EYFP groups or PVN-injected males, and no main effects of sex, condition, or site emerged.

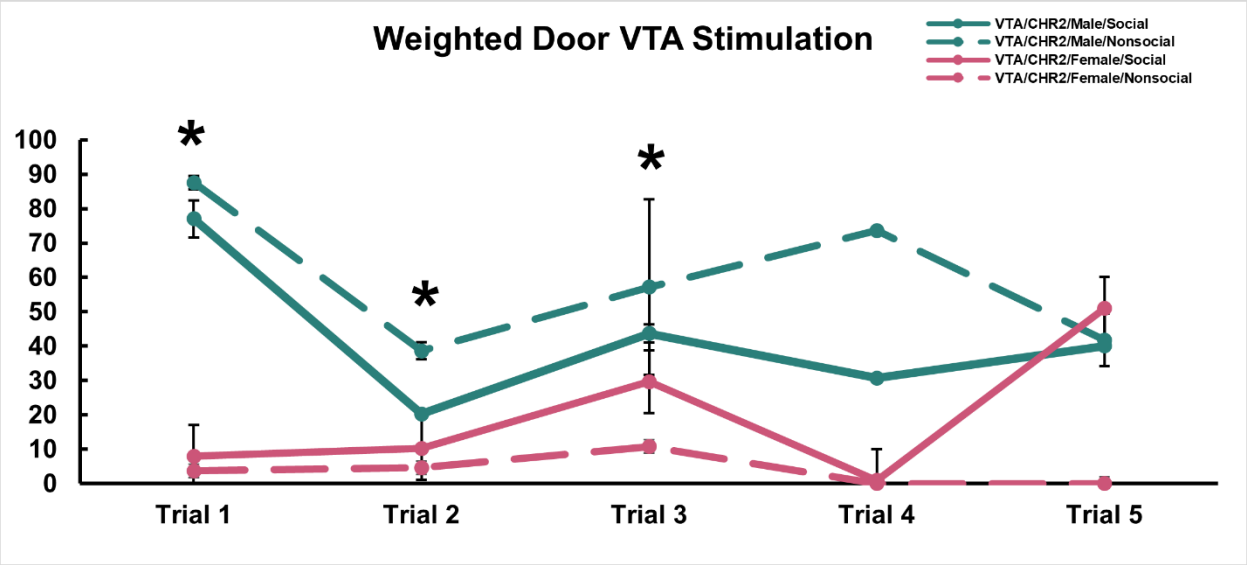

Figure 10: VTA CHR2 Males Push More in the Nonsocial Condition in Trial 1, Trial 2, and Trial 3.

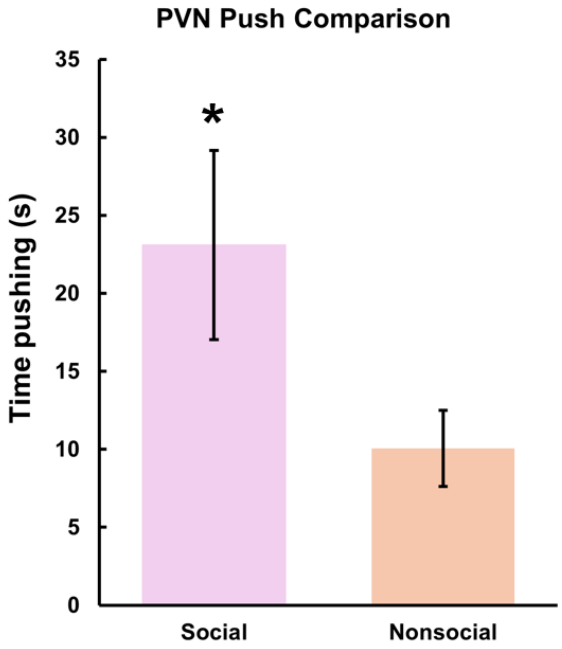

Figure 11: Stimulation in the PVN for Females Increased Pushing Time in Social Conditions, but not Nonsocial Conditions.

Social Conditioned Place Preference

A univariate analysis indicated no significant main effects of sex, condition, or site on time spent in the conditioned social bedding. Pairwise comparisons revealed a notable effect within the CHR2–VTA group: CHR2 males ($M = 81.07$, $SD = 32.68$_) spent significantly less time in the social bedding than CHR2 females ($M = 267.75$, $SD = 224.55$; $p < .05$). No other sex differences or condition effects were observed in PVN groups or EYFP controls.

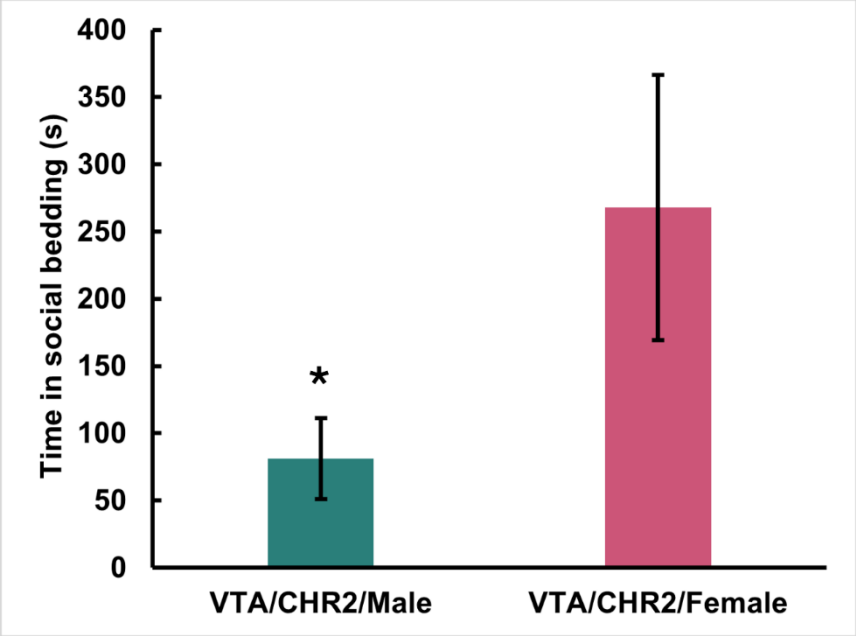

Figure 12: VTA-stimulated Males Spent Less Time on the Social Bedding than VTA-stimulated Females.

CHAPTER IV

DISCUSSION

Across all behavioral assays, a clear site- and sex-dependent pattern emerged in how optogenetic stimulation shaped social and effort-related behavior. Most notably, VTA stimulation produced opposite behavioral trends in males versus females, increasing exploratory and motivated actions in males while reducing these same behaviors in females, suggesting that VTA-driven modulation of DA signaling interacts differently with sex-linked physiological or

circuit-level factors. In contrast, PVN stimulation more context-specific behavioral changes, aligning with the PVN's known role as a modulatory hub integrating social, stress, and hormonal signals rather than directly driving motivational output.

In the three-chamber novelty phase, FDSI approach behavior, and ladder climb tasks, male VTA-CHR2 mice displayed heightened exploratory and goal-directed behavior, including increased novelty preference, greater social approach, and superior climb performance at moderate and high difficulty levels. Female VTA-CHR2 mice showed attenuated or opposite effects, such as lower novelty investigation, reduced approach behavior, and declining climb success under high effort. These sex differences were absent in EYFP controls and PVN-stimulated groups, indicating that they reflect a sex-specific sensitivity to VTA activation rather than baseline behavioral differences.

These findings align with literature demonstrating sex and hormone-dependent differences in dopaminergic function. Although baseline measures of DA signaling do not always differ between males and females, studies demonstrate sex-dependent differences in how DA systems respond to modulation. For example, striatal D1 receptor expression has been reported to be ~10% higher in males than females in rodent models, and estradiol produces rapid, sex-specific modulation of D2 receptor binding and dopaminergic responsiveness (Bazzett & Becker, 1994). Estradiol also enhances DA release and reward sensitivity in females, particularly in the mesolimbic pathway, whereas males show more stable dopaminergic responses across hormonal states (Becker & Chartoff, 2019). Additionally, mesolimbic DA neurons exhibit sex-specific differences in excitability, synaptic plasticity, and responses to stimulants or stressors (Calipari et al., 2017; Kuhn et al., 2010). Taken together, these findings suggest that VTA excitation may shift males into a more active, motivation-enhanced state while in females the same stimulation

may disrupt DA homeostasis or interact with hormone-dependent circuits in ways that reduce exploratory drive or effort engagement.

By contrast, PVN-CHR2 mice exhibited variable, context-dependent behavioral effects. Increases or decreases in social exploration, novelty preference, or effort-based behavior depends on task demands, social context, and effort level. This pattern reflects the PVN's role as a multifunctional integrator of neuroendocrine stress responses, OXT release, and social-affiliative signaling, rather than a driver of motivation action. Literature indicates that PVN output is highly state-dependent, shaped by circulating hormones, stress exposure, and social context (Jurek & Neumann, 2018; Herman & Tasker, 2016). Work in rodents further shows that PVN OXT neurons can either facilitate or inhibit social and stress-related behaviors depending on internal physiological conditions and environmental cues (Steinman et al., 2016; Knobloch et al., 2012). Taken together, these findings suggest that PVN stimulation alone is not expected to produce uniform increases in motivated behavior but instead modulate behavioral output in a highly state-dependent manner.

In summary, these results highlight the distinct and sex-dependent roles of the VTA and PVN in shaping motivated and social behaviors. VTA activation drives robust, sex-specific changes in exploratory and effortful behavior, enhancing motivation in males while diminishing it in females, likely through interactions between dopaminergic circuits and hormone-dependent mechanisms. In contrast, PVN stimulation produces subtler, context-dependent effects. Together, these findings emphasize that motivated behavior is orchestrated by multiple, interacting neural circuits, with the VTA acting as a dimorphic driver of effort and reinforcement and the PVN serving as a regulator sensitive to state and environment. This work underscores the importance

of considering both sex and circuit specificity when investigating the neural mechanisms of motivation and social behavior.

Limitations

One important limitation of this study is the small sample size. Several methodological challenges contributed to reduced cohort numbers, most notably difficulties maintaining the integrity of the implanted optical fibers. Animals frequently dislodged or damaged the probes, and replacement components required extended fabrication times due to their custom design. These issues resulted in delays in data collection and constrained statistical power. Adjustments to implantation procedures were incorporated over time to prevent damage to the probes. These include scoring the skull after incision to enhance adhesion, increasing the amount of acrylic surrounding the probe, reducing cage-mate numbers to two per cage, and applying animal-safe anti-chew spray to reduce chewing behavior. Future research would benefit from additional preventative measures including a external cap placed on the probe while the mouse is recovery from surgery, an item now offered by the manufacturer Amuza, Inc.

A second limitation concerns the quality and consistency of the histological material. Establishing a reliable immunohistochemistry protocol for the paraffin-embedded brain tissue proved challenging; repeated attempts were hindered by tissue brittleness and fragmentation during microtome sectioning or water-bath transfer. These difficulties impeded the acquisition of high-quality sections necessary for accurate verification of viral expression or targeting. Future research will be conducted using amended procedures for the storage and dehydration of the brain to prevent the loss of tissue integrity.

Despite these limitations, the present findings indicate that optogenetic stimulation of the VTA and PVN produces distinct, sex-dependent patterns across social, exploratory, and effort-based behaviors. VTA activation consistently enhanced motivated responding in males while attenuating or reversing these effects in females, whereas PVN stimulation generated more subtle and context-dependent outcomes consistent with its modulatory role. Beyond the behavioral results, this project demonstrates the feasibility of implementing optogenetic approaches within the laboratory and identifies key procedural domains that require refinement. Accordingly, this study serves as foundational preliminary work. Future replications with larger cohorts, improved tissue-processing methods, and more rigorous confirmation of viral expression will allow for a more definitive characterization of the circuit- and sex-specific mechanisms underlying social motivation.

Taken together, these findings demonstrate that optogenetic stimulation of the VTA and PVN produces distinct, sex-dependent patterns across social, exploratory, and effort-based behaviors, with VTA activation reliably enhancing motivated responses in males while reducing or reversing these behaviors in females. In contrast, PVN stimulation generated more subtle and context-dependent effects, aligning with its role as a modulatory rather than a motivational hub. Importantly, beyond the behavioral outcomes themselves, this project establishes the feasibility of implementing optogenetic methods in our laboratory and highlights critical procedural considerations, particularly in maintaining optical implant integrity and refining downstream histology protocols. As such, the study functions as foundational preliminary data, setting the stage for expanded and methodologically strengthened replications. The lab intends to repeat and extend this work with larger sample sizes, improved tissue processing, and enhanced verification

of viral expression to characterize the circuit- and sex-specific mechanisms underlying social motivation more definitively.

SUPPLEMENTAL MATERIAL

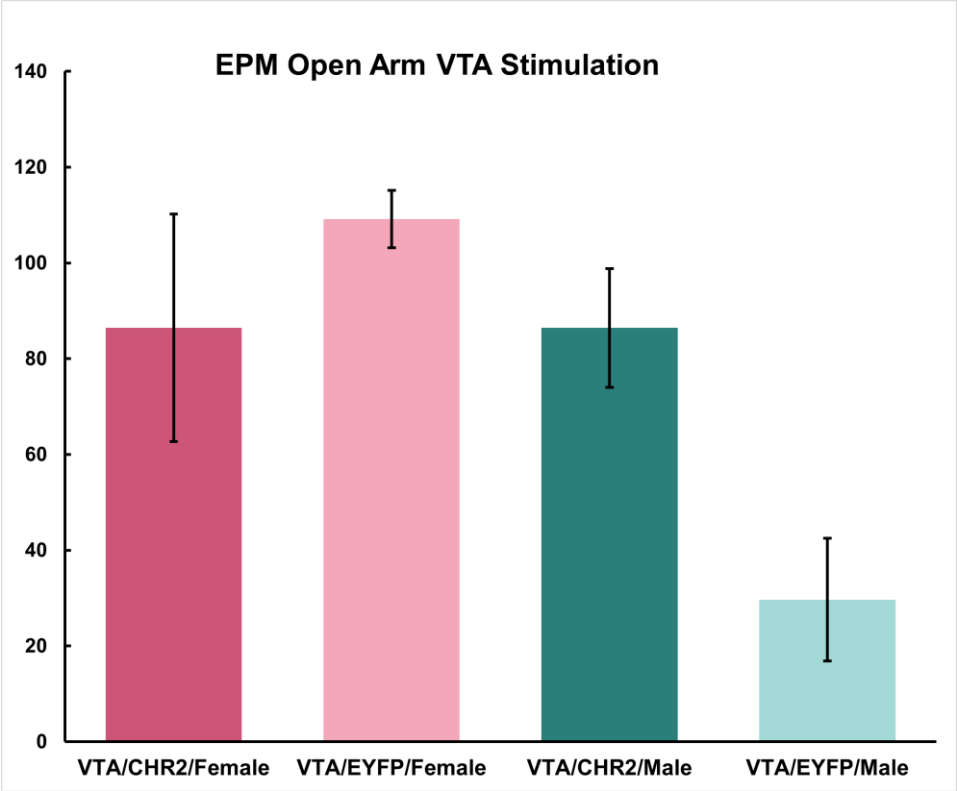

Figure 13: Stimulation in the VTA Had No Effect on Total Open Arm Time in EPM

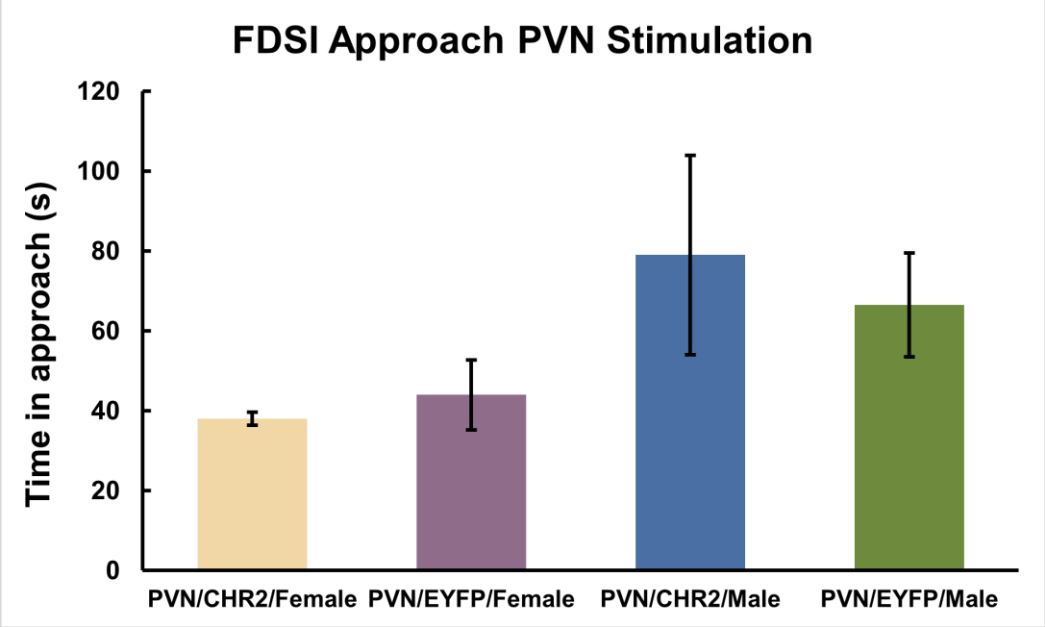

Figure 14: Stimulation in the PVN Had No Effect on Approach Behaviors

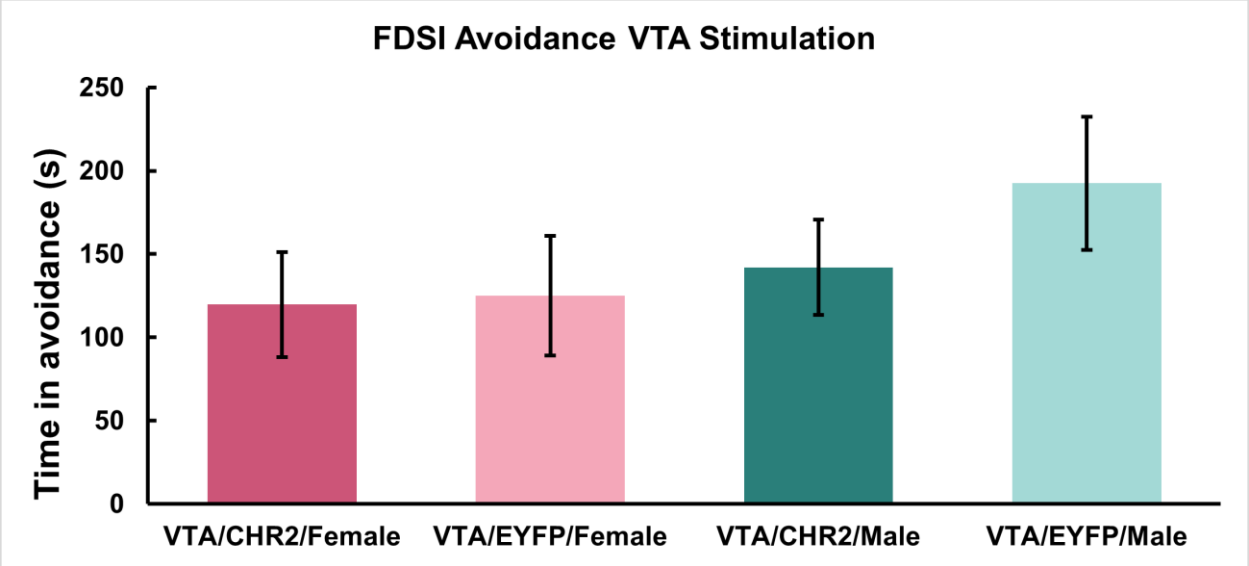

Figure 15: VTA Stimulation Had No Effect on Avoidance During FDSI

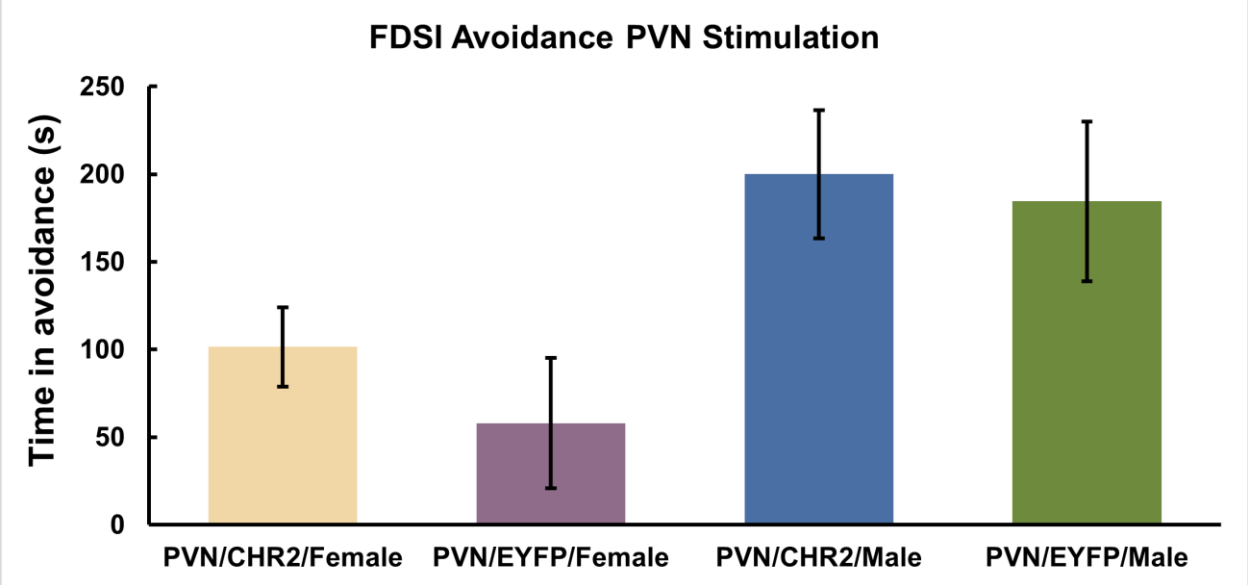

Figure 16: PVN Stimulation Had No Effect on Avoidance During FDSI

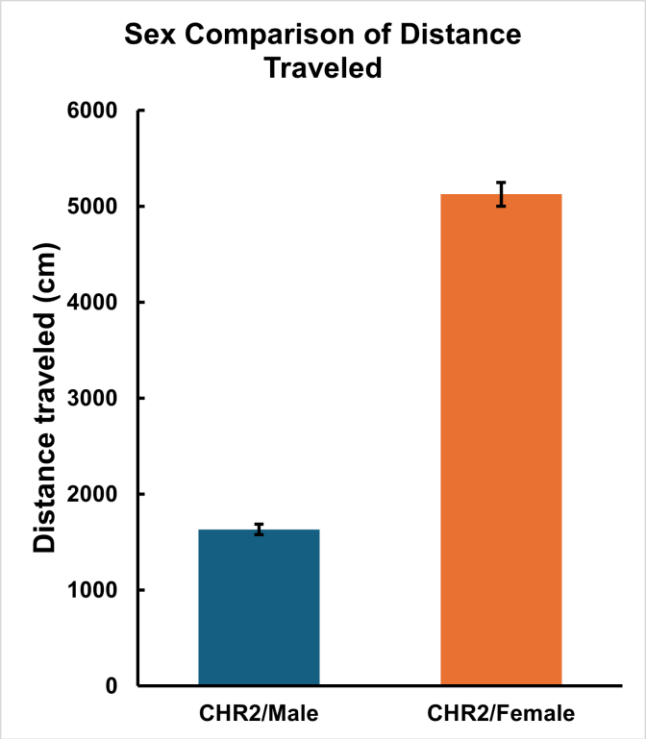

Figure 17: Stimulation Based on Sex Had No Effect in Distance Traveled

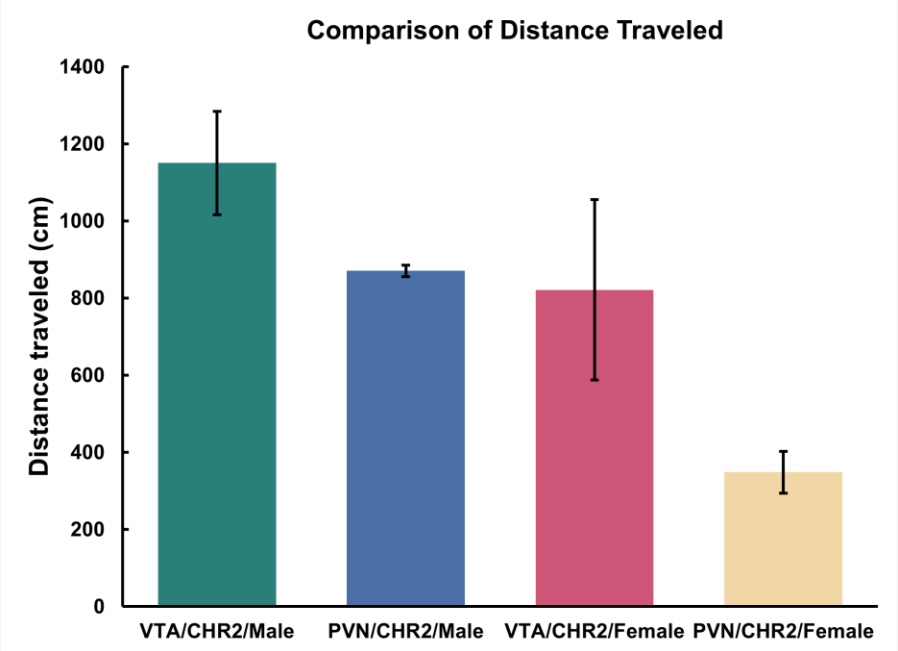

Figure 18: Specific Brain Regions had no Significant Difference in Distance Traveled when Stimulated

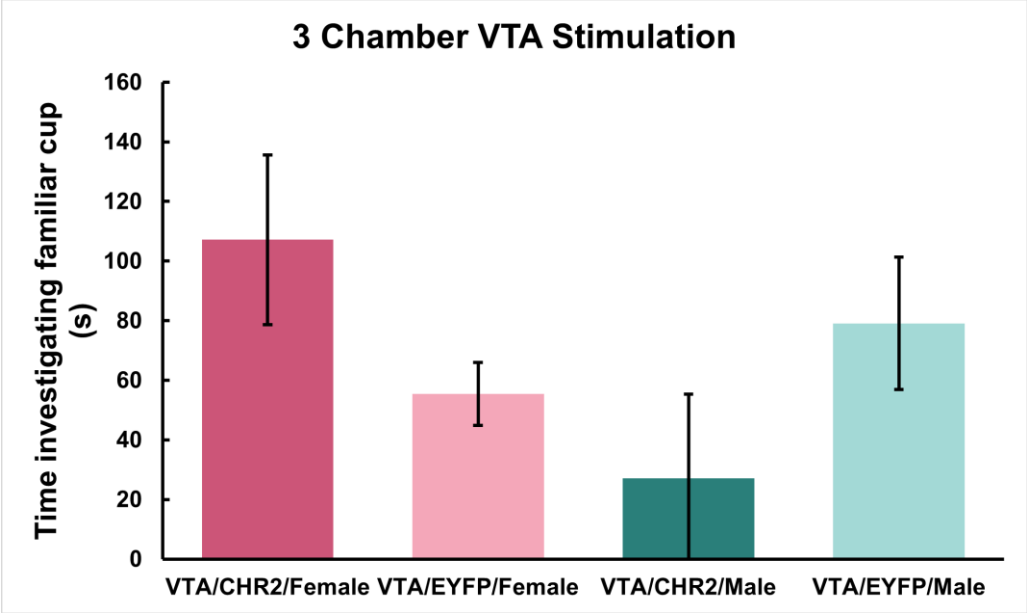

Figure 19: While Not Significant, VTA Stimulation in Males Seem to Drive Down Preference for Familiarity While Increasing it In Females

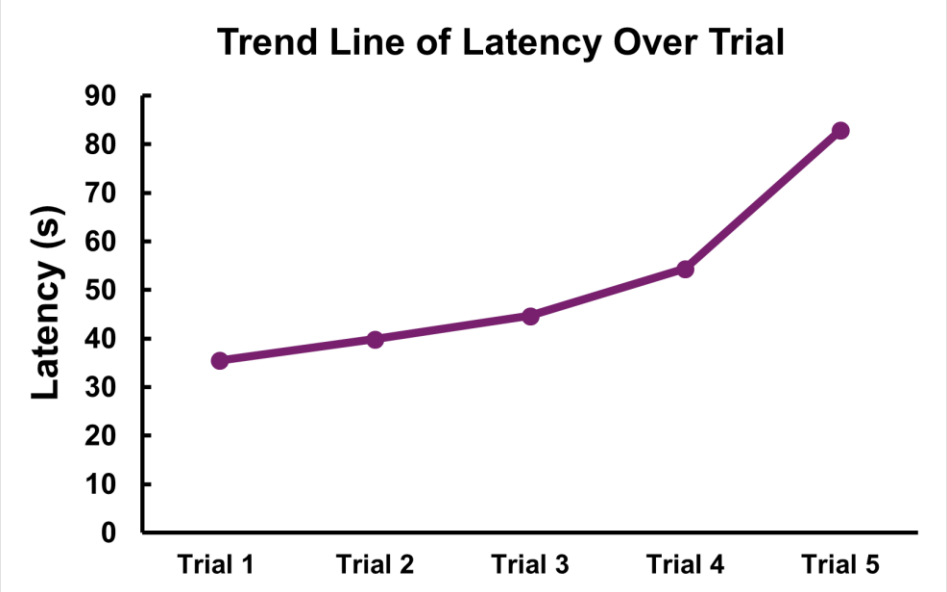

Figure 20: Overall Latency during the Ladder Task Increased with each Subsequent Trial

TASK	EPM	FDSI	THREE CHAMBER	LADDER	WEIGHTED	sCPP
TEST TYPE	Univariate ANOVA	MANOVA	MANOVA	Repeated Measures ANOVA	Repeated Measures ANOVA	Univariate
DV	-Open arm duration	-Approach -Avoidance	-Time in social chamber -Time in nonsocial chamber -Time investigating social cup -Time investigating nonsocial cup	-Latency to reach platform -Time climbing ladder	-Time pushing	-Time in social bedding

Table 3: Representation of Statistical Analyses. All Independent Variables were Sex, Condition, and Site, Making All a Three-Way Factorial. Two-Way Hypothesis with the Alpha Value = 0.05. LSD Corrected Post-Hoc was Used for all Analyses.

Tests of Between-Subjects Effects

Dependent Variable: OpenTotal

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	21857.506[a]	7	3122.501	1.710	.198
Intercept	130714.903	1	130714.903	71.588	<.001
Sex	3528.064	1	3528.064	1.932	.190
Condition	1597.900	1	1597.900	.875	.368
Site	592.025	1	592.025	.324	.580
Sex * Condition	15331.838	1	15331.838	8.397	.013
Sex * Site	710.450	1	710.450	.389	.544
Condition * Site	9.806	1	9.806	.005	.943
Sex * Condition * Site	1425.485	1	1425.485	.781	.394
Error	21911.104	12	1825.925		
Total	185864.119	20			
Corrected Total	43768.610	19			

a. R Squared = .499 (Adjusted R Squared = .207)

Table 4: SPSS Output of EPM Open Arm Time

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Approach	24776.767[a]	7	3539.538	1.990	.192
	Avoidance	24007.567[b]	7	3429.652	1.058	.471
Intercept	Approach	90078.626	1	90078.626	50.654	<.001
	Avoidance	265668.971	1	265668.971	81.989	<.001
Sex	Approach	2792.006	1	2792.006	1.570	.250
	Avoidance	19225.523	1	19225.523	5.933	.045
Condition	Approach	47.592	1	47.592	.027	.875
	Avoidance	9.661	1	9.661	.003	.958
Site	Approach	8680.695	1	8680.695	4.881	.063
	Avoidance	422.075	1	422.075	.130	.729
Sex * Condition	Approach	5781.661	1	5781.661	3.251	.114
	Avoidance	825.523	1	825.523	.255	.629
Sex * Site	Approach	24.282	1	24.282	.014	.910
	Avoidance	4360.006	1	4360.006	1.346	.284
Condition * Site	Approach	164.144	1	164.144	.092	.770
	Avoidance	3224.144	1	3224.144	.995	.352
Sex * Condition * Site	Approach	3505.523	1	3505.523	1.971	.203
	Avoidance	10.626	1	10.626	.003	.956
Error	Approach	12448.167	7	1778.310		
	Avoidance	22682.167	7	3240.310		
Total	Approach	141225.000	15			
	Avoidance	348582.000	15			
Corrected Total	Approach	37224.933	14			
	Avoidance	46689.733	14			

a. R Squared = .666 (Adjusted R Squared = .331)

b. R Squared = .514 (Adjusted R Squared = .028)

Table 5: SPSS Output of FDSI Approach/Avoidance

Tests of Between-Subjects Effects

Dependent Variable: Time_SocialBedding

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	43483.278[a]	7	6211.897	.948	.517
Intercept	310960.928	1	310960.928	47.447	<.001
Sex	7390.562	1	7390.562	1.128	.316
Condition	6934.366	1	6934.366	1.058	.331
Site	1063.859	1	1063.859	.162	.696
Sex * Condition	6990.001	1	6990.001	1.067	.329
Sex * Site	6961.641	1	6961.641	1.062	.330
Condition * Site	10.536	1	10.536	.002	.969
Sex * Condition * Site	11932.776	1	11932.776	1.821	.210
Error	58984.531	9	6553.837		
Total	462904.482	17			
Corrected Total	102467.809	16			

a. R Squared = .424 (Adjusted R Squared = -.023)

Table 6: SPSS Output of sCPP Time in Social Bedding

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	SOCIAL_TOTAL2	36666.520[a]	7	5238.074	2.359	.098
	NS_TOTAL2	56231.979[b]	7	8033.140	1.914	.161
Intercept	SOCIAL_TOTAL2	806476.648	1	806476.648	363.246	<.001
	NS_TOTAL2	400210.484	1	400210.484	95.366	<.001
Sex	SOCIAL_TOTAL2	8754.688	1	8754.688	3.943	.073
	NS_TOTAL2	15895.995	1	15895.995	3.788	.078
Condition	SOCIAL_TOTAL2	5.624	1	5.624	.003	.961
	NS_TOTAL2	25734.821	1	25734.821	6.132	.031
Site	SOCIAL_TOTAL2	4250.298	1	4250.298	1.914	.194
	NS_TOTAL2	13.303	1	13.303	.003	.956
Sex * Condition	SOCIAL_TOTAL2	5065.931	1	5065.931	2.282	.159
	NS_TOTAL2	3100.315	1	3100.315	.739	.408
Sex * Site	SOCIAL_TOTAL2	1053.976	1	1053.976	.475	.505
	NS_TOTAL2	2639.968	1	2639.968	.629	.444
Condition * Site	SOCIAL_TOTAL2	17730.511	1	17730.511	7.986	.016
	NS_TOTAL2	1688.625	1	1688.625	.402	.539
Sex * Condition * Site	SOCIAL_TOTAL2	555.474	1	555.474	.250	.627
	NS_TOTAL2	6972.833	1	6972.833	1.662	.224
Error	SOCIAL_TOTAL2	24422.126	11	2220.193		
	NS_TOTAL2	46162.498	11	4196.591		
Total	SOCIAL_TOTAL2	1018533.110	19			
	NS_TOTAL2	610171.858	19			
Corrected Total	SOCIAL_TOTAL2	61088.646	18			
	NS_TOTAL2	102394.477	18			

a. R Squared = .600 (Adjusted R Squared = .346)

b. R Squared = .549 (Adjusted R Squared = .262)

Table 7: SPSS Output of Phase 2 Three Chamber Social vs Nonsocial Chamber

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	FAMCUP_TOTAL2	13117.445[a]	7	1873.921	.935	.518
	NOVELCUP_TOTAL2	7713.494[b]	7	1101.928	1.162	.395
Intercept	FAMCUP_TOTAL2	99820.178	1	99820.178	49.791	<.001
	NOVELCUP_TOTAL2	34198.361	1	34198.361	36.070	<.001
Sex	FAMCUP_TOTAL2	2097.903	1	2097.903	1.046	.328
	NOVELCUP_TOTAL2	17.673	1	17.673	.019	.894
Condition	FAMCUP_TOTAL2	1059.728	1	1059.728	.529	.482
	NOVELCUP_TOTAL2	2.903	1	2.903	.003	.957
Site	FAMCUP_TOTAL2	1986.857	1	1986.857	.991	.341
	NOVELCUP_TOTAL2	.426	1	.426	.000	.983
Sex * Condition	FAMCUP_TOTAL2	2326.064	1	2326.064	1.160	.304
	NOVELCUP_TOTAL2	4774.982	1	4774.982	5.036	.046
Sex * Site	FAMCUP_TOTAL2	125.248	1	125.248	.062	.807
	NOVELCUP_TOTAL2	867.942	1	867.942	.915	.359
Condition * Site	FAMCUP_TOTAL2	1077.733	1	1077.733	.538	.479
	NOVELCUP_TOTAL2	1880.311	1	1880.311	1.983	.187
Sex * Condition * Site	FAMCUP_TOTAL2	3204.239	1	3204.239	1.598	.232
	NOVELCUP_TOTAL2	115.398	1	115.398	.122	.734
Error	FAMCUP_TOTAL2	22052.487	11	2004.772		
	NOVELCUP_TOTAL2	10429.124	11	948.102		
Total	FAMCUP_TOTAL2	155475.316	19			
	NOVELCUP_TOTAL2	57530.767	19			
Corrected Total	FAMCUP_TOTAL2	35169.932	18			
	NOVELCUP_TOTAL2	18142.618	18			

a. R Squared = .373 (Adjusted R Squared = -.026)

b. R Squared = .425 (Adjusted R Squared = .059)

Table 8: SPSS Output of Phase 2 Three Chamber Social Cup vs Nonsocial Cup

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	SOCIAL_TOTAL3	51609.641[a]	7	7372.806	1.338	.319
	NS_TOTAL3	73025.731[b]	7	10432.247	2.637	.073
Intercept	SOCIAL_TOTAL3	659365.093	1	659365.093	119.661	<.001
	NS_TOTAL3	760164.913	1	760164.913	192.165	<.001
Sex	SOCIAL_TOTAL3	1047.422	1	1047.422	.190	.671
	NS_TOTAL3	15220.321	1	15220.321	3.848	.076
Condition	SOCIAL_TOTAL3	2829.389	1	2829.389	.513	.489
	NS_TOTAL3	193.400	1	193.400	.049	.829
Site	SOCIAL_TOTAL3	327.227	1	327.227	.059	.812
	NS_TOTAL3	1172.360	1	1172.360	.296	.597
Sex * Condition	SOCIAL_TOTAL3	398.362	1	398.362	.072	.793
	NS_TOTAL3	6723.026	1	6723.026	1.700	.219
Sex * Site	SOCIAL_TOTAL3	43623.376	1	43623.376	7.917	.017
	NS_TOTAL3	29728.989	1	29728.989	7.515	.019
Condition * Site	SOCIAL_TOTAL3	51.265	1	51.265	.009	.925
	NS_TOTAL3	9961.976	1	9961.976	2.518	.141
Sex * Condition * Site	SOCIAL_TOTAL3	61.182	1	61.182	.011	.918
	NS_TOTAL3	2230.994	1	2230.994	.564	.468
Error	SOCIAL_TOTAL3	60612.926	11	5510.266		
	NS_TOTAL3	43513.762	11	3955.797		
Total	SOCIAL_TOTAL3	902698.103	19			
	NS_TOTAL3	966990.808	19			
Corrected Total	SOCIAL_TOTAL3	112222.567	18			
	NS_TOTAL3	116539.493	18			

a. R Squared = .460 (Adjusted R Squared = .116)

b. R Squared = .627 (Adjusted R Squared = .389)

Table 9: SPSS Output of Phase 3 Three Chamber Social Chamber vs Novel Chamber

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	FAMCUP_TOTAL3	15208.775[a]	7	2172.682	2.297	.105
	NOVELCUP_TOTAL3	2110.161[b]	7	301.452	.353	.911
Intercept	FAMCUP_TOTAL3	79894.984	1	79894.984	84.478	<.001
	NOVELCUP_TOTAL3	102491.400	1	102491.400	120.034	<.001
Sex	FAMCUP_TOTAL3	1855.301	1	1855.301	1.962	.189
	NOVELCUP_TOTAL3	319.881	1	319.881	.375	.553
Condition	FAMCUP_TOTAL3	1037.166	1	1037.166	1.097	.317
	NOVELCUP_TOTAL3	355.811	1	355.811	.417	.532
Site	FAMCUP_TOTAL3	16.200	1	16.200	.017	.898
	NOVELCUP_TOTAL3	47.752	1	47.752	.056	.817
Sex * Condition	FAMCUP_TOTAL3	765.456	1	765.456	.809	.388
	NOVELCUP_TOTAL3	602.744	1	602.744	.706	.419
Sex * Site	FAMCUP_TOTAL3	1202.071	1	1202.071	1.271	.284
	NOVELCUP_TOTAL3	43.955	1	43.955	.051	.825
Condition * Site	FAMCUP_TOTAL3	9872.064	1	9872.064	10.438	.008
	NOVELCUP_TOTAL3	575.397	1	575.397	.674	.429
Sex * Condition * Site	FAMCUP_TOTAL3	151.082	1	151.082	.160	.697
	NOVELCUP_TOTAL3	17.381	1	17.381	.020	.889
Error	FAMCUP_TOTAL3	10403.194	11	945.745		
	NOVELCUP_TOTAL3	9392.402	11	853.855		
Total	FAMCUP_TOTAL3	103392.839	19			
	NOVELCUP_TOTAL3	126215.211	19			
Corrected Total	FAMCUP_TOTAL3	25611.969	18			
	NOVELCUP_TOTAL3	11502.563	18			

a. R Squared = .594 (Adjusted R Squared = .335)

b. R Squared = .183 (Adjusted R Squared = -.336)

Table 10: SPSS Output of Phase 3 Three Chamber Familiar Cup vs Novel Cup

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	789257.639	1	789257.639	72.165	<.001
Sex	4326.375	1	4326.375	.396	.545
Condition	1049.736	1	1049.736	.096	.764
Site	47334.504	1	47334.504	4.328	.067
Sex * Condition	11390.552	1	11390.552	1.041	.334
Sex * Site	10382.719	1	10382.719	.949	.355
Condition * Site	7413.646	1	7413.646	.678	.432
Sex * Condition * Site	62589.153	1	62589.153	5.723	.040
Error	98432.109	9	10936.901		

Table 11: SPSS Output of Ladder Task Latency

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	53482.573	1	53482.573	120.007	<.001
Sex	391.471	1	391.471	.878	.373
Condition	1382.238	1	1382.238	3.102	.112
Site	1818.842	1	1818.842	4.081	.074
Sex * Condition	456.250	1	456.250	1.024	.338
Sex * Site	2190.520	1	2190.520	4.915	.054
Condition * Site	828.694	1	828.694	1.859	.206
Sex * Condition * Site	17.700	1	17.700	.040	.846
Error	4010.975	9	445.664		

Table 12: SPSS Output of Ladder Climb Time

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	44807.142	1	44807.142	54.105	<.001
Sex	11265.524	1	11265.524	13.603	.004
Condition	4177.161	1	4177.161	5.044	.046
Site	421.286	1	421.286	.509	.491
Sex * Condition	2081.250	1	2081.250	2.513	.141
Sex * Site	8117.752	1	8117.752	9.802	.010
Condition * Site	9543.372	1	9543.372	11.524	.006
Sex * Condition * Site	.000	0	.	.	.
Error	9109.736	11	828.158		

Table 13: SPSS Output of Weighted Door Time Pushing on Door

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Application Logo

PI :	Rogers, Tiffany Danielle
Protocol #	2024-0054
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Approved :	12/12/2024
Expires :	12/12/2027
Title :	Completion of Optogenetic and Behavioral Analysis of Social Interaction in Mice

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