The effects of psilocybin on prefrontal-cortical-dependent cognitive and behavioral processes in mice

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November 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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Abstract

Major Depressive Disorder (MDD) is a debilitating psychiatric illness impacting millions of individuals globally. Environmental stressors and genetic predispositions are believed to underly altered neural circuitry in MDD. Existing pharmacological interventions targeting serotonergic modulation, implicated in the neurobiology of MDD, are inadequate. Presently available treatment options are slow to take effect, are not efficacious for many MDD patients, and may give rise to various undesirable side effects. The discovery and development of superior treatment compounds and protocols is critical in improving the disease burden of MDD. Psilocybin is a classical serotonergic psychedelic compound found in many species of fungi. Recent clinical evidence suggests its promising therapeutic potential, but basic scientific investigations are lacking. The present thesis aimed to explore how psilocybin modulates mouse behavior in preclinical models of stress and behavior. Prior to undertaking this body of work, little was known about how psilocybin would affect the behavior of stress-naïve and chronically-stressed mice in both simple and complex cognitive tests.

In the first section of this thesis, we performed a standard preclinical test of psilocybin's prefrontal-cortical serotonergic agonism to observe differential head twitch responses in escalating drug doses. Psilocybin administered at 1.0mg/kg induced a sharp inflection in number of head twitches, suggesting adequate serotonin receptor subtype 2A (5-HT2AR) agonism in the prefrontal cortex (PFC) (Erkizia-Santamaría et al., 2022; González-Maeso et al., 2007; Halberstadt & Geyer, 2018; Schmitz et al., 2022). Following drug testing, we incorporated a battery of simple behavioral tests to determine whether psilocybin alters depression- and anxiety-relevant behaviors in stress-naïve mice. Alterations in behavior were not observed at 24

hours and 7 days post-drug treatment for either sex. In the second section of this thesis, we used two robust chronic stress paradigms to induce quantifiable stress responses in mice. Chronic Social Defeat Stress and Chronic Witness Defeat Stress induced a strong stress-susceptible phenotype in both female and male mice. Stress was followed by simple behavioral testing and Probabilistic Reversal Learning, an operant reward learning paradigm. In the third section of this thesis, we combined the stress and behavioral testing protocols from the second section with 1.0mg/kg systemic psilocybin to observe any drug-induced behavioral alterations. Unstressed and stressed female and male mice did not exhibit pre-treatment or post-treatment changes in reward-oriented behaviors. This thesis presents a novel protocol of preclinical behavioral pharmacology with relevance for MDD. It may be expanded to include testing of other psychedelic compounds of interest, and provides a unique platform of screening novel MDD therapeutics in a clinically-translational task measuring cognitive processes.

Resumé

Le trouble dépressif majeur (TDM) est une maladie psychiatrique invalidante qui touche des millions de personnes dans le monde. Il est généralement admis que des facteurs de stress environnementaux et des prédispositions génétiques sont à l'origine de l'altération des circuits neuronaux dans le TDM. Les interventions pharmaceutiques existantes qui modulent la sérotonine, impliquée dans la neurobiologie du TDM, sont inadéquates, notamment parce qu'elles sont lentes à faire effet, ne sont pas efficaces pour de nombreux patients atteints de TDM, et peuvent donner lieu à divers effets secondaires indésirables. La découverte et le développement de molécules et de protocoles de traitement plus efficaces sont essentiels pour soulager les millions de personnes souffrants de TDM. La psilocybine est une molecule psychédélique sérotoninergique classique présente dans de nombreuses espèces de champignons. Des études cliniques récentes suggèrent que la psilocybine est un antidépresseur, mais il existe peu d'études scientifiques fondamentales sur son mode d'action. La présente thèse visait à explorer comment la psilocybine affecte le comportement des souris dans des modèles précliniques de stress chronique. Avant d'entreprendre ce travail, nous savions peu de choses sur la façon dont la psilocybine affecterait le comportement des souris naïves au stress et chroniquement stressées, que ce soit dans des tests cognitifs simples ou complexes.

Dans notre première expérience, nous avons utilisé un test préclinique établi qui mesure des mouvements rapides et involontaires de la tête de la souris comme indicateur de l'agonisme au niveau des récepteurs de la sérotonine dans le cortex préfrontal (CPF). Nous avons mesuré une augmentation de ces mouvements de la tête après injection de 1,0 mg/kg de

psilocybine, ce qui indique l’activation du sous-type 2A des récepteurs de la sérotonine dans le CPF (Erkizia-Santamaría et al., 2022; González-Maeso et al., 2007; Halberstadt & Geyer, 2018; Schmitz et al., 2022). Ensuite, nous avons utilisé plusieurs tests simples de comportement pour observer les changements de comportement en relation avec l'anxiété et la dépression. Nous n'avons pas observé de changements 24 heures ou 7 jours après administration de la psilocybine. Deuxièmement, nous avons utilisé des modèles de stress chronique pour observer les effets du stress sur les comportements anxieux, dépressifs et anhédoniques. Nous avons observé des altérations du comportement chez les souris des deux sexes. Enfin, nous avons combiné le stress chronique avec la pharmacologie comportementale pour observer les effets de 1,0 mg/kg de psilocybine sur ces mêmes comportements. Nous n'avons pas découvert les effets du traitement. Ce travail de thèse contient un nouveau protocole pour la recherche préclinique de medicaments.

Contribution of Authors

Chapter 1: Introduction

Juliet Meccia wrote this section in collaboration with Dr. Rosemary Bagot.

Chapter 2: Literature Review

Juliet Meccia wrote this section in collaboration with Dr. Rosemary Bagot.

Chapter 3: Rationale and Hypothesis

Juliet Meccia wrote this section in collaboration with Dr. Rosemary Bagot.

Chapter 4: Methods

Juliet Meccia designed the experiments and protocols in collaboration with Dr. Rosemary Bagot.

Chapter 5: Results

Drug administration and testing, stress protocols, and behavioral training and testing were conducted by Juliet Meccia. Undergraduate students Sophia Cumplido-Wilson and Anil Esleben assisted with behavioral training in the third experiment. Behavioral analysis and scoring were completed by Juliet Meccia. Eshaan Iyer assisted with the processing of operant behavioral data through custom R scripts. Dr. Rosemary Bagot guided interpretations of the data and results.

Chapter 6: Discussion

Juliet Meccia wrote this section in collaboration with Dr. Rosemary Bagot.

Acknowledgements

Over the past two years as a graduate student, many folks have played important roles and deserve acknowledgement. First, I would like to thank my thesis supervisor Dr. Rosemary C. Bagot for her interest in fostering my new ideas despite the novel and unfamiliar research directions, and her guidance in the completion of important milestones as a graduate student. Thank you to my committee members Dr. Jonathan Britt and Dr. Tak Pan Wong for their time and feedback on my research plans and experiments. Thank you to my IPN mentor Dr. Reza Sharif-Naeini for the important discussions and chairing my MSc seminar.

I would also like to thank members of the Bagot lab for their support over the years. This is a group of talented folks whose skills and expertise collectively span a broad range of scientific interests. Thank you to Dr. Joelle Lopez for tirelessly working through complicated red tape and editing my manuscript. Sophia Cumplido-Wilson and Anil Esleban, two undergraduate research volunteers who assisted with several behavioral experiments, were a pleasure to work with and get to know. I also express my thanks to Eshaan Iyer for assistance with processing raw operant behavioral data. Thank you to Gabrielle Siemonsmeier for the comradery, on-point pop culture references and proofreading my French to ensure any accidental faux-pas were avoided.

To my friends, scattered as we may be across the globe, thank you for being there for me, making me laugh, and reminding me that the truly important thing in life is human interaction. To the Grateful Dead, ABBA, and Frank Zappa, who on long lab days were relied upon as auditory sources of motivation and inspiration to keep it real. Thank you to the fungus among us – what a long, strange trip it's been.

Most importantly, best-for-last, thank you to my beyond-amazing family – your constant support has been uplifting and always buoyed my spirits, and for this I am eternally grateful. I am exceptionally lucky to have such loving network of wonderful people who never fail to be my biggest cheerleaders. To my parents, and to Jeff, my life partner, ‘thank you’ does not even begin to cover how grateful I am for your enduring support, your constant readiness to be there for me through anything and everything. To Cleo – thank you for always knowing just the right moment to demand cuddles and belly rubs.

Chapter 1: Introduction

Major depressive disorder (MDD) is a debilitating psychiatric illness estimated by the World Health Organization to impact 322 million individuals worldwide. Traditional pharmacological interventions are often ineffective and may cause undesirable and potentially dangerous side effects – there is a pressing need to discover more effective and well-tolerated anti-depressant compounds (Jakobsen et al., 2017; Penn & Tracy, 2012). Interest in the anti-depressant and therapeutic potential of serotonergic psychedelic compounds such as psilocybin has surged in recent years (Vollenweider & Kometer, 2010; Vollenweider & Preller, 2020). While human clinical research suggests psilocybin holds promise as a rapid and long-lasting antidepressant (Barrett et al., 2020; Carhart-Harris et al., 2016; Griffiths et al., 2016), little is known about how its acute mechanisms of action result in long-term changes in behavior and neural circuit connectivity. Human neuroimaging studies point to both acute and sustained modulation of functional connectivity in key brain networks (Barrett et al., 2020; R. L. Carhart-Harris et al., 2012, 2016, 2017; Girn et al., 2022), and emerging preclinical models evidence implicates psilocybin-induced prefrontal cortical (PFC) and hippocampal alterations as therapeutically important (Cao et al., 2022; Hesselgrave et al., 2021; Shao et al., 2021b). It is unknown how psilocybin may alter stress-induced cognitive and affective impairments in complex and translatable PFC-dependent preclinical behavioral models. To address this fundamental knowledge gap, the author developed a novel protocol combining established mouse stress paradigms with pharmacological manipulations to observe the effect of psilocybin on behavioral tests of anxiety-like behavior and a translational reward learning paradigm probing

anhedonia and cognitive processes. To our knowledge, this unique combination is the first reported instance of utilizing translational stress manipulations and complex cognitive tasks to reveal psilocybin-induced changes in female and male mouse behaviors.

Chapter 2: Literature Review

2.1 Depression

Major Depressive Disorder (MDD) is a mood disorder arising from a confluence of factors, including genetic predisposition, neurobiological underpinnings, environmental stressors, psychological processes, health status, and social determinants (Schotte et al., 2006). The long-term consequences of MDD greatly impact patient quality of life – depression is linked to poor health and disease outcomes (Gaynes et al., 2002), social isolation (Santini et al., 2015), unemployment (Lerner et al., 2004), and increased risk of mortality (Simon & VonKorff, 1998; Wulsin et al., 1999). MDD presents as a combination of various cognitive and affective symptoms that give rise to functional impairments and endure for at least two weeks – episodes of depression may be singular, recurring, or enduring without periods of remission (Malhi & Mann, 2018). Cognitive symptoms such as alterations in executive functioning lead to decreased attention and focus, memory impairments, and dysfunctions in goal-directed behavior (DeBattista, 2005; Knight & Baune, 2018; Lam et al., 2014). Affective symptoms present as depressed mood, feelings of hopelessness, apathy, and anhedonia (Hasin et al., 2018; Marin et al., 1993; Rakel, 1999). Anhedonia, or the reduction or inability to experience pleasure, is a key affective symptom in MDD and affects at least 70% of the patient population (Cao et al., 2019; Franken et al., 2007). The overlap between affective and cognitive symptoms is exhibited by anhedonia, which contributes to increased and unstable emotional variability (Bylsma et al., 2008; Rottenberg et al., 2005) thought to arise from dysfunctional and inappropriate reward processing and reactivity (Heininga et al., 2019; Kuppens & Verduyn, 2017). Aberrant functionality of reward pathways that are particularly sensitive to stress are believed to

contribute to anhedonia in MDD (Admon & Pizzagalli, 2015; Pizzagalli, 2014). Collectively, anhedonia and other MDD symptoms culminate in functional impairments that are diagnostically important as they represent the debilitating effects MDD has on a patient's livelihood and well-being (Malhi & Mann, 2018).

2.1.1 Stress as a risk factor for depression

Observations of what we now classify as depression and MDD have been reported throughout history for thousands of years (Jackson, 1986). Since the advent of modern epidemiology, the association between one or more stressful life events followed by psychiatric illness has been clear (Shorter, 2008). Stress is a primary causal factor in the development of single depressive episodes and MDD (Hammen, 2005). Disentangling the complex pathogenesis of MDD is confounded by the fact that while all individuals experience stress events over their lifetime, many prove to be resilient to such stressors and do not develop psychiatric illness. Over the past century, a plethora of clinical research has established that the percentage of individuals who report experiencing at least one adverse life event are significantly more likely to also suffer from MDD than individuals who have not (Mazure, 1998). For stress-susceptible individuals, MDD may present after isolated or chronic stressful events, and clinical evidence suggests many who are predisposed to the disorder are more frequently exposed to high-risk environments (Kendler et al., 1999). A year-long twin study exploring the causality of stressful life events on MDD estimates 75% of such events can be directly responsible for the onset of this psychiatric illness (Kendler et al., 1999). Understanding the link between external experiences and their influence on internal neurobiological processes as well as elucidating how stress impacts brain structure

and function with consequential effects on cognition and behavior is a primary goal of psychiatry research today. Furthering our comprehension of such complex processes is critical in treating and preventing MDD.

The brain is a neuroplastic organ, where the processing of both external and internal stimuli drives molecular and cellular processes which shape neuronal structural and functional connectivity (Holtmaat & Svoboda, 2009). Experienced stress alters dynamics of brain functioning, and some forms of temporary stressors are adaptively advantageous, providing important information about an individual's environment that are necessary for survival (McEwen et al., 2014). These acute forms of stress generally do not result in deleterious long-term consequences. Chronic stress, however, is known to play a role in the onset of various psychiatric disorders (such as MDD) and can result in lasting alterations in brain structure and function (de Kloet et al., 2005; McEwen, 2000; McEwen et al., 2016). Aberrant endogenous serotonergic neurotransmission and receptor morphology are observed in patients with MDD (Rajkowska, 2000), and serotonergic hypofunction is a postulated contributor (Mann, 1999). Recent frameworks propose that the importance of this serotonergic dysfunction may lie in its role as a modulator of glutamatergic transmission (Dale et al., 2016; Pehrson & Sanchez, 2014). Glutamatergic hypotheses of depression focus on the culpability of dysregulated brain-wide circuits and aim to integrate a holistic understanding of how stress drives molecular and cellular processes that alter excitatory and inhibitory transmission in glutamatergic pathways, ultimately resulting in affective, cognitive, and behavioral impairments (Paul & Skolnick, 2003; Sanacora et al., 2012; Sarawagi et al., 2021).

2.1.2 Sex differences in depression

Sex differences in MDD are known yet understudied. Women across cultures develop MDD at a higher rate than men (Albert, 2015; Kessler et al., 2009; Salk et al., 2017), though several confounding factors, such as women's greater likelihood of seeking treatment (Parker & Brotchie, 2010), may influence reported numbers. In women, MDD presents earlier and co-occurs with anxiety more frequently than in men (Piccinelli & Wilkinson, 2000). MDD in men may manifest as mood instability and substance use disorder (Marcus et al., 2005). The variation in symptoms and incidence rate between sexes suggests biological differences in stress sensitivity and susceptibility (Bangasser & Wiersielis, 2018; Wellman et al., 2018).

Treatment tactics and subsequent successes as well as concerns vary between the sexes. During psychotherapy treatment, men are more responsive to interpretive psychotherapy while women fare better with supportive psychotherapy (Ogrodniczuk et al., 2001). There are also sex differences in treatment response to pharmacological interventions – evidence points to women showing greater responsivity to selective serotonin reuptake inhibitors than men (Khan et al., 2005; Kornstein et al., 2000; Sramek et al., 2016), though such differences are not reliably observed in response to older-generation antidepressants, such tricyclics (Quitkin et al., 2002). Women are prescribed antidepressant drugs twice as frequently as men (Brody, 2020) and though some continue treatment during pregnancy (Andrade et al., 2008; Bénard-Laribière et al., 2018; Cohen et al., 2006), evidence suggests the drugs may be teratogenic (Alwan et al., 2016; Gao et al., 2018). Sex differences in MDD from disorder presentation, differential treatment response, and biological considerations in drug treatment are understudied. It is imperative that

both preclinical and clinical fields consider these disparities in psychiatry and drug discovery research to move towards an equitable understanding of MDD.

2.1.3 Pharmacological treatment of depression – current understandings and limitations

While psychotherapy and cognitive behavioral therapy (CBT) are evidence-based practices effective in treating MDD (Compton et al., 2004; David et al., 2018; Leichsenring et al., 2006), pharmacological interventions are the most frequently prescribed treatment protocol (Olfson et al., 2002; Olfson & Marcus, 2009; Robinson et al., 2005). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressant, with prescription rates skyrocketing since their initial development (Mojtabai & Olfson, 2014; Pirraglia et al., 2003). While we do not understand the complete pharmacodynamic profile of SSRIs, their antidepressant effects are believed to originate from their actions in increasing extracellular levels of serotonin by inhibiting presynaptic re-uptake (Nutt et al., 1999). Despite the broad use of SSRIs in the treatment of depression, only about half of patients find them efficacious, and such large discrepancies in response contribute to the complexities of adequate treatment (Jakobsen et al., 2017; Penn & Tracy, 2012). It is also unclear how large a role the placebo effect plays in existing studies, a notoriously difficult hurdle in clinical trials (Kirsch, 2014; Rief et al., 2009). Well-documented in psychiatric research, the interplay of treatment expectation and emotional and contextual information can contribute to beneficial effects observed in the control group (Rutherford et al., 2017; Wager & Atlas, 2015). Such effects can obfuscate contrast between treatment and control groups – solutions are limited, and while the use of active placebos has become more common, a reconceptualization of clinical trial design to include more

holistic, patient-tailored care may be warranted (Jonas & Chez, 2004; Mora et al., 2011). Robust evidence shows that SSRIs alone are less efficacious than when used in tandem with psychotherapy or CBT (Cuijpers et al., 2010, 2012; de Jonghe et al., 2001; Pampallona et al., 2004), but most patients do not receive individually-tailored treatment protocols despite evidence-based recommendations (Keller, 2003; Olfson et al., 2016; Westen et al., 2004). There are also patients who find no relief from pharmacological or psychotherapeutic interventions – treatment-resistant MDD has devastating impacts on patient quality of life and deleterious effects on physical and mental health (Greden, 2001; Rathod et al., 2022).

With all pharmacological treatment there exists the possibility of side effects, and many associated with antidepressant drugs are unpleasant and undesirable, leading to discontinuation of treatment regardless of success (Anderson, 1998; Hu et al., 2004; Hunot et al., 2007). Gastrointestinal and metabolic disturbances are common (Moretti et al., 2003; Oliva et al., 2021). Decreased sexual libido in women and sexual dysfunction in men are among the top reasons patients report cessation of treatment (Balon, 2006; Rothmore, 2020). Gastrointestinal and sexual side effects are commonly linked to the serotonergic action of antidepressant drugs – serotonin receptors (5-HTRs) are widespread not only in the central nervous system, but peripherally and systemically, and are involved in almost every homeostatic function (Berger et al., 2009). Even when side effects are minimal or tolerable, female patients who are pregnant or may become pregnant may discontinue use due to their understudied teratogenic potential (Alwan et al., 2016; Gao et al., 2018; Koren & Nordeng, 2012). Patient intolerability of side effects and concerns about fetal developmental risks highlight the inadequacies in our existing treatment protocols.

Given that SSRI antidepressants are unsuitable for many individuals, developing safe and rapid-acting compounds lacking unwanted effects is crucial in improving patient quality of life and disease outcome. The past decade of revitalized research into serotonergic psychedelic compounds has revealed promising antidepressant effects and prompted a flurry of clinical research testing the efficacy of drugs like psilocybin in cohorts of MDD patients (Carhart-Harris et al., 2018; Carhart-Harris et al., 2016, 2017; Davis et al., 2021; Gukasyan et al., 2022). Our current clinical and preclinical comprehension of psilocybin's therapeutic efficacy is discussed below in Section 2.3.

2.1.4 Towards a comprehensive neurobiological understanding of MDD: from the prefrontal cortex to psilocybin

It is imperative that we broaden our understanding of MDD, its complex pathophysiology, and develop favorable antidepressant treatments. Considering psilocybin as our drug of interest, we can explore its pharmacological profile and make connections with clinical and preclinical findings indicating long-term therapeutic changes in depressed patients and animal models of depression. The influence of stress on the PFC is implicated in cognitive and affective psychiatric symptomatology, and such effects have long-reaching consequences via alterations to PFC-linked neural circuitry. Understanding PFC 5-HTR dynamics reveals how serotonergic psychedelic agonists such as psilocybin may drive local modulation, with downstream consequences. Reviewing the role of such extended circuits and the implications of their impairments in MDD supports a theoretical framework that psilocybin acutely alters PFC-linked circuit functioning and gives rise to long-lasting antidepressant and effects.

2.2 The prefrontal cortex and depression

2.2.1 Prefrontal cortical subdivisions collectively govern higher-order processes

The PFC is the brain's top-down regulator, widely studied for its essential role in executive functioning and its involvement in many neural circuits (Euston et al., 2012; Miller, 2000). The PFC is an important cortical area comprised of anatomically and functionally distinct loci. In humans, the PFC can be subdivided into dorsolateral, ventrolateral, dorsomedial, and ventromedial areas. Each subdivided locus is involved in the governance of essentially every aspect of cognition. The dorsolateral PFC maintains working memory processes (Petrides, 2000) and contextually-dependent decision-making and subsequent behavioral responses (Heekeren et al., 2006; Philiastides et al., 2011). The ventrolateral PFC drives response inhibition and behavioral flexibility (Aron et al., 2004; Fellows, 2003; Levy & Wagner, 2011). The dorsomedial PFC regulates social cognition (Eickhoff et al., 2016), emotional valence of familiarity (Gobbini et al., 2004), and self-referential cognition (Wagner et al., 2012). Through its vast connectivity with limbic regions, striatum, the ventral tegmental area, and thalamic nuclei, the ventromedial PFC is critically important in emotional cognition (Winecoff et al., 2013), reward-based and goal-oriented motivational behaviors (Gläscher et al., 2009; Hiser & Koenigs, 2018), and decision making (Hampton et al., 2006). In general, these PFC loci can be categorized based on anatomical and functional characteristics. Efforts to map cross-connectivity and understand which areas are responsible for specific cognitive processes have emphasized the dorsolateral PFC and ventromedial PFC as subdivisions critical for typical and perturbed cognitive functioning.

The dorsolateral PFC and the ventromedial PFC are generally considered to differ in their responsibilities. The dorsolateral PFC sits above the ventromedial PFC, an area comprised of two

highly-interconnected loci, the medial PFC, and the orbitofrontal cortex. The orbitofrontal cortex and dorsolateral PFC both process stimuli related to reward sensitivity and outcome valuation to drive goal-oriented and decision-making behavior (Gourley et al., 2016; Grabenhorst & Rolls, 2011). The orbitofrontal cortex maintains flexible value representations that reflect real-time information and future predictions (Gottfried et al., 2003; Schoenbaum et al., 2003), and sends excitatory projections to the ventromedial PFC which drives goal-directed behaviors (Der-Avakian & Markou, 2012). Dysregulation in orbitofrontal cortical and ventromedial prefrontal cortical connectivity is observed in fMRI scans of patients with MDD, and drives alterations in affective reward sensitivity and anhedonia (Keedwell et al., 2005; Steinmann et al., 2022; Young et al., 2016). These distinct PFC loci regulate typical functioning states necessary for myriad behaviors, and it is imperative we use this knowledge to guide our exploration of core symptoms of MDD.

2.2.2 The prefrontal cortex and its extended circuits in Major Depressive Disorder

Advances in modern neuroscience have unveiled key brain regions responsible for systematic integration and processing of stressful stimuli. Research into the neurobiological underpinnings of MDD has given rise to conceptual frameworks highlighting the importance of stress-induced alterations in neural activity (Hammen, 2005) and cortically-linked circuit impairments as drivers of cognitive and affective symptoms (Hare & Duman, 2020). The PFC is widely studied for its essential role in executive functioning and its involvement in many neural circuits (Euston et al., 2012; Miller, 2000). Because of its hierarchical position as a primary regulator of neural processes, the PFC is also heavily implicated in MDD symptomatology (George

et al., 1994; Rogers et al., 2004). PFC loci moderate responsivity to emotionally-salient and stressful stimuli, ultimately driving behavioral output (Arnsten, 2009). Interconnected and bidirectional PFC projections with the hippocampus, nucleus accumbens, amygdala, ventral tegmental area, and thalamus (among other regions) comprise neural circuits that govern many cognitive and behavioral processes (Anastasiades & Carter, 2021; Fanselow & Dong, 2010; Groenewegen et al., 1999; Miller, 2000). Important inter-regional circuit dynamics contribute to synchronous communication, and neural circuit dysfunction results in psychiatric impairment (Ressler & Mayberg, 2007). Ventromedial PFC projections to the amygdala are involved in fear learning, emotional memory, and anhedonia (Gee et al., 2013; Herry et al., 2008; Malin & McGaugh, 2006; Orsini et al., 2011; Young et al., 2016). PFC projections to the ventral tegmental area are involved in reward, motivation and cognitive processes (Carr & Sesack, 2000). Reciprocal PFC-thalamic connections, comprised of spatially distinct layer- and cell-specific divisions, are critically involved in cognitive functioning (Anastasiades et al., 2021; Collins et al., 2018; Morishima et al., 2011). PFC projections to the nucleus accumbens are integrated with incoming signals from other glutamatergic and dopaminergic inputs to regulate cognition, social behavior, reward, motivation and emotion (Floresco, 2015; Goto & Grace, 2008). Dysregulation of this integration is thought to contribute to the affective and behavioral deficits of mood disorders, including anhedonia (Liu et al., 2021; Nestler et al., 2002).

2.2.3 Chronic stress as a tool for preclinical models of MDD

Species-specific brain differences and disease states are common obstacles in the cross-translation of preclinical and clinical neuroscience. Despite such innate distinctions, important

genomic, structural, and functional conservations between the murine and human brain allow for basic scientific investigations into psychiatric illnesses (Assaf et al., 2020; Sjöstedt et al., 2020; Song et al., 2020; Strand et al., 2007). While it is not possible to develop animal models that fully mirror psychiatric illnesses like MDD, a clinically-informed focus allows us to profile specific symptoms and deficits (Nestler & Hyman, 2010). The effects of stress on brain morphology, structure, and function are well-understood to be primary contributors in MDD (Arnsten, 2009; Belleau et al., 2019; McEwen, 2000; McEwen et al., 2016). Preclinically, we can use stress as a tool to model depression and observe consequences on animal behavior. Such models provide access to an expansive scientific toolkit and allow for observations without the inherent confounds of clinical work. Additionally, animal models are essential in causal and mechanistic explorations. Preclinical models have contributed to our fundamental understanding of how stress alters epigenetic (Bagot et al., 2014), developmental (Murthy & Gould, 2018), and brain-wide circuits (Knowland & Lim, 2018), contributing to depression-related behaviors.

Chronic stress alters cellular and molecular processes in the PFC and interconnected regions with deleterious effects on cognitive and affective behaviors (Bittar et al., 2021; Gilabert-Juan et al., 2013; W.-Z. Liu et al., 2020; Lowery-Gionta et al., 2018). Methods for inducing chronic stress in rodents may be physical, hormonal, environmental, or social – chronic social defeat stress (CSDS) is widely used as a manipulation that results in social withdrawal and anhedonia-like and anxiety-like behavior in male mice (Kudryavtseva et al., 1991; Rygula et al., 2005). CSDS compromises the PFC and extended neural circuits implicated in emotion, reward, and anhedonia (Cao et al., 2010; Diaz & Lin, 2020; Hultman et al., 2016; Venzala et al., 2013). Enduring changes to neuronal structure (Colyn et al., 2019) and function (Santos-Costa et al., 2021; Veeraiah et al.,

2014; Wang et al., 2016) are commonly observed following CSDS. In layer V PFC pyramidal neurons, CSDS induced long-term decreases in apical dendritic spine density with associated increases in anxiety-like behavior and social avoidance (Colyn et al., 2019). CSDS enduringly decreases PFC GABA levels and leads to glutamatergic dysfunction (Venzala et al., 2013; Wang et al., 2016), and recent evidence suggests lateralization of PFC glutamatergic control over anxiety-like behaviors following CSDS (Santos-Costa et al., 2021). After CSDS, mice exhibit decreased metabolism of PFC GABA and glutamate that is correlated with increased anhedonia-like and anxiety-like behavior (Veeraiah et al., 2014). Widespread consequences on corticolimbic circuits originate from CSDS's effects on the PFC and are observed as impairments in anxiety-like, anhedonia-like, and social behaviors (Colyn et al., 2019; Hultman et al., 2016). Taken together, there is robust evidence that CSDS alters PFC neurochemistry and structure and results in behavioral deficits relevant to depression.

Given the importance of sex differences in MDD (see Section 2.1.2), ensuring preclinical depression modeling includes female animals is paramount (Lopez & Bagot, 2021). While CSDS is widely used as a stressor specifically for male mice, use of social stress paradigms in females are less frequent and most existing assays have focused on unpredictable changes to home-cage composition (Koert et al., 2021; Schmidt et al., 2010) or using the presence or odor of male mice to induce aggression (Newman et al., 2019; van Doeselaar et al., 2021). Chronic witness defeat stress (CWDS) has recently been developed as a CSDS-analogous manipulation involving the vicarious observation of CSDS by female mice (Iñiguez et al., 2018; Warren et al., 2020). Using CSDS in tandem with CWDS provides opportunities to observe the effects of directly-related

stressors and minimizes the confounds of exposing female and male animals to different assays, allowing for sex-inclusive investigations with rigorous experimental design.

2.2.4 Preclinical profiling of anhedonia and reward in translatable prefrontal-cortex-dependent paradigms

Disruptions of extended cortical circuits result in cognitive and behavioral symptoms observed in depression and mood disorders. Combining stress-based models of depression with PFC-dependent behavioral tasks and paradigms disrupted in MDD results in a robust protocol that can be used in testing novel antidepressants. By using behavioral tests that capture the fundamental symptoms of anhedonia, anxiety, and reward dysfunction, we can map deficits to well-established neural circuits governing such processes.

Simple assays probing affective behavior are frequently used as indicators of therapeutic and antidepressant potential in psychiatric drug discovery research (Hånell & Marklund, 2014). The PFC plays a role in the neural circuit governing forced swim testing (Warden et al., 2012), commonly used to quantify effects of potential antidepressant pharmaceutical compounds. Multiple interpretations of what types of behaviors this test measures exist – one model postulates that duration of animal immobility (floating; not actively swimming) indicates increased anhedonia and 'behavioral despair', while another proposes increased duration of active swimming indicates coping and behavioral adaptation and therefore decreased anhedonia (Can et al., 2012; Molendijk & de Kloet, 2015; Yankelevitch-Yahav et al., 2015). Social interaction testing uses a naturalistic approach to observe the strength of social approach and avoidance behavior, is sensitive to stress, and involves complex regulation by the PFC of many subcortical regions such as the amygdala, striatum, and hippocampus (Kaidanovich-Beilin et al., 2011; Ko,

2017). The open field test is a widely-used measure of anxiety-like and fear behavior in rodents, and involves PFC-amygdala pathways (W.-Z. Liu et al., 2020; Murray et al., 2011). The social preference test is another naturalistic task measuring social cognition, reward and motivation, and anxiety, behaviors which are dysfunctional in MDD, and which are dependent on the PFC's broad regulatory capabilities (Bicks et al., 2015; File & Seth, 2003; Overstreet, 2012).

Recent frameworks focusing on the overlap between reward cognition and anhedonia in MDD have proposed utilizing clinical paradigms and findings to reconceptualize assays used in preclinical animal models (Kangas, Der-Avakian, et al., 2022). As previously discussed, aberrant functioning of extended PFC circuits drives dysfunctional reward sensitivity and processing, resulting in anhedonia (Admon & Pizzagalli, 2015; Der-Avakian & Markou, 2012; Keedwell et al., 2005; Pizzagalli & Roberts, 2022). Reversal learning tasks, which are used across species, utilize probabilistic reward contingencies to measure PFC-dependent aspects of cognition and behavior (Butter, 1969; Fellows, 2003; Schoenbaum et al., 2000). Probabilistic reversal learning (PRL) paradigms may also be used to test an individual's motivation and sensitivity to rewarding stimuli and their behavioral strategy in response to reward or loss. Patients with MDD and other psychiatric illnesses show decreased sensitivity to rewards in reversal learning tasks, with performance impairments linked to circuit dysfunction (Waltz & Gold, 2007; Mukherjee et al., 2020; Clark et al., 2004; Dombrovski et al., 2015; Cools et al., 2002; Murphy et al., 2003). Human studies have revealed that specific PFC loci are engaged during and responsible for different aspects of reversal learning tasks, with the dorsolateral PFC playing a role during decision-making (Mitchell et al., 2009; Remijnse et al., 2005), the orbitofrontal cortex updating expected outcomes through stimulus-based information to guide behavior (Hornak et al., 2004; O'Doherty

et al., 2001; Tsuchida et al., 2010), the ventromedial PFC governing reward and feedback valuation inhibitory cognitive processes (Freyer et al., 2009; Hornak et al., 2004), and the ventrolateral PFC integral to reversal learning (Cools et al., 2002; Rygula et al., 2010).

Preclinical investigations have used PRL in operant chambers where an animal can engage with its environment to obtain consumable food rewards. Used in this way, PRL can probe the neural mechanisms underlying anhedonia by quantifying reward-seeking measures indicating motivation in the pursuit of gain, and to examine how sensitivity to gain and loss are incorporated into learning and behavioral strategies. In rodents, stress impairments on PRL task performance mirrors clinical findings from cohorts of patients with MDD. Following exposure to chronic stress, rodents exhibit deficits in reward learning that are associated with impaired function of the PFC and its extended reward circuits (Der-Avakian et al., 2017; Joffe et al., 2019; Lamontagne et al., 2018). These findings point to the direct effects of stress on neurobiological function and highlight the link between reward processing and anhedonia. Expanding the use of PRL paradigms in preclinical models of MDD to include screening of novel compounds like psilocybin can provide greater insight into treatment protocols that may address deficits in circuit-level functioning to ameliorate core symptoms such as anhedonia.

2.3 Psilocybin as a novel therapeutic

Mushrooms containing psilocybin have been used in North, Central, and South America for millennia (Furst, 1972; Schultes et al., 1992). Indigenous use of psilocybin-containing mushrooms in the Western Hemisphere is thought to date at least as far back at 1000 B.C. (Schultes, 1972). Western science's interest in therapeutic potential of the indoleamine

compound was piqued in 1958, when Albert Hoffman isolated the drug from mushrooms brought back from Mexico (Hofmann et al., 1958). Hofmann, the Sandoz chemist who first synthesized LSD, held great curiosity about therapeutic effects of psychedelic drugs, and during the 1960s Sandoz produced psilocybin tablets for use in tandem with psychotherapy (Nichols, 2020). In 1970, psilocybin was classified as a Schedule I substance by the United States Drug Enforcement Agency, rendering further research difficult. Psychedelic research remained a dormant field until recently, when a growing resurgence of interest opened the doors to exploring the effects of these drugs.

2.3.1 Psilocybin in clinical research

Renewed investigations into the therapeutic potential of psilocybin in human experimental research and clinical trials support the use of psilocybin to treat mood disorders, including MDD. In foundational research, healthy participants who ingested 30mg/70kg of psilocybin during two or three experimental sessions reported feelings of intense joy, peace, and harmony during sessions, as well as lasting positive mood changes and contentedness two months post-ingestion (Griffiths et al., 2006). This seminal finding of psilocybin-induced positive mood has paved the way for research investigating potential benefits for patients with depression and various other psychiatric illnesses. In patients with advanced-stage cancer, psilocybin administration decreased anxiety and lowered scores on the Beck Depression Index, with effects lasting six months post-drug (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). A two-part trial testing 10mg and 25mg of psilocybin in treatment-resistant depression reported symptom reductions at 5 weeks, 3 months, and 6 months post-treatment (Carhart-

Harris et al., 2018). These findings were recently replicated in cohorts of patients with MDD, with antidepressant effects enduring as long as 12 months after psilocybin therapy sessions (Carhart-Harris et al., 2021; Davis et al., 2021; Gukasyan et al., 2022). The lasting amelioration of depression symptoms established in these studies suggests that psilocybin exerts sustained antidepressant effects, yet the mechanism remains to be determined.

Recent studies have investigated the potential pro-cognitive effects of psilocybin therapy in patients with MDD, which may be linked to the drug's modulation of ACC and PCC activity (Doss et al., 2021). In this open-label study, non-medicated MDD patients underwent baseline testing followed by two psilocybin-assisted (20mg/70kg and 30mg/70kg) therapy sessions over two weeks. To control for non-specific symptom changes, a second group received treatment only two months after baseline screening. Following psilocybin therapy, patients reported fewer depression symptoms, and this was accompanied by increased cognitive flexibility and decreased perseverative errors in a set-shifting task (Doss et al., 2021). Longitudinal fMRI scans four weeks prior and one-week post-drug showed a general increase in dynamic functional connectivity between the anterior cingulate cortex and posterior cingulate cortex. Post-psilocybin connectivity increases were highest in patients with lowest baseline connectivity (Doss et al., 2021) suggesting that the drug may be especially beneficial for certain patient populations. Cognitive behavioral data from the previously-discussed study of retreat participants suggest that psilocybin post-acutely promotes cognitive creativity. (Mason et al., 2019). One day after psilocybin, participants exhibited increased divergent thinking in a picture concept task, generating a greater number of associations with more originality than at baseline and at 7-days, convergent thinking, measured by correct answers in the picture concept task, was increased.

Given mood and cognitive impairments in depression, the pro-cognitive effects of psilocybin may contribute to long-term therapeutic benefits.

2.3.2 Pharmacology of psilocybin

Psilocybin shares a similar chemical structure to serotonin (5-hydroxytryptamine; 5-HT) (Nichols, 2004). Psilocybin (4-phosphoryloxy-N,N -dimethyltryptamine) is an indoleamine pro-drug that, upon ingestion, is dephosphorylated into the active metabolite psilocin (4-hydroxy-dimethyltryptamine) (Hofmann et al., 1958; Nichols, 2004). Both are used in preclinical and clinical scientific research, though the compounds differ in chemical structure and bioavailability (Hasler et al., 1997; Passie et al., 2002). Once converted, psilocin crosses the blood-brain-barrier and directly binds with 5-HT receptors (Dinis-Oliveira, 2017).

Psilocybin signaling through 5-HTRs has been confirmed via radioligand binding assays, in vitro electrophysiology, and human and rodent pharmacological studies (Halberstadt et al., 2020; Halberstadt & Geyer, 2011a; Halberstadt & Nichols, 2010; Inserra et al., 2021; Nichols, 2004). 5-HTRs are comprised of fourteen receptor subtypes, thirteen of which are G-protein coupled receptors (GPCRs) (McCorvy & Roth, 2015; Nichols & Nichols, 2008), and are widely expressed throughout the brain. Serotonergic psychedelics bind both 5-HT1ARs and 5-HT2ARs to exert opposing effects of inhibition or excitation, respectively. Cortical 5-HT2ARs are known targets of psilocybin binding and responsible for mediating the drug's psychoactive and hallucinogenic effects (Quednow et al., 2012). The cortex is an important locus of the drug's actions (Aghajanian & Haigler, 1975; Blair et al., 2000; Halberstadt et al., 2011a; Halberstadt & Geyer, 2011a; Mckenna et al., 1990; Sard et al., 2005). In particular, acute drug-induced changes in PFC

functional connectivity (Carhart-Harris et al., 2017) and longer-term architectural alterations (Shao et al., 2021b) indicate that this cortical subdivision is directly targeted by psilocybin.

Preclinical investigations have revealed pharmacological mechanisms of psilocybin. 5-HT2ARs mediate psilocybin-induced rodent head-twitch response, a benchmark measure of acute psychedelic activity that is induced by all serotonergic psychedelics (Corne et al., 1963; Corne & Pickering, 1967; Halberstadt et al., 2011a, 2020). Acute psilocin-induced head-twitch response is absent in 5-HT2AR knockout mice (González-Maeso et al., 2007; Halberstadt et al., 2011a), and psilocybin-induced head-twitch is blocked by pre-treatment with the 5-HT2A/2CR antagonist ketanserin (Hesselgrave et al., 2021; Shao et al., 2021b). In rats, psilocin induces head-twitches in both male and female rats, with females showing an increased sensitivity, suggesting a potential sex difference (Tylš et al., 2016, p. 2016). In mice, 5-HT1AR signaling mediates psilocybin-induced suppression of locomotor and investigative activity (Halberstadt et al., 2011a). Psilocybin may show binding-affinity to other receptors, though more research is needed to determine specific interactions (National Institute of Mental Health - Psychoactive Drug Screening Program; Nichols, 2004; Ray, 2010; Roth et al., 2000).

2.3.3 Psilocybin in preclinical investigations

While rodent studies have demonstrated important aspects of psilocybin's pharmacological profile, we presently lack a comprehensive understanding of the drug's more complex actions, from acute cellular and molecular alterations to enduring behavioral changes. Basic investigations into acute drug-induced changes in simple locomotor behaviors do not provide clinically-relevant information (Halberstadt & Geyer, 2011b). fMRI data from mice

scanned during acute intravenous psilocybin administration shows correlative changes in functional connectivity networks associated with 5-HT and dopamine activity (Grandjean et al., 2021), suggesting that the drug may modulate both serotonergic and non-serotonergic circuits. This supports the idea that psilocybin may acutely modulate activity across neural circuits.

Exploration into the synaptogenic effects of psilocybin report intriguing findings – the drug acts as a psychoplastogen and promotes neural plasticity with lasting alterations in connectivity (Shao et al, 2021b). Increases in dendritic spines number and width were observed in deep-layer PFC pyramidal neurons of female and male mice for up to 34 days following a single systemic injection of 1.0mg/kg psilocybin (Shao et al, 2021b). The same study profiled the consequences of psilocybin-induced plasticity on behavioral processes. Chronically-stressed mice were tested in a learned-helplessness paradigm, and stress-susceptible subjects pretreated with psilocybin one day before testing showed reduced failed escape attempts following aversive foot-shocks, compared with controls (Shao et al., 2021a). Male mice who were subjected to chronic multimodal stress and exhibited decreased sucrose preference and female urine preference showed a restoration of such preferences 24-48 hours following 1.0mg/kg systemic psilocybin (Hesselgrave et al., 2021). These findings suggest psilocybin can reduce stress-induced behavioral impairments, though longer-term experiments focusing on complex MDD-associated behaviors are needed to profile potential long-lasting increases in spineogenesis and associated changes in behavior.

2.3.4 Finding a neural commonality for psilocybin across the research spectrum – the PFC

Current models of psychedelic activity all consider acute modifications of cortical control via 5-HTARs a key contributing factor in drug-induced perceptual, affective, and experiential changes. In the PFC, activation of 5-HT1ARs reduce membrane excitability and induces hyperpolarization, while activation of 5-HT2ARs increases membrane excitability to induce depolarization (Araneda & Andrade, 1991). It is hypothesized that psilocybin acutely acts as neuromodulator of 5-HTR signaling within the PFC, altering local microcircuit activity and potentially longer-range PFC-linked neural circuits. Findings from human clinical studies and preclinical pharmacological and behavioral interrogations point to the PFC as a primary target of psilocybin-induced acute neural alterations and enduring therapeutic effects (Cameron et al., 2023; Doss et al., 2021; Girn et al., 2022; Jefsen et al., 2021; Shao et al., 2021b). Exploring how PFC 5-HTR dynamics are involved in the modulation of cognitive and affective processes and their respective circuits is an important step in understanding the reach of psilocybin's therapeutic capabilities. Circuit dysfunction is thought to underlie the cognitive and behavioral impairments in MDD (Knowland & Lim, 2018). Given the importance of extended cortical circuit functions, understanding how psilocybin alters circuit dynamics is a crucial step in understanding its efficacy as a rapid-acting and long-lasting anti-depressant. The PFC is an important component of extended corticocortical, corticostriatal, and corticolimbic circuits which contribute to emotional, affective, motivational, and learning processes that are known to be impaired in psychiatric illness (Deisseroth, 2014; Heshmati & Russo, 2015; Nestler et al., 2002). Determining the extent to which psilocybin-induced PFC modulation may alter functionality of these extended circuits requires preclinical investigations aimed at capturing molecular, cellular, and behavioral signatures of the drug's acute and long-term effects. Preclinical experimental investigations

integrating clinical knowledge with an understanding of the neural circuit bases of behavior and cognition, such as this body of thesis work, have the potential to significantly advance efforts to uncover the mechanisms of action and therapeutic efficacy of novel antidepressants such as psilocybin.

Chapter 3: Rationale and Hypothesis

Preclinical investigations into the effects of psilocybin on simple and complex rodent behavior are few. Studies employing stress paradigms to examine the drug's modulatory actions of stress-induced behavioral deficits are essentially non-existent. A behavioral pharmacological protocol to test psilocybin is therefore necessary in determining preclinical profiles relevant to MDD. The aims for this project were:

1) **Establish appropriate and observable pharmacological actions of psilocybin in the Rodent Head Twitch Response test and explore subsequent changes in simple tests measuring anxiety-like behaviors.**
2) **Determine whether two widely used chronic stress paradigms induce a stress phenotype with alterations in a complex operant task of PFC-dependent cognitive processes.**
3) **Explore how psilocybin modulates behavioral metrics in stress-naïve and chronically-stressed mice.**

We hypothesize that, as reported in the literature, acute psilocybin will dose-dependently increase the number of head twitches and subsequently decrease anxiety-like behaviors exhibited by male and female mice. We also hypothesize that chronic stress will alter PFC functioning with such deficits observable in a probabilistic reversal learning operant paradigm. We finally hypothesize that psilocybin will reverse such stress-induced deficits.

Chapter 4: Methods

4.1 Animals

For all experiments, adult female and male C57 BL/6 mice from Jackson Laboratory (Bar Harbour, Maine) were used. Animals arrived at 7 weeks of age and habituated undisturbed to the main colony for 7 days prior to the commencement of experiments. Animals were group housed (5 animals per cage) for all experiments, with the exception of stress manipulations (see Section 4.3.2) and post-stress operant behavioral experiments (see Section 4.4.6). Animals were provided food and water *ad libitum* for the duration of the experiments, except during operant behavioral testing phases when food restriction is necessary – in such circumstances, mice were given 0.5-1 pellets of food daily following training, and maintained at a 80-90% of their pre-experimental body weight. All animals were kept on a 12 hour light/12 hour dark light cycle, with lights turning on at 7am and off at 7pm. All procedures were conducted in accordance with McGill University's Animal Care Committee and the Canadian Council on Animal Care.

4.2 Drugs

Psilocybin was provided by the Usona Institute in Fitchburg, WI under the Investigational Drug & Material Supply Program. A stock solution prepared by dissolving 2mg psilocybin powder in 10ml of 0.9% sterile saline was used to prepare further dilutions of 0.25mg/kg, 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg. Injection volume per animal was 0.01ml/g. Route of administration was intraperitoneal injection.

4.3 Stress protocols

4.3.1 CD1 screening for aggressive behavior

Male CD1 mice obtained from Charles River (Quebec, Canada) were used as aggressors in chronic social defeat stress and chronic witness defeat stress, and as target mice in social interaction testing (see section 4.4.1). Before commencing stress protocols (see section 4.3.2), CD1s were screened for aggressiveness to determine experimental selection of animals exhibiting adequate, but not extreme, aggressive behavior. Screening sessions took place over three consecutive days. Non-experimental male C57s were placed in the home cage of a CD1, where they remained until a criterion of either three minutes or 5 attacks by the CD1. Metrics recorded included latency to the first attack and total number of attacks. CD1s were selected as aggressors for subsequent stress protocols if they met a criterion of day 3 attack latency < 30 seconds and at least five attacks.

4.3.2 Chronic social defeat stress and chronic witness defeat stress

Chronic Social Defeat Stress (CSDS; for male mice) and Chronic Witness Defeat Stress (CWDS; for females) is a 10-day paradigm used to induce anxiety-like and depressive-like behavioral phenotypes in mice. These manipulations took place in a separate colony room used strictly for CSDS and CWDS. Large rat cages were divided by a custom perforated plexiglass insert. CD1 male aggressor mice (selected as per the criterion in 4.3.1) were placed on the right-hand side of the cage for 24 hours prior to beginning the experiment. This allowed the CD1 to establish its territory and ensured that subsequent entries by experimental male C57 mice were interpreted by the CD1 as intrusions. Control mice were housed in separated pairs, in the same room, and weighed daily. Female experimental mice were single-housed. On the first day of

CSDS, an experimental female witness mouse was placed in the empty left-hand side of the divided rat cage. An experimental male C57 was placed in the right-hand side of the cage containing the CD1 for eight minutes, or a maximum of 25 attacks by the CD1. CD1 attacks were logged by the experimenter, and if 25 attacks were met before the eight-minute trial duration, the experimental C57 was removed and replaced with a "buddy" male C57 (non-experimental). Through the perforated plexiglass divider, the female C57 witnessed CD1 attacks on the male C57. At the end of the trial, the female was removed and placed back in her home cage, and the male C57 was placed on the left-hand side of the divided cage. Each day, the pairing of male and female C57 mice and CD1 aggressor mouse was rotated, to ensure each day the C57 was exposed to a new CD1. Upon the completion of the final CSDS and CWDS session, all experimental C57s were single housed to prepare for subsequent behavioral testing.

4.4 Behavioral testing

4.4.1 Social interaction testing

Social interaction behaviors were recorded, tracked, and quantified using an overhead camera and Noldus Ethovision software. Twenty-four hours after the final defeat session, experimental mice were placed in a 44cm x 44cm white matte acrylic open arena under red light containing an empty social target cage on the perimeter of one wall and allowed to freely explore for 2.5 minutes. The experimental mouse was then removed, and a novel CD1 placed into the social target cage. The experimental mouse was then placed back into the arena and allowed to freely explore for 2.5 minutes. Quantification included total time spent in corners of the arena, total time in the interaction zone (defined as the area immediately around the social target cage),

velocity of movement, and total distance traveled. Calculation of the social interaction ratio (SI ratio) was used to determine stress susceptibility and resiliency, ultimately indicating the efficacy of the CSDS and CWDS protocols. SI ratio was calculated as *total time in the interaction zone during social target trial / total time in the interaction zone during non-social-target trial.* Animals with an SI ratio of less than 1 were considered stress-susceptible, while animals with an SI ratio of greater than 1 are considered stress-resilient.

4.4.2 Open field testing

Open field behaviors were recorded, tracked, and quantified using an overhead camera and Noldus Ethovision software. Immediately following social interaction testing, open field testing was performed. This test is a well-established and frequently used measure to determine anxiety-like behaviors in rodents (Bailey & Crawley, 2009; Carola et al., 2002). Mice were placed in the corner of a 44cm x 44cm white matte acrylic open arena under red light and allowed to freely move and explore for one five-minute trial. Quantification included total time (in seconds) spent in the center of the arena, the frequency of entries into the center of the arena (defined as a 27.5cm x 27.5cm central zone), velocity of movement, and total distance traveled.

4.4.3 Social preference testing

Social preference behaviors were recorded, tracked, and quantified using an overhead camera and Noldus Ethovision software. Social preference testing was performed 48 hours after the final CSDS and CWDS session. This test is used to determine whether stress affects social reward behavior, and to further investigate any stress-induced anxiety-like behaviors (Kaidanovich-Beilin et al., 2011). The testing arena (60cm x 40cm) was divided by plexiglass panels into three chambers (20cm x 13.3cm) with 6cm center passages allowing for free movement

between each chamber. Chambers were designated as one social target section, one neutral middle section, and one non-social target section. Location of social target was counterbalanced across trials to ensure an even distribution of target mouse location. An empty mesh cup was placed in the middle of both social target and non-social target sections. Experimental mice were placed into the neutral middle section and allowed to freely explore all areas for five minutes. Following this trial, mice were removed, and a same-sex conspecific mouse was placed in the mesh pencil cup. Mice were again placed in the neutral middle section and allowed to freely explore for another five minutes. Testing was completed under red light. The amount of time spent in each area and frequency of entry into each area was quantified. Mice were determined to show social preference behavior if they exhibited increased time spent in the social arena during the social target trial (with a same-sex conspecific) as compared to the non-social target condition.

4.4.4 Forced swim testing

Glass Pyrex beakers (3500ml) were filled with 3000ml of 25^{o} Celsius water and placed in a dedicated behavioral testing room under fluorescent lighting. A camera mounted to a tripod and connected to the Ethovision system captured real-time behavior, which was recorded and analyzed via Ethovision. Mice were placed into the beaker and allowed to swim or float for a duration of five minutes. After the trial was completed, mice were removed and returned to their home cage. Water was changed between sexes. The amount of time spent immobile (floating, not actively swimming) measured in seconds was quantified.

4.4.5 Rodent head twitch response testing

Head twitch response is a reliably observed behavior exhibited by rodents in acute response to serotonergic psychedelic drugs, including psilocybin (Corne et al., 1963; Corne & Pickering, 1967; Halberstadt et al., 2011a). In response to activation of 5-HT2ARs, rodents exhibit frequent rapid side-to-side shaking motions of the head. Head twitches begin within 60-120 seconds of drug administration and typical increase in frequency for 15-30 minutes, followed by a steady decline as receptor occupancy gradually decreases (Passie et al., 2002; Shao et al., 2021b). This behavior is dose-sensitive, and the appropriate dose for subsequent experimental use is determined by the inflection point of a generated dose-response curve quantifying number of head twitches during acute drug activity (Halberstadt et al., 2011a; Halberstadt & Geyer, 2011b). In a red-light behavioral testing room, empty home cages were positioned under a camera. Immediately following intraperitoneal injection of vehicle or drug, animals were placed in a home cage and video recording was prompted for the duration of 30 minutes. Video files were then uploaded to Ethovision and manually analyzed for number of head twitches exhibited in a 30-minute testing timeframe.

4.4.6 Probabilistic reversal learning

Probabilistic reversal learning (PRL) is a translatable operant paradigm measuring various aspects of cognition (such as reward learning) and is analogous to similar tasks used in clinical research. Reward learning in PRL is dependent on PFC engagement (Hornak et al., 2004) and patients with MDD and other psychiatric illnesses exhibit task deficits (Cools et al., 2002; Evers et al., 2005; Metha et al., 2020). All testing was undertaken in operant boxes furnished by Med Associates Inc, using a consumable reward of chocolate milk solution (one parts Nestle Nesquik Chocolate Milkshake to two parts water). Animals were introduced to operant chambers and

underwent one week of lever training (after which operant training was paused, and CSDS and CWDS was completed). Animals began on an FR1 schedule, in which both right and left levers inside the operant chamber and presented. Thirty ul of chocolate milk solution was dispensed 100% of the time in response to the animal pressing either left or right lever. Sessions lasted for 30 minutes. Following the completion of CSDS and CWDS, and other behavioral testing, animals commenced lever training with a 60-minute FR1 'refresher' session. Upon meeting the criterion of 25 or more lever presses in one session, animals advanced to the first phase of PRL training. In this phase (of 30-minute sessions), the reward contingencies of each lever are reduced to 50%; thus each lever has a 50/50 probability of dispensing a reward. After two consecutive days of 40 or more lever presses, animals moved on to the second phase of PRL training. In this phase (of 30-minute sessions), the 50/50 lever contingencies remain and each lever is presented for 10 seconds. After five consecutive days of 75 or more lever presses, animals moved on to the final phase of PRL testing. Each PRL testing session lasted for 60 minutes and involved changing lever reward contingencies of 80% and 20%. The number of PRL testing sessions completed varied depending on experimental design: for PRL testing in Chapter 5.2, all animals completed six sessions of PRL; in Chapter 5.3, all animals completed five pre-treatment sessions and five post-treatment sessions. PRL metrics of task engagement, reward-oriented behavior, and reward sensitivity were collected. Daily task metrics for each animal grouping were averaged across the total number of PRL testing days (details on grouping are described in Chapter 5). The total number of trials completed, total number of rewards delivered, and reward rate (total rewards delivered/total number of trials completed) were quantified as metrics of task engagement and reward behavior. Reward sensitivity and behavioral strategy were quantified as win-stay and

lose-shift probabilities. Win-stay probabilities were calculated as the proportion of trials where a previously rewarding trial was followed by a choice of the same rewarding lever. Lose-shift probabilities were calculated as the proportion of trials where a previously non-rewarding trial was followed by a choice of the opposite lever. Raw data was processed using Bagot Lab custom Python scripts.

4.5 Data analysis

All data were analyzed with IBM SPSS Statistics Version 28.0.0.0 and/or PRISM Graphpad 9. For PRL, raw data was processed using Bagot Lab custom Python scripts.

4.5.1 Statistical analysis

All statistical analyses and comparisons were made within sex group and between stress group (stress-naïve females compared with stressed females; stress-naïve males compared with stressed males). In experiment 5.1, ordinary one-way ANOVAs were used to compare head twitch counts for escalating doses of psilocybin. Unpaired t-tests were used to compare behavioral metrics between saline treated and psilocybin treated animals. In experiment 5.2, unpaired t-tests were used to compare behavioral metrics between control and stressed animals. In experiment 5.3, unpaired t-tests were used to determine the effect of stress on social interaction ratio. Two-way ANOVAs with multiple comparisons were used to compare PRL metrics between groups at pre-treatment and post-treatment timepoints. Two-way ANOVAs with multiple comparisons were used to compare PRL metrics between stress and treatment groups across

pre-treatment and post-treatment timepoints. Three-factor mixed-design ANOVAs with stress manipulation and treatment as between-subjects factors and timepoint as a within-subjects factor were used to determine the effect of drug treatment on behavior in control and stress animals.

Chapter 5: Results

5.1 Psilocybin acutely induces head twitches in female and male stress-naïve mice but does not alter anxiety-like or depression-like behaviors

The rodent head twitch response test is a well-established test used to determine the pharmacodynamic activation of 5-HT2A receptors (Corne et al., 1963; Corne & Pickering, 1967). In rodents, all serotonergic psychedelic compounds elicit an observable rapid back-and-forth movement of the head and neck (Canal & Morgan, 2012; Halberstadt et al., 2011a, 2020; Nabeshima et al., 1987). This behavior is dose-sensitive, and experimentally the head twitch response test is a necessary first step in establishing a reliable response to psilocybin. Completion of this testing allowed for the appropriate choice of dose to use for all subsequent experiments. Test doses included a saline control group and psilocybin at 0.25mg/kg, 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg. Combining drug testing with behavioral testing (open field test, social preference test, and forced swim test) at variable time points provided insight into any time effects of psilocybin on anxiety and depression-like behavior in mice.

5.1.1 The rodent head twitch response test in response to acute psilocybin

Female (N=25) and male (N=25) mice were divided into five groups for pharmacological testing (female n=5 + male n=5): saline, 0.25 mg/kg psilocybin, 0.5 mg/kg psilocybin, 1.0 mg/kg psilocybin, and 2.0 mg/kg psilocybin. Head twitch count was quantified for each dose group for females and males (Figure 2)**.** For female mice, an ordinary one-way ANOVA revealed significant effect of treatment ($F(4,20)=14.26$, $p=<0.0001$). Post-hoc tests (Sidak) confirmed that head twitch count significantly differed between female mice treated with 0.5mg/kg and 1.0mg/kg psilocybin

(p=0.002), 0.0mg/kg and 1.0mg/kg (p<0.0001) and 0.0mg/kg and 2.0mg/kg (p=<0.0005). For male mice, an ordinary one-way ANOVA revealed significant effect of treatment (F(4,20)=30.42, p<0.0001). Post-hoc tests (Sidak) confirmed that head twitch count significantly differed between male mice treated with 0.5mg/kg and 1.0mg/kg psilocybin (p<0.0001), 1.0mg/kg and 2.0mg/kg psilocybin (p=0.005), 0.0mg/kg and 1.0mg/kg (p<0.0001) and 0.0mg/kg and 2.0mg/kg (p<0.0002). Replicating findings from previous work (Halberstadt et al., 2011a; Halberstadt & Geyer, 2011b; Shao et al., 2021a), the significant difference in head twitch count between 0.5mg/kg and 1.0mg/kg psilocybin for females (p=0.002) and males (p<0.0001) indicated a pharmacodynamically-appropriate experimental dose.

5.1.2 Psilocybin does not alter anxiety-like, anhedonia-like, or social behavior in stress-naïve mice

Recent clinical and preclinical studies report psilocybin rapidly and enduringly ameliorates MDD symptoms and depressive-like behaviors (Barrett et al., 2020; Davis et al., 2021; Hesselgrave et al., 2021; Shao et al., 2021b). To investigate whether such effects are observable in stress-naïve mice, we followed drug and head-twitch response testing with a battery of open field and social preference tests (24 hours post-treatment) and the forced swim test (48 hours post-treatment). Seven days later, the animals repeated the same sequence of tests, to determine if psilocybin induced any delayed effects on behavior. Results from saline-treated animals were compared to those from animals treated with 1.0mg/kg psilocybin, the experimental dose determined from the experiment outlined in Section 5.1.1.

To determine whether psilocybin altered anxiety-like behavior, we analyzed results from open field testing to compare behaviors of female and male mice treated with either saline or

1.0mg/kg psilocybin at 24 hours and 7 days following treatment. Unpaired t-tests comparing mice treated with saline or 1.0mg/kg psilocybin revealed no significant differences in the time spent in the center or total distance travelled in either sex at either time point (n=3-5) (Figure 4), indicating the drug was not anxiolytic.

The social preference test captures a range of behaviors relevant to social reward, motivation, and anxiety. Results from social preference testing were analyzed to compare behaviors of mice treated with either saline or 1.0mg/kg psilocybin for both females and males at 24 hours and 7 days following treatment. Unpaired t-tests comparing mice treated with saline or 1.0mg/kg psilocybin revealed no significant differences in the target trial social preference ratios in either sex at either time point (n=3-5) (Figure 3). These null results indicate psilocybin did not alter socially linked behaviors.

Finally, forced swim testing was conducted to probe for drug-induced changes in anhedonia-like or active/passive coping behaviors. Results were analyzed to compare behaviors of mice treated with either saline or 1.0mg/kg psilocybin for both females and males at 48 hours following treatment and again 7 days later. Unpaired t-tests comparing mice treated with saline or 1.0mg/kg psilocybin revealed no significant differences in time spent immobile in either sex at either time point (n=3-5) (Figure 4), suggesting that drug treatment did not influence anhedonia-like behaviors and did not alter coping strategy.

5.2 The effects of chronic stress on probabilistic reversal learning

The second experiment aimed to establish the effects of Chronic Social Defeat Stress (CSDS) and Chronic Witness Defeat Stress (CWDS) on animal behavior in open field, social

interaction, social preference, and operant probabilistic reversal learning (PRL) (see Figure 1 for timeline). CSDS is a well-validated stress manipulation used extensively in rodent models to induce anxiety- and depression-like behavioral phenotypes (Berton et al., 2006; Golden et al., 2011; Krishnan et al., 2007). Using CSDS and CWDS allowed us to model anxiety-like and anhedonia-like behaviors in simple behavioral testing and explore how stress disrupts facets of reward sensitivity and learning in PRL. Detailed explanations of methodological procedures are outlined in Section 4.4. Briefly, animals underwent one week of operant lever pre-training followed by 10 days of CSDS and CWDS. Upon completion of chronic stress, animals were tested on social interaction, from which the robustness of effects from stress manipulations are determined. Open field and social preference testing followed, providing more insight into how stress affects anxiety-like and socially rewarding behaviors in animals who are stress-susceptible and stress-resilient. PRL training phases commenced, culminating in five days of PRL testing to collect an adequate number of trials for post-experimental modeling.

5.2.1 CSDS and CWDS induces a robust stress phenotype in male and female mice

Twenty-four hours following the final CSDS or CWDS session, experimental and control mice were tested in the social interaction test (Figure 5). Stressed mice frequently spend less time engaging with a novel CD1 mouse, exhibiting anxiety-like behavioral phenotypes that indicate sensitivity to chronic stress manipulations (Kaidanovich-Beilin et al., 2011; Ko, 2017; Venzala et al., 2012). Unpaired t-tests revealed significant difference between control and stressed females' social interaction ratio ($F(9,9)=1.016$, $p=0.0002$). Unpaired t-tests revealed significant differences between control and stressed males' social interaction ratio ($F(8,9)=1.984$,

p=0.0318). These results confirm that CSDS and CWDS were effective in inducing observable behavioral deficits in female and male mice.

To measure alterations in anxiety-like behavior following chronic stress, mice were then tested in the open field test. Mice naturally avoid open spaces which are anxiogenic and prefer enclosed environments which are presumably evolutionarily advantageous – open field testing is commonly used to measure levels of anxiety-like behavior in rodent models of depression (Seibenhener & Wooten, 2015). Unpaired t-tests revealed a significant difference between control and stressed males' total time in the center of the open field arena ($F(8,9)=8.383$, $p=0.0416$) and total distance moved ($F(8,9)=1.807$, $p=0.0201$) (Figure 6), but not for females. These results indicate that stress increased anxiety-like behavior in male but not female mice.

To determine whether chronic stress altered preference for social novelty, mice were then tested in the social preference test. Unpaired t-tests revealed a significant difference between the target trial social preference ratio of control and stressed males ($F(9,8)=3.179$, $p=0.0018$) (Figure 6) but not females. These results indicate that stress altered preference for novel social interaction in males but not females.

5.2.2 The effects of chronic stress on engagement and reward sensitivity in Probabilistic Reversal Learning

Our overarching goal in this experiment was to explore how chronic stress affects behavior in PRL. Following six sessions of PRL testing, an average of each animal's overall performance was generated and used for analysis. Data analyses were performed to investigate basic metrics of reward-oriented task performance (total trials completed, total number of

rewards, reward rate) and behavioral strategy based on sensitivity to reward (win-stay, lose-shift) in stress-naïve and chronically stressed mice.

Quantification of PRL reward-oriented behaviors provided the opportunity examine specific effects of chronic stress. Reward-oriented task performance metrics included total trials completed, total number of rewards, and reward rate. Unpaired t-tests revealed no significant differences in the total trials completed, total number of rewards, or reward rate for control or stressed animals of either sex (n=7-9) (Figure 7). Taken together, these results indicate that stress did not alter reward-seeking behavior or task engagement in female or male mice.

Patients with MDD exhibit deficits in reward processing of gain and loss that contribute to anhedonia (Mukherjee et al., 2020). To capture similar aspects of reward sensitivity in our preclinical PRL task, we used win-stay and lose-shift ratios to represent behavioral strategies based on sensitivity in response to rewarded and unrewarded trials, respectively. Unpaired t-tests revealed no significant differences in win-stay or lose-shift probabilities of control or stressed animals of either sex (n=7-9) (Figure 8). These results indicate that stress did not alter reward or loss sensitivity in female or male mice.

5.3 The effects of psilocybin on probabilistic reversal learning in stress-naïve and chronically-stressed female and male mice

As it is presently unknown how psilocybin modulates cognitive and affective behavior in both chronically stressed and unstressed mice, the third experiment combined previously defined behavioral paradigms and testing with psilocybin, to determine the drug's effects on behavior in both stressed and unstressed animals. Experimental protocol expanded on the timeline employed in Section 5.2 to add five days of post-stress PRL testing, the results of which

were used to group animals into four treatment groups for each sex: control + saline (n=3), control + 1.0mg/kg psilocybin (n=4), stress + saline (n=5), and stress + 1.0mg/kg psilocybin (n=6). Treatment of saline or 1.0mg/kg psilocybin was administered, and 48 hours post-treatment all animals completed another five-day block of PRL testing.

5.3.1 Replication of CSDS- and CWDS-induced social interaction deficits in male and female mice

Twenty-four hours following the final CSDS or CWDS session, experimental and control mice were tested in the social interaction test. Unpaired t-tests revealed a significant difference in social interaction ratio between control and stressed females ($F(11,7)=1.319$, $p=0.0025$) and males ($F(9,7)=1.284$, $p=0.0054$) (Figure 9). These results confirm that CSDS and CWDS were effective in again inducing observable behavioral deficits in female and male mice and exhibit the replicability of these stress paradigms.

Following social interaction testing, animals were tested in the open field test. Unpaired t-tests revealed a significant difference in the total time in center between control and stress males ($F(7,11)=2.567$, $p=0.0018$) but not females, and no significant difference in the total distance moved by control or stressed animals of either sex (n=8-12) (Figure 10). These results confirm findings from Section 5.2.1 that stress increases anxiety-like open field behavior in males but not females.

5.3.2 Stress does not alter reward-oriented behavior or reward learning strategies in female or male mice

After successfully progressing through PRL training phases (see Section 4.4.6 for detailed training protocol), animals completed five consecutive days of PRL training to determine baseline stress effects on reward-oriented behavior and learning prior to drug treatment. Control and stress groups were then assigned to saline or psilocybin treatment groups, with groups matched for mean lever presses across the five days of PRL. For female mice, groups were created for control + saline (n=3, group lever press M=892), control + 1.0mg/kg psilocybin (n=4, M=829), stress + saline (n=5, M=860), and stress + 1.0mg/kg psilocybin (n=6, M=831). For male mice, groups were created for control + saline (n=3, group lever press M=807), control + 1.0mg/kg psilocybin (n=4, M=803), stress + saline (n=5, M=856), and stress + 1.0mg/kg psilocybin (n=6, M=864). Breakdown of animals into the above groupings were implemented into the analysis of pre-treatment PRL data, to allow for comparison with subsequent post-treatment results.

Reward metrics were analyzed to determine any effects of stress on total number of trials completed, total number of rewards, and reward rate (Figure 11). Two-way ANOVAs revealed no significant effect of group on total number of trials, total number of, or reward rate in either sex (n=3-6). These results indicate that stress did not alter reward-seeking behavior or task engagement in female or male mice.

As in Section 5.2.2, analysis was completed to investigate win-stay and lose-shift ratios, which represent behavioral strategies in response to positively or negatively rewarded trials (Figure 11). Two-way ANOVAs revealed no significant effect of group on win-stay or lose-shift probabilities in female or male mice. These results indicate that stress did not alter sensitivity to reward or subsequent behavioral strategy in female or male mice (n=3-6).

5.3.3 Psilocybin does not alter reward-oriented behavior or reward learning strategies in control or stressed female or male mice

Following the protocol described above in Section 5.3.2, mice progressed to the final experimental phase. Depending on grouping, animals received intraperitoneal injections of saline or 1.0mg/kg psilocybin. Forty-eight hours following administration animals commenced five days of PRL testing. Previously described metrics quantifying reward-oriented behavior and learning based on reward sensitivity were analyzed post-treatment to observe the effects of drug on behavior. Analyses of pre-treatment and post-treatment data were performed to reveal the relationship between behavior prior to and following drug treatment.

Reward metrics were analyzed to determine any effects of treatment on total number of trials completed, total number of rewards, and reward rate. Two-way ANOVAs revealed no significant effect of treatment on total number of trials, total number of rewards, or reward rate in control or stressed animals of either sex (n=3-6). These results indicate that 1.0mg/kg psilocybin did not affect reward-seeking behavior or task engagement in female or male mice.

Analysis of win-stay and lose-shift ratios was performed with two-way ANOVAs, and revealed no significant effect of treatment on win-stay or lose-shift probabilities in control or stressed female or male mice. These results indicate that 1.0mg/kg did not affect sensitivity to reward or subsequent behavioral strategy in female or male mice (n=3-6).

Further analysis was completed to explore interactions between stress and drug treatment testing timepoints. Three-way repeated measures mixed design ANOVAs with timepoint (pre-treatment or post-treatment) as a within-subjects factor and group (control or stress) and treatment (saline or 1.0mg/kg psilocybin) as between-subjects factors did not reveal a significant main effect of timepoint or significant interactions between timepoint x group,

timepoint x treatment, or timepoint x group x treatment for total trials completed, total number of rewards, or reward rate either sex. This indicates that psilocybin did not affect reward-oriented behavior. A significant main effect of timepoint was revealed in females' lose-shift ($F(1,14)=7.779$, $p=0.014$, $\eta^2=0.357$) but not in males', with females' lose-shift ratios increasing from pre-treatment to post-treatment. A significant interaction was revealed between timepoint x group for males' win-stay ($F(1,14)=5.835$), $p=0.03$, $\eta^2=0.294$), but not for females. Stressed males treated with 1.0mg/kg psilocybin trended towards increased win-stay ratios (Figure 12). Taken together, these analyses indicate repeated exposure to testing resulted in sex-specific effects on reward sensitivity and PRL behavioral strategies – females' sensitivity to loss and incorporation of such feedback into subsequent choice behavior increased over repeated PRL testing , while stressed males who received drug treatment exhibited slight increases sensitivity to gains.

Chapter 6: General Discussion

The overarching goal of this body of work was to bolster our preclinical understanding of how the psychedelic compound psilocybin alters behavior in mouse models translatable to depression. Compelling clinical evidence supports the use of psilocybin in the treatment of depression, with long-term ameliorations in affective symptoms observed in many studies (Davis et al., 2021; Doss et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Gukasyan et al., 2022). However, the effects of psilocybin in preclinical studies are understudied and there exist few preclinical protocols for testing antidepressant psychedelic drugs which employ clinically relevant manipulations or behavioral paradigms. The work presented in this thesis aimed to contribute to our basic scientific knowledge of how stress (a primary factor in depression and other psychiatric illnesses) can be implemented with ethologically valid manipulations and utilized in tandem with paradigms capturing facets of animal behavior and pharmacological testing.

Chronic stress has deleterious effects on brain structure and function, as discussed in detail in the Literature Review. How stress alters neural morphology and activity is understood in part through preclinical investigations which reveal impairments in affect, cognition, and behavior as a consequence of chronic stress (McEwen, 2000; McEwen et al., 2014, 2016; McEwen & Morrison, 2013). We selected CSDS and CWDS as stress manipulations due to their established efficacy and clinical relevancy as chronic stressors (Golden et al., 2011; Krishnan et al., 2007; Lopez & Bagot, 2021).

As the “conductor” of executive function, the PFC orchestrates affective and cognitive processes via extensive cortical and subcortical neural circuits. Depression symptomatology is linked to both local PFC and broader, circuit-wide dysfunction; it was therefore imperative that

we select behavioral paradigms that capture behavioral relevant to our region of interest. Corticolimbic circuits govern anxiety, fear, and stress response (Shin & Liberzon, 2010). The open field test is used to measure these responses in rodents (Gründemann et al., 2019), and various kinds of stress contribute to increases in anxiety-like behaviors (F. K. Johnson et al., 2018; W.-Z. Liu et al., 2020; Seibenhener & Wooten, 2015). Social interactions can be either stressful or socially rewarding and recruit reward (Franklin et al., 2017; Kawamichi et al., 2016; Kelley & Berridge, 2002) and corticolimbic (Huang et al., 2020; Rincón-Cortés & Sullivan, 2016; Robinson et al., 2014) circuits. Processing of rewarding and punishing stimuli is disrupted in depression (Eshel & Roiser, 2010). Stress-sensitive reversal learning paradigms can be used to measure how individuals across species respond to and learn from situations that are rewarding or non-rewarding (Ironside et al., 2018; Izquierdo et al., 2017; Kangas, Short, et al., 2022). By combining well-known behavioral tests that recruit extended PFC circuits and measure anxiety-like, anhedonia-like, and socially rewarding behaviors with a more complex operant task, we aimed to capture a broad spectrum of depression-relevant observations.

6.1 Interpretation of results

6.1.1 Psilocybin induced head twitches but did not alter behaviors generalizable to depression in stress-naïve female and male mice

Ensuring an appropriate experimental dose is an important foundational step in behavioral pharmacology. The rodent head twitch response test is well-established and frequently used as an indicator of acute 5-HT2AR activation by psychedelic compounds like psilocybin (Corne et al., 1963; Corne & Pickering, 1967; Halberstadt et al., 2011a). However, the

test is specific to rodents and does not screen for antidepressant effects or indicate therapeutic potential. We chose to incorporate simple assays measuring anxiety-like and anhedonia-like behaviors following drug testing to determine if stress-naïve mice exhibited any drug-induced behavior alterations. Open field tests, social preference tests, and forced swim tests were selected to capture previously-described behaviors.

During 30-minute rodent head twitch response testing sessions, we observed escalating dose-dependent head twitches in line with reports from the literature (Halberstadt et al., 2011b; Hesselgrave et al., 2021; Shao et al., 2021a). Mice of both sexes exhibited statistically significant increases in number of head twitches between 0.5mg/kg and 1.0mg/kg of psilocybin, indicating adequate occupancy of 5-HT2ARs – thus, we selected the 1.0mg/kg dose for subsequent experimental use. In our battery of post-drug behavioral tests, we failed to observe any significant differences between saline-treated or psilocybin-treated mice of either sex. Animals treated with 1.0mg/kg of psilocybin did not exhibit increases or decreases the time spent in the center of an open field, time spent immobile in forced swim testing, or time spent engaging with a novel peer in the social preference test. These null findings bring up several interesting points to consider. First, our cohort of animals had no exposure to acute or chronic stressors prior to drug and behavioral testing. Given that clinical and preclinical evidence of psilocybin's antidepressant efficacy have utilized cohorts of MMD patients (Davis et al., 2021; Goodwin et al., 2022; Gukasyan et al., 2022) or laboratory stress manipulations (Hesselgrave et al., 2021; Shao et al., 2021b), it is possible that we failed to capture changes in anxiety-like or anhedonia-like behaviors because our stress-naïve animals did not possess deficits or sensitivities in the first place. Another potential contributor to our lack of findings may have been the experimental

timeline and duration. Psilocybin's sustained antidepressant effects are postulated to originate from acute triggering of plasticity processes, which gradually and enduringly alter dendritic morphology (Shao et al., 2021b) and amelioration of symptoms (Barrett et al., 2020; R. Carhart-Harris et al., 2018; Gukasyan et al., 2022). We performed the first battery of tests 24-48 hours following drug administration and repeated them again 7 days later. It is possible that not enough time elapsed for the drug's psychoplastogenic effects to proliferate. Experimenters may wish to include longer-term protocols in future study designs.

The foundational experiment was of overall importance to the body of work presented in this thesis. By testing psilocybin at exponentially increasing doses and quantifying acute head twitches, we were able to generate a dose response curve to determine an appropriate dose and found that mice of both sexes responded with similar increases in head twitch behavior at the 1.0mg/kg dose, indicating that this behavior is not sensitive to sex differences in stress-naïve animals. In subsequent behavioral testing, drug treatment was not found to alter anxiety-like, anhedonia-like, or social behaviors. Together these findings confirm the validity of the rodent head twitch as an observable behavior during acute psilocybin, replicating previous work (Halberstadt et al., 2011a; Shao et al., 2021b), and provide the first evidence known to us of how psilocybin-treated mice of both sexes behave in simple paradigms used frequently in preclinical depression modelling.

6.1.2 Chronic social defeat stress and chronic witness defeat stress increased anxiety-like and social behavior, but did not affect reward-seeking or reward sensitivity

Chronic stress, as previously discussed, is a major risk factor for MDD. The wide spectrum of neurobiological effects due to chronic stress is exemplified through structural and

morphological changes that result in brain-wide functional alterations (Drevets et al., 2008), ultimately contributing to behavioral impairments (Hammar & Årdal, 2009; Malhi & Mann, 2018). The PFC is a crucial conductor of affective and cognitive processes and is sensitive to stress – as such, it is a clinically relevant region of major focus for both preclinical and clinical investigations (Hare & Duman, 2020; McEwen et al., 2016; McEwen & Morrison, 2013; Miller, 2000). Focusing on stress and PFC-linked symptoms of depression, such as anhedonia, were paramount in our development of a novel preclinical protocol relevant to MDD. In this vein, we combined CSDS and CWDS, two socially based stress paradigms, with simple assays and a complex operant task dependent on PFC recruitment. We tested this protocol to determine whether chronically stressed animals showed impairments in social interaction, open field, and social preference tests, as well as in a PRL task.

Following CSDS and CWDS, chronically stressed mice of both sexes showed significant decreases in the amount of time spent interacting with a novel CD1 mouse in the social interaction test, compared with controls. This follows previous reports of similar findings (Golden et al., 2011; Iñiguez et al., 2018; Krishnan et al., 2007), indicating that CSDS and CWDS were effective and induced a robust stress response. Male mice that underwent CSDS showed significant decreases in the total time in the center, total velocity, and total distance moved in an open field, compared with controls. These findings, which were not mirrored in females, indicate CSDS increased anxiety-like behavior in males, and suggests sex differences may play a role in how male and females differentially exhibit anxiety-like impairments. Chronically stressed males, but not females, also showed an increase in time spent in the same chamber as a novel conspecific, compared with controls. This is surprising, as males' increased anxiety-like behaviors

in social interaction and open field tests might suggest a preference to avoid novel, potentially threatening environments and interactions. One theory for our observed increases may be that social interaction provided positive buffering, or coping, to chronically stress male mice. Such effects have been variously reported in animals across species following stress exposure (Beery & Kaufer, 2014).

Patients with MDD show impairments in reversal learning where deficits are linked to PFC dysfunction and thought to relate to anhedonia (Mukherjee et al., 2020; Clark et al., 2004; Dombrovski et al., 2015; Cools et al., 2002; Murphy et al., 2003). To ensure our preclinical modeling used translatable metrics relevant to MDD, we tested mice in PRL and captured various metrics pertaining to anhedonia, including reward-oriented engagement and behavioral strategy. Chronically stressed mice of either sex showed no difference compared with controls in the total trials completed, total number of rewards obtained, or reward rate. These findings signify CSDS and CWDS did not disrupt task engagement or reward-seeking behavior. We also failed to observe stress-induced differences in win-stay and lose-shift ratios, which quantify an animal's sensitivity to reward gain and loss as a function of its future choice behavior. Taken together, these findings indicate that our chronic stress protocols did not induce anhedonia-like effects in mice of either sex as quantified in our PRL task. There are several potential indications of these findings. PRL testing was completed three weeks after the termination of chronic stress and social interaction, open field, and social preference tests. It may be that our stress manipulation resulted in stress deficits of a more acute variety, and by the time PRL testing commenced the animals who showed initial impairments were no longer sensitive.

6.1.3 Psilocybin did not alter behaviors in stress-naïve or chronically stressed female and male mice

The body of this thesis work was completed with the overarching goal to investigate the effects of psilocybin in a translatable preclinical mouse model. Compelling human data highlights the antidepressant effects of psilocybin, a serotonergic psychedelic compound (Davis et al., 2021; Doss et al., 2021; Gukasyan et al., 2022; Ross et al., 2016). Recent preclinical work has revealed the psychoplastogenic effects of psilocybin in deep-layer PFC pyramidal neurons (Shao et al., 2021b), and it is postulated that the drug's therapeutic effects arise from PFC-driven plasticity processes that alter neural circuit connectivity and function (Vollenweider & Preller, 2020). In our final experiment, we combined CSDS and CWDS, simple behavioral assays, and PRL with psilocybin treatment to observe drug effects on previously described anhedonia-related behaviors.

In replication of our second experiment, we found that CSDS and CWDS increased anxiety-like behaviors and social avoidance in the social interaction test for both male and female mice. Stressed male mice, but not female mice, also showed decreased time spent in the center of the open field arena. Together, these results indicate CSDS and CWDS, two social chronic stress paradigms, are effective at inducing deficits in mouse behavior. Independent analysis of pre-treatment and post-treatment PRL testing blocks did not reveal differences between groups in number of trials completed, number of rewards obtained, reward rate, win-stay, or lose-shift metrics for either sex. Comparing pre-treatment and post-treatment results directly revealed a significant main effect of time for females' lose-shift ratios, with increased post-treatment means for all groups, suggesting that over time sensitivity to loss increased independent of group or treatment. A significant interaction between time and group was revealed for males' win-stay

ratios, and through observation of group means we determined that ratios of control males decreased while those of stressed males increased from pre-treatment to post-treatment. This indicates that, independent of treatment, stress increased males' sensitivity to positively-rewarding trials over time. Together, these PRL results indicate stress may sex-differentially alter reward sensitivity in mice.

There are several potential considerations for the lack of observed treatment effect. Prior to psilocybin treatment, we did not observe any effects of stress on PRL performance. Even though our animals showed increased anxiety-like behavior post-stress, stress effects may not have been robust enough to induce anhedonia-like behavior as quantified by PRL performance. A previous study reporting positive results in reversal learning performance following treatment with ketamine (a novel rapid-acting antidepressant) also established baseline stress deficits (Paredes et al., 2018) – it may be that our null post-treatment results are directly linked to the lack of pre-treatment group differences. Resilient or susceptible stress phenotype are thought to be important in understanding the variable effects of chronic stress on brain function and behavior (Bagot et al., 2015; Krishnan et al., 2007; McEwen et al., 2014). Future expansions of this work contributing to a greater sample size may help elucidate whether susceptible and resilient phenotypic breakdowns contribute to a more nuanced view of anhedonia-like behavior and psilocybin treatment in PRL.

6.2 General limitations

While the work completed for this thesis has contributed to the body of preclinical psychedelic research and presented a novel behavioral pharmacological protocol that can be

used for future investigations, it is not without limitations. Several factors can be considered in the development of experimental extensions to this body of work. Preclinical stress models of psychiatric disorders, such as our CSDS and CWDS manipulations, cannot capture the multitude of factors contributing to clinical MDD (Koolhaas et al., 2017; Planchez et al., 2019). Stress is well-established as a risk factor in many psychiatric illnesses including MDD (Hammen, 2005; Mazure, 1998) but is experienced in many forms and our understanding of how specific types of stressors impact specific facets of affective and cognitive function is lacking. Using animal behavior as a proxy for symptoms of clinical depression warrants caution against overinterpretation, and recent perspectives question whether behaviors traditionally viewed as 'impaired' in response to stress are actually adaptive (Radley & Herman, 2022). We found replicable post-stress deficits in social interaction tests and observed various sex-specific effects in open field testing, social preference testing, and probabilistic reversal learning, but the presence of or absence of specific behavioral differences between control and stress animals does not indicate that stress failed to alter neurobiological processes. When comparing behavioral changes it is important to consider observations as approximations of potential underlying processes – to disentangle direct causality in such relationships requires increased micro-level investigations. Long-term stress alters neuroplasticity (Pittenger & Duman, 2008); incorporating a more longitudinal timeline into the behavioral design may highlight delayed effects of stress. Our use of vicarious social stress for females and social defeat stress for males was limited to adulthood and therefore inadequate in modeling developmental effects of stress. In humans, chronic stress experienced prior to adulthood is associated with future development of depression (Syed & Nemeroff, 2017). Future

investigations can incorporate early life stress paradigms to reveal whether experiences at critical timepoints promote specific behavioral deficits in adulthood.

6.2.1 Limitations in psychedelic behavioral neuroscience

Preclinical investigations into the effects of psychedelic drugs like psilocybin present limitations that are perhaps novel in neuroscientific and psychiatric research and necessitate extensive consideration. Psilocybin (and serotonergic psychedelics broadly) induces acute experiences unlike any other known class of drugs and involve subjective alterations in sensation and perception, dissolution of ego and sense-of-self, and transformative mystical and spiritual experiences – all of which are extremely difficult to scientifically capture and quantify. While recent investigations have attempted to determine whether such effects are necessary for antidepressant and therapeutic benefits (Cao et al., 2022; Hesselgrave et al., 2021; Olson, 2021), clinical studies consistently report that these aspects are individually meaningful and integral (Barrett et al., 2020; Barrett & Griffiths, 2018; Griffiths et al., 2006; Nayak et al., 2022; Yaden & Griffiths, 2021). Self-perception, identity, ego, spirituality, and metaphysical thinking are thought to be uniquely human, thanks to our highly-developed and extensively-complex cerebral cortices which maintain dynamic subcortical functional connectivity (Johnson et al., 2002; Mohandas, 2008; Northoff, 2011; Stuss, 1991). Our human brains are exponentially more complex than rodents', and we assume that our higher-order functioning is exponentially more complex as well. Quantification of observed animal behaviors does not necessarily reflect direct or temporally-precise neurobiological changes – rather, specific behaviors can be used broadly as proxies to model symptoms of disease states. With this in mind, animal models may be best

suited to measure drug-induced molecular and cellular changes in regions of interest relevant to pathophysiology and symptomatology of psychiatric conditions like MDD (Hanks & González-Maeso, 2012).

6.3 Future directions in preclinical psychedelic neuroscience: beyond behavioral pharmacology

The field of psychedelic neuroscience is nascent – basic scientific studies have only just begun to uncover the myriad effects of drugs like psilocybin. The human literature suggests that psilocybin's enduring anti-depressant effects are mediated by modulation of PFC-linked neural circuits involved in affective, cognitive, and behavioral processes. Preclinical investigations can use clinically informed symptom-based approaches to profile how psilocybin regulates basic behavioral processes with relevance to MDD. Stress is a key risk factor for MDD, and as the presented body of work exhibits, chronic stress paradigms paired with behavioral pharmacology can be useful for revealing whether novel drugs alter anxiety-like and anhedonia-like behaviors.

Foundational studies investigating psilocybin's psychoplastogenic effects (Hesselgrave et al., 2021; Shao et al., 2021b) highlight the importance of using the toolkit of modern neuroscience to examine cell-specific, regional, and circuit-level effects. Future work can utilize combinations of animal models with viral vectors and *in vivo* calcium imaging techniques such as fiber photometry and two-photon microscopy to disentangle how neural circuits involved in MDD (Muir et al., 2019) are altered by psilocybin by measuring temporally-precise, cell-type specific changes in dynamic neuronal activity. Increasingly popular techniques that profile cell-specific transcriptome-wide changes, such as single-cell RNA sequencing (Ziegenhain et al., 2017), provide the unique opportunity to investigate how psilocybin alters gene expression in regions

of interest like the PFC. Combining sequencing with chronic stress protocols and calcium imaging will contribute greatly to our mechanistic framework of psilocybin's antidepressant effects. With such investigations we can begin to understand how psilocybin modulates both acute and sustained alterations in neural signalling as well as lasting effects on circuit dynamics.

6.4 Conclusion

The overarching goal of this body of work was to determine whether the psychedelic serotonergic drug psilocybin altered the behavior of chronically stressed mice. Experiments were designed to focus on translatable stress and behavioral paradigms and to exhibit how such protocols can be used in psychedelic neuroscientific research. We first demonstrated that acute psilocybin dose-dependently alters head twitches in both female and male mice stress-naïve mice, and that the drug does not alter simple anxiety-like and social reward behaviors up to one week following drug treatment. We then incorporated CSDS and CWDS manipulations into both simple and complex behavioral tests and observed alterations in learning rates of stressed female mice. Finally, we combined drug treatment with our stress and operant paradigms to investigate any effects of 1.0mg/kg psilocybin in the behavior of stress-naïve and chronically stressed mice. As measured by social interaction, our stress manipulations were successfully repeated. We did not observe behavioral impairments in stressed animals' performance in PRL, nor did we find alterations in PRL behavior of control or stressed mice following treatment with 1.0mg/kg of psilocybin. Expanding the repertoire and scope of behavioral paradigms used will provide greater insight as to how stress modifies cognitive processes and if psilocybin has pro-cognitive effects. As the PRL task utilized in these experiments examines reward sensitivity, it may be that other domains of cognition and behavioral strategy are more sensitive to stress. This novel combination

of translatable stress manipulations and behavioral pharmacology serves as a foundation for future preclinical investigations into the therapeutic potential of psychedelic compounds.

Figures

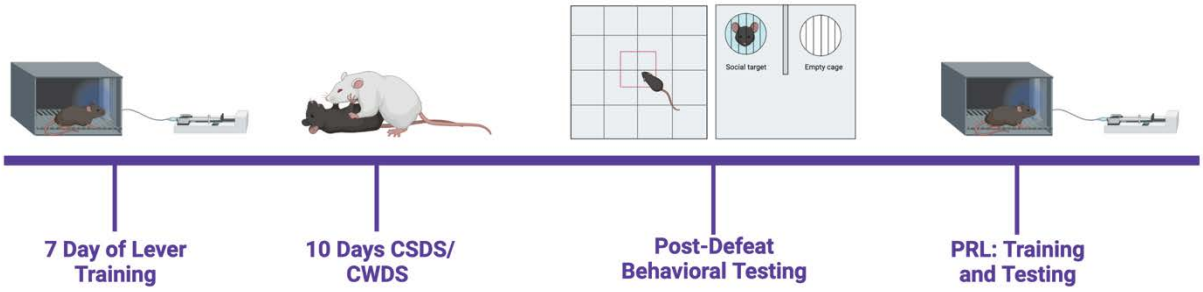

Figure 1. Experiment 2 timeline schematic. Seven days of operant lever training are followed by 10 days of CSDS and CWDS. After the completion of these stress paradigms, animals are tested in social interaction, open field, and social preference behaviors. Animals then commence with PRL training phases, and ~5 days of PRL testing days.

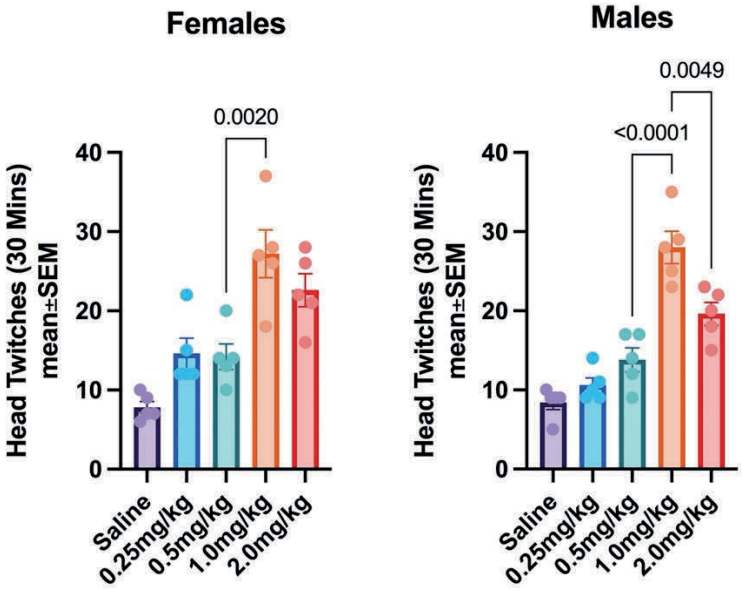

Figure 2. Total number of head twitches observed over a 30-minute period for female and male mice at 0.0mg/kg (saline control), 0.25mg/kg, 0.5mg/kg, 1.0mg/kg, and 2.0mg/kg psilocybin.

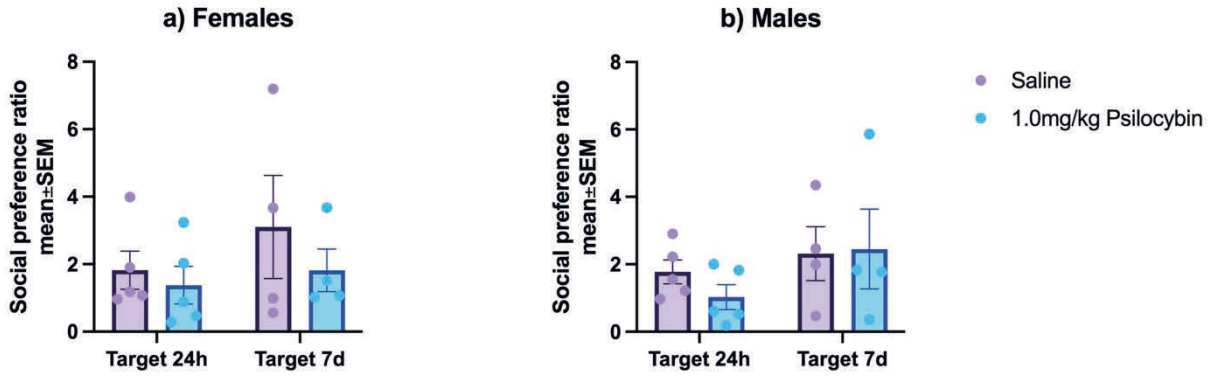

Figure 3. Social preference testing results. No significant differences in social preference ratio were revealed between saline and 1.0mg/kg psilocybin-treated **a)** female mice at 24h (F(4,4)=1.037, p=0.5907) or 7 days (F(3,3)=5.900, p=0.4662) or for **b)** male mice at 24 hours(F(4,4)=1.097, p=0.1808) or 7 days (F(3,3)=2.198, p=0.9288) after treatment.

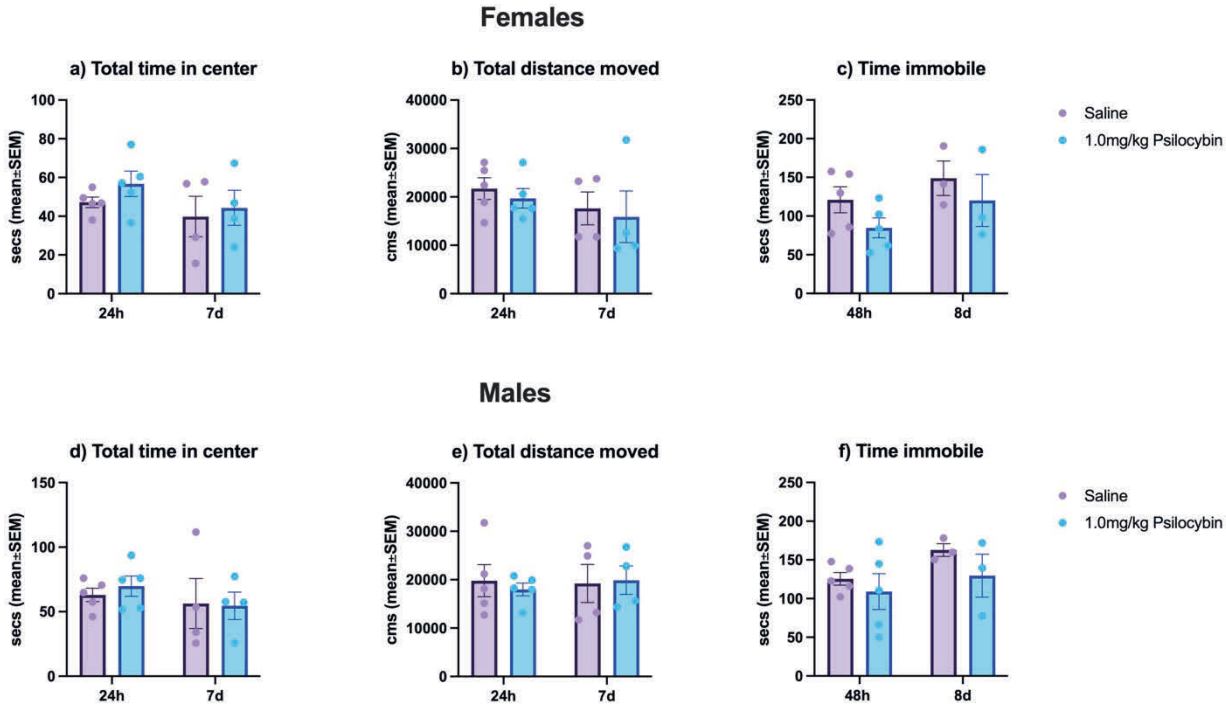

Figure 4. Open field and forced swim test results. For female mice, no significant differences were revealed between saline-treated and 1.0mg/kg psilocybin-treated animals in **a)** open field

total time in center at 24 hours (F(4,4)=5.709, p=0.2135) or 7 days (F(3,3)=1.342, p=0.7568), **b)** open field total distance moved at 24 hours(F(4,4)=1.242, p=0.5236) or 7 days (F(3,3)=2.484, p=0.7938), or **c)** time spent immobile in the forced swim test at 48 hours (F(4,4)=1.676, p=0.1259) or 8 days (F(2,2)=2.268, p=0.5160) following treatment. For male mice, no significant differences were revealed between saline-treated and 1.0mg/kg psilocybin-treated animals in **d)** open field total time in center at 24 hours (F(4,4)=2.304, p=0.4932) or 7 days (F(3,3)=3.317, p=0.9392), **e)** open field total distance moved at 24 hours (F(4,4)=6.237, p=0.6278) or 7 days (F(3,3)=1.779, p=0.8964), or **f)** time spent immobile in the forced swim test at 48 hours (F(4,4)=8.165, p=0.5219) or 8 days (F(2,2)=11.41, p=0.3161) following treatment.

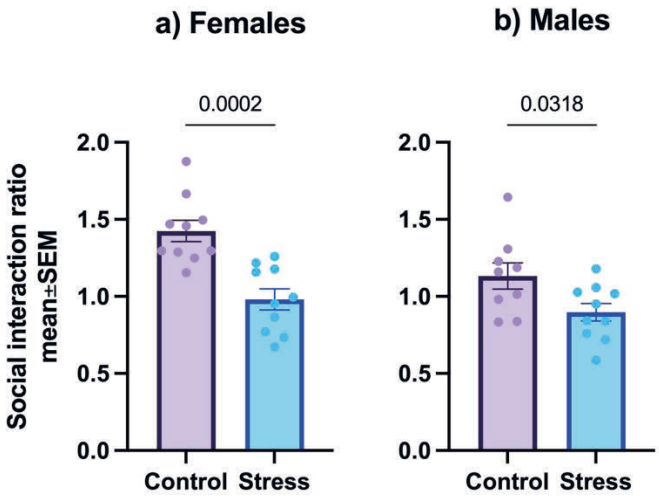

Figure 5. Social interaction ratios for control and stress female and male mice. **a)** Female mice who underwent CWDS manipulations and **b)** male mice who underwent CSDS showed significantly less time in the interaction zone than controls (females: (F(9,9)=1.016, p=0.0002); males: (F(8,9)=1.984, p=0.0318)).

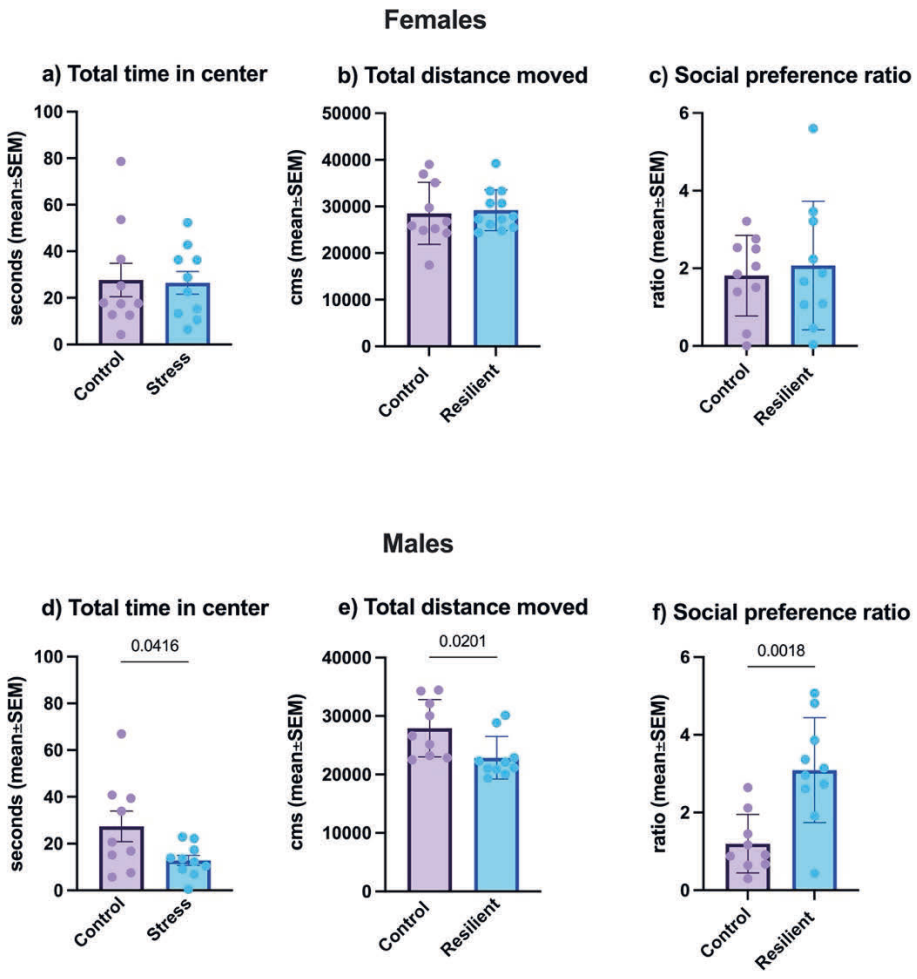

Figure 6. Open field test and social preference test results. There were no significant differences between control and stress females in **a)** total time in the center (F(9,9)=2.297, p=0.8920) and **b)** total distance moved (F(9,11)=2.293, p=0.7751) in an open arena, or in **c)** social preference ratio (F(9,9)=2.545, p=0.6791). **d)** Compared with controls, male CSDS mice spent significantly less time the center of (F(8,9)=8.383, p=0.0416) and **e)** moved significantly less distance (F(8,9)=1.807, p=0.0201) in an open field arena. In **f)** social preference testing, CSDS males spent significantly more time in an arena chamber containing a novel peer mouse (F(9,8)=3.179, p=0.0018) than controls.

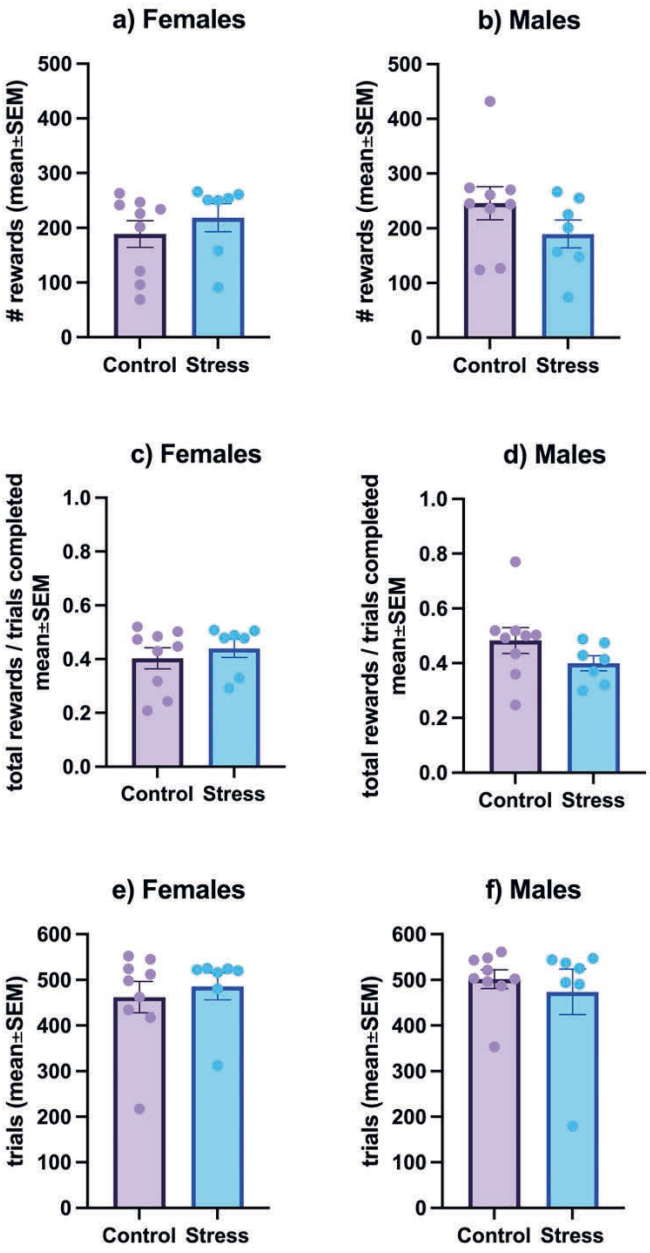

Figure 7. PRL metrics related to reward. No significant difference was revealed in the total number of rewards obtained by control and stressed **a)** females ($F(8,6)=1.179$, $p=0.8359$) or **b)** males ($F(8,6)=1.762$, $p=0.1922$). No significant difference was revealed in the reward rates of control and stressed **c)** females ($F(8,6)=1.681$, $p=0.4980$) or **d)** males ($F(8,6)=3.759$, $p=0.1779$). No significant difference was revealed in the total number of trials completed by control and stressed **e)** females ($F(8,6)=1.175$, $p=0.6291$) or **f)** males ($F(8,6)=4.628$, $p=0.5820$).

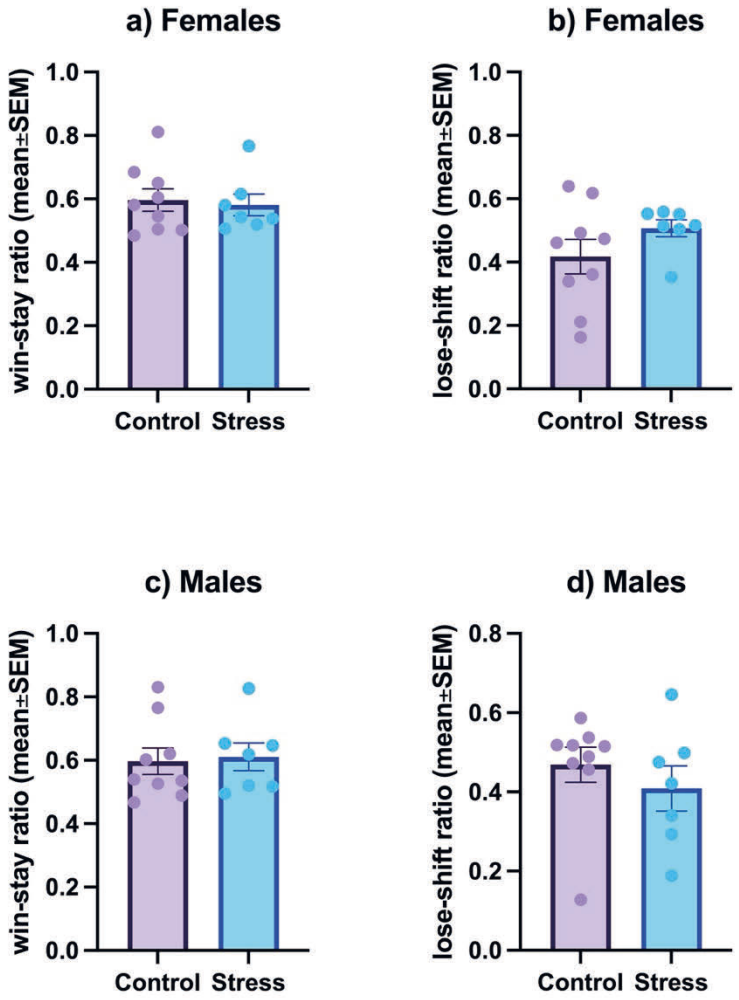

Figure 8. PRL win-stay and lose-shift ratios. Between control and stressed female mice, no significant differences were revealed in **a)** win-stay ($F(8,6)=1.388$, $p=0.7643$) or **b)** lose-shift ($F(8,6)=5.336$, $p=0.2029$) ratios. Between control and stressed male mice, no significant differences were revealed in **c)** win-stay ($F(8,6)=1.165$, $p=0.8272$) or **d)** lose-shift ($F(8,6)=1.271$, $p=0.4114$) ratios.

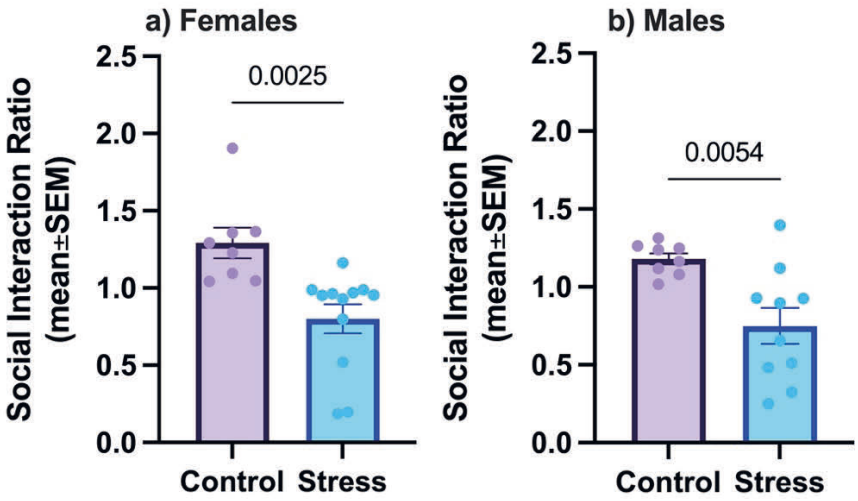

Figure 9. Effects of CSDS and CWDS on social interaction testing. **a)** Female mice who underwent CWDS manipulations and **b)** male mice who underwent CSDS showed significantly less time in the interaction zone than controls (females: ($F(11,7)=1.319$, $p=0.0025$); males: ($F(9,7)=1.284$, $p=0.0054$)).

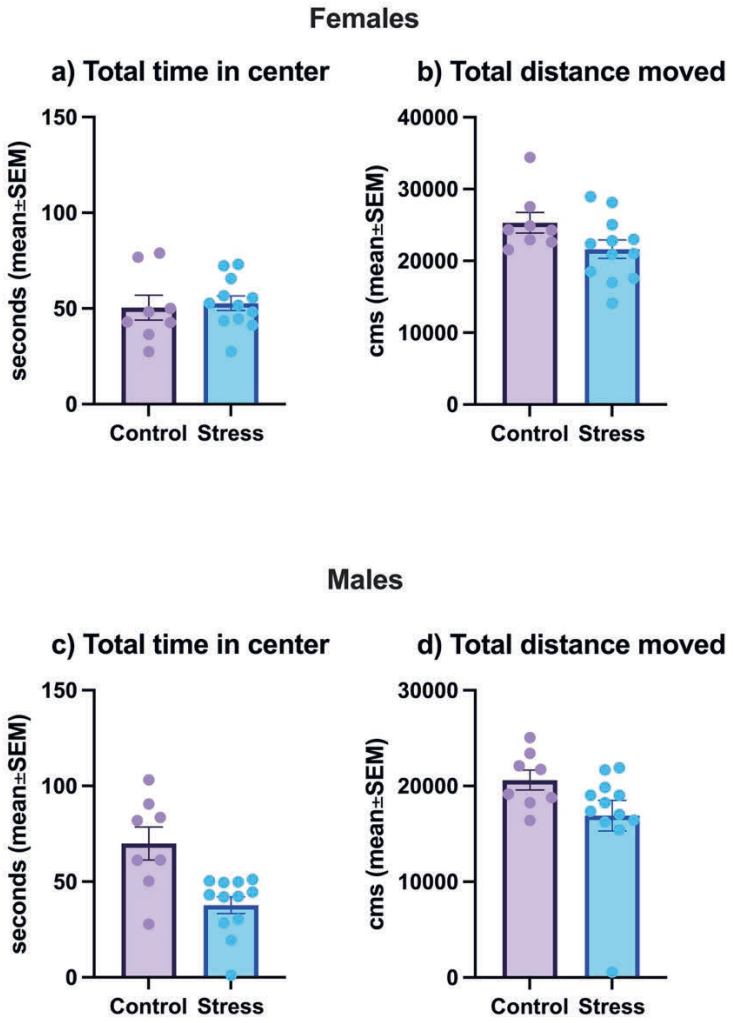

Figure 10. Post-stress open field testing results. No significant differences were revealed between control and stressed females' **a)** total time in the center ($F(7,11)=1.915$, $p=0.7531$) or **b)** total distance moved ($F(7,11)=1.180$, $p=0.0786$) in an open field arena. CSDS males spent **c)** significantly less time in the center ($F(7,11)=2.567$, $p=0.0018$) but **d)** did not show differences in total distance moved ($F(7,11)=3.597$, $p=0.1005$) in an open field arena.

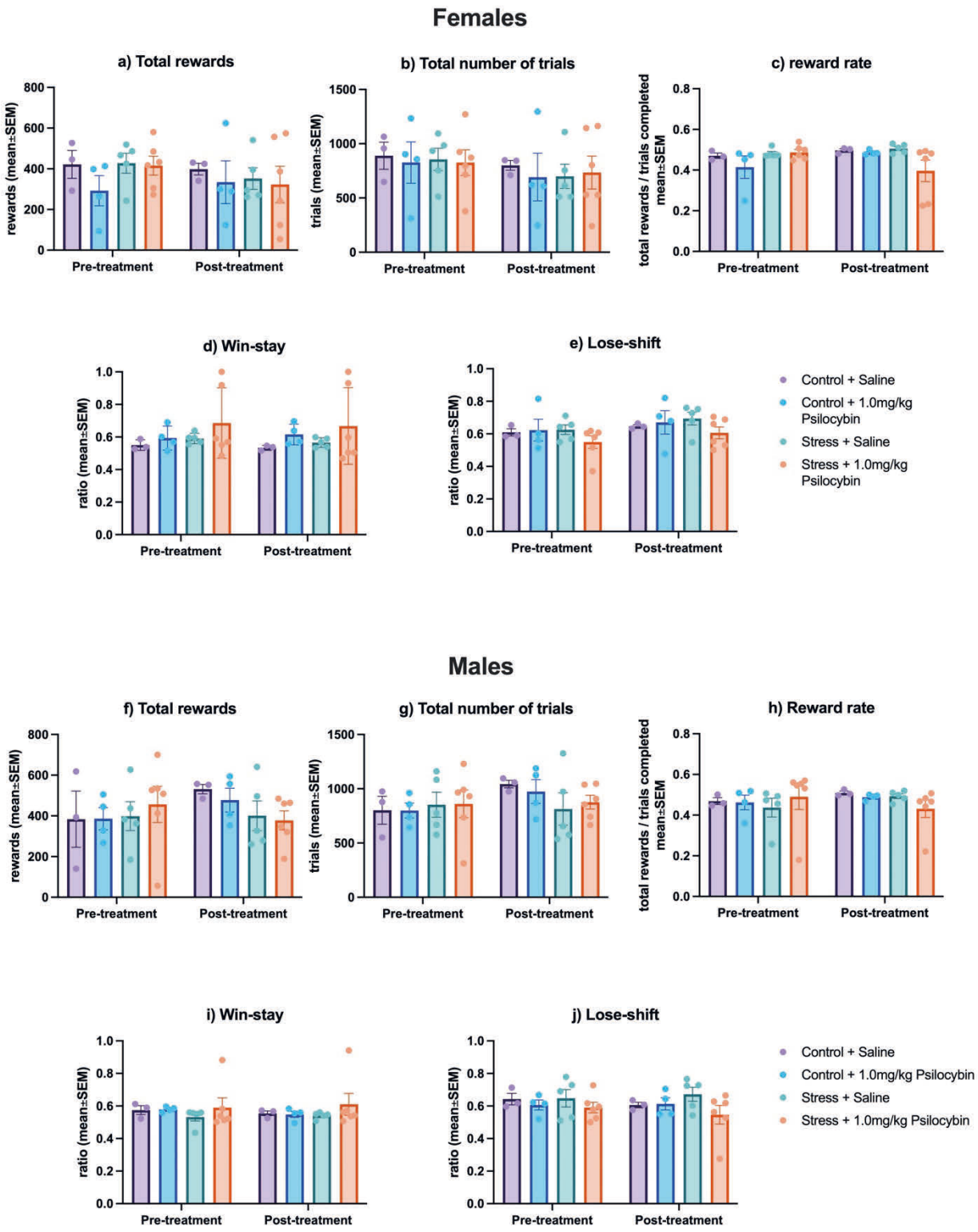

Figure 11. Pre-treatment and post-treatment PRL results. For females, two-way ANOVAs revealed no significant effect of group or interaction between group and timepoint on **a)** total number of rewards, **b)** total number of trials, **c)** reward rate, **d)** win-stay ratios, or **e)** lose-shift

ratios (n=3-6). For males, two-way ANOVAs revealed no significant effect of group or interaction between group and timepoint on **f)** total number of rewards, **g)** total number of trials, **h)** reward rate, **i)** win-stay ratios, or **j)** lose-shift ratios (n=3-6).

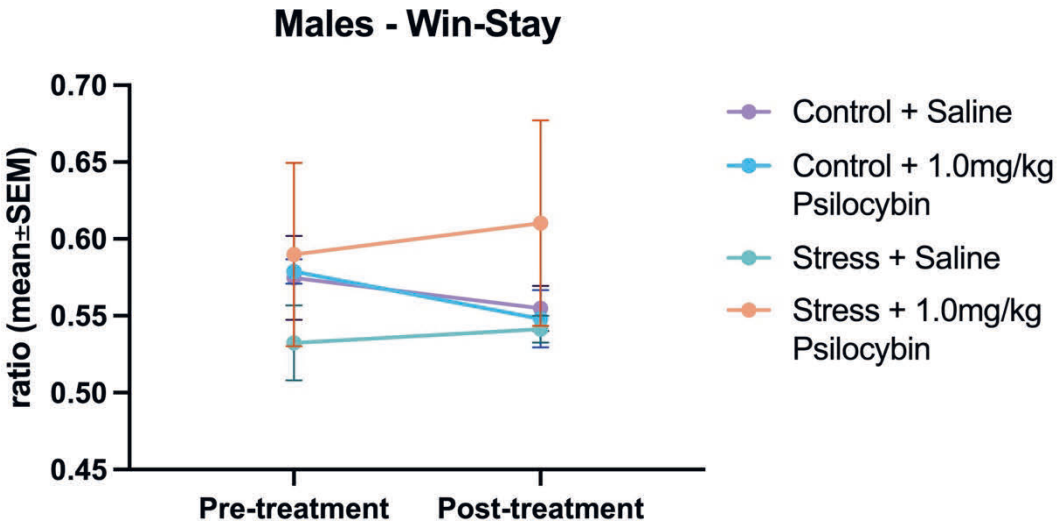

Figure 12. A three-way repeated measures ANOVA revealed a significant group x timepoint interaction between for males' win-stay ratios ($F(1,14)=5.835$), $p=0.03$, $\eta^2=0.294$).

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