INVESTIGATING THE IMPACT OF CHRONIC STRESS ON ANHEDONIA VIA ALTERATIONS IN STRIATAL DOPAMINE AND REWARD CIRCUITRY FUNCTIONING

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ABSTRACT

Rachel Deanna Phillips; Investigating the Impact of Chronic Stress on Anhedonia via Alterations in Striatal Dopamine and Reward Circuitry Functioning.
(Under the direction of Gabriel Dichter)

In preclinical and human studies, long-term exposure to chronic stress causes distinctive changes in neurobiological systems, including alterations in striatal dopamine (DA) functioning and functional brain reward circuitry (i.e., mesolimbic) that mediate hedonic functioning. However, most of the research linking alterations in brain reward circuitry and anhedonia has been in depressed populations. This is the first study of striatal dopamine functioning and reward circuitry in a transdiagnostic sample of adults with anhedonia, ranging in exposure to chronic stress. Participants completed a reward-processing task during simultaneous positron emission tomography and magnetic resonance (PET-MR) imaging with the D2/D3 receptor antagonist, [^{11}C]raclopride, which selectively binds to striatal DA receptors. Results presented here provide evidence for reduced striatal DA functioning during reward processing and decreased mesocorticolimbic network functional connectivity in a transdiagnostic sample with clinically significant anhedonia. This research has the potential to advance our understanding of conditions marked by dysfunctional reward processing, including depression, addiction, and schizophrenia.

This thesis is dedicated to both my grandmothers. For my maternal grandmother, Brenda Louise Rice, who cheered my love of science and research, and was the first person I called when I was accepted to graduate school. She passed away just prior to the start of my graduate career. For my paternal grandmother, Patsy Jean Phillips, who instilled my passion for creating and my interest in hobbies, like watercolor painting, which framed my Master's thesis presentation. My success is due in large part to the love, support, and encouragement from them and my entire family and friends.

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CHAPTER 1: INTRODUCTION

Chronic Stress and Anhedonia

Stress, a physiological or emotional challenge, is highly motivating when experienced acutely and infrequently. In small doses, stress prompts a reaction to stimuli in the environment and the body's physiological stress response is typically appropriate and proportional. The autonomic nervous system is activated, causing a rush of hormones that elicits necessary adrenal, cardiac, and respiratory changes (Lucassen et al., 2014). Such physiological responses prime an organism for a 'fight, flight, or freeze' response. From an evolutionary perspective, this innate stress response to acute challenges is adaptive and conserved across time (Lucassen et al., 2014). However, residing in high stress environments for extended periods of time can be harmful for emotional and physical health (Nusslock & Miller, 2016). Chronic stress that is prolonged, uncontrollable, and inescapable may promote adverse effects on physiology and behavior (McEwen, 2017; G. Miller et al., 2007).

There is strong evidence that chronic stress alters reward sensitivity and contributes to the emergence of anhedonic behaviors (Ironside et al., 2018; Pizzagalli, 2014). Anhedonia, a multifaceted construct, is defined as the loss of interest or reduced pleasure in activities that were previously rewarding (APA, 2013; Tolentino & Schmidt, 2018). In major depressive disorder (MDD), there is growing support that anhedonia is characterized as an impairment in appetitive motivation and reward-based decision-making (Salamone & Correa, 2012; Thomsen et al., 2015; Treadway et al., 2012). In preclinical and human studies, anhedonia is operationalized as a deficit in one or more subtype of reward processing, including reward wanting, reward liking,

and reward learning (Berridge & Kringelbach, 2008; Borsini et al., 2020). Reward wanting can be further divided into subconstructs of incentive motivation, or the process of gauging the amount of effort to expend to receive a reward (Treadway et al., 2012), and reward anticipation, or the act of planning or looking forward to receipt of a reward. Each of these constructs is uniquely impacted by stress, dependent upon stress chronicity (Hollon et al., 2015; Ironside et al., 2018). Acute stress potentiates incentive motivation (Kumar et al., 2014) while chronic stress is associated with blunted incentive motivation and altered reward anticipation (Ironside et al., 2018).

One possible mechanism for the emergence of anhedonia in the context of stress is the downregulation of mesocorticolimbic dopamine reward circuitry functioning (Der-Avakian & Markou, 2012; Kumar et al., 2015; Stanton et al., 2018). Specifically, chronic stress alters dopamine (DA) transmission, resulting in dysfunctional mesocorticolimbic reward circuitry, and reduces goal-directed behavior, resulting in increased habitual behavior and decreased reward responsiveness. Consequently, as maladaptive stress responses are maintained, risk for psychological disorders and poor clinical outcomes increases. These effects combine to create a stress-sensitized system that is more vulnerable to subsequent stressors. The goal of this review is to first detail the impact of chronic stress on anhedonia and reward-oriented (e.g., goal-directed) behavior more broadly, followed by a review of the unique relations between chronic stress, anhedonia, and brain reward circuitry functioning.

Animal Models of Chronic Stress and Anhedonia

Chronic stress leads to decreased motivation and goal-directed behavior (Hollon et al., 2015; Soares et al., 2012). This pattern was first elucidated by animal models of chronic mild stress and social defeat stress (Krishnan et al., 2007; Riga et al., 2015; Willner et al., 1992), which show that uncontrollable and unpredictable stressors lead to anhedonic-like behaviors.

Both objective stressors and perceived lack of control over stressors, referred to as learned helplessness (Abramson et al., 1978), have been shown to reduce reward responsiveness in preclinical model organisms (Pizzagalli, 2014). Chronic mild stress is a reliable model through which animals are randomly exposed to periods of food and water deprivation, wet bedding, paired housing, and a 45-degree cage tilt (Willner, 2017; Willner et al., 1992) for weeks at a time. Following chronic mild stress, animals show reduced sensitivity to reward, demonstrated through (1) reduced intake of sucrose solutions, and (2) attenuated place preference for reward-associated locations (Willner et al., 1992). Social defeat stress is a paradigm by which a smaller and meeker mouse is repeatedly forced to intrude into the cage of a larger mouse, bred to be more aggressive, resulting in dramatic social avoidance and reduced locomotion (Berton et al., 2006; Krishnan et al., 2007). Functionally, animals adapt to unpredictable and uncontrollable stress by shifting to more habitual behaviors that are predictable and reducing social approach. While these models are not perfect proxies for the types of chronic stress that humans face, they strongly support the stress-induced anhedonia paradigm.

Chronic Stress, Anhedonia, and Psychopathology

The National Institute of Mental Health (NIMH) has underscored the importance of considering the complex and heterogeneous consequences of stressors on psychopathology (Simmons et al., 2020). Chronic stress is a risk factor in the etiology of several psychopathologies marked by reward processing deficits, many of which are predated by major life events and other sources of stress. Chronic stressors that include a lack of control, entrapment, or humiliation (Kendler et al., 2003) are particularly debilitating. In adolescents and adults, chronic stressors include long-term maltreatment via abuse or neglect, sustained poverty or economic disadvantage, individual or familial illness, or major difficulties that threaten goals and aspirations for the future (Muscatell et al., 2009; Sheth et al., 2017). Understanding the

relationship between stress and reward-oriented behavior has significant implications for psychopathology, including major depressive disorder (MDD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD).

A leading model of the relationship between stress and affective disorders is the "kindling" or stress sensitization theory (Post, 1992), which posits that the relationship between stress and affective episodes changes over time, whereby an initial episode is more likely to follow a stressful life event and recurrent episodes are triggered by less severe (i.e., minor) stressors that confer greater risk over time. Evidence for the stress sensitization theory in adults with a history of depression includes the finding that while the onset of depression is strongly associated with severe life events, recurrences are associated with lower severity events (Hammen, 2005; Stroud et al., 2011). Neurobiological changes induced by stress and in response to depression are thought to contribute to this sensitization (Kumar et al., 2015), and these changes are discussed in more detail with regard to chronic and prolonged stressors in the subsequent section, *Chronic Stress and Mesocorticolimbic Dopamine Functioning*.

Although the severity of lifetime stressors is important, the perception of stressful events is equally, if not more so critical in understanding the etiology and recurrence of psychopathology. Perceived stress provides insight into the sense of control and predictability over stressors (Hewitt et al., 1992). A perceived lack of control and unpredictability of stressors is linked to a depressive attributional style, wherein there is a tendency to attribute stressors to causes that are "internally located, stable in time, and global in scope" (Willner et al., 1990). Furthermore, perceptions of stress as uncontrollable and unpredictable predict reduced goal-directed behavior (Haeffel et al., 2008; Pizzagalli, 2014). Specifically, perceived lack of control over stressors has been shown to reduce reward responsiveness (Abramson et al., 1978; Pizzagalli, 2014), which in turn may predict anhedonia or be associated with compensatory

reward-seeking behavior (Pechtel et al., 2013; Pechtel & Pizzagalli, 2013). Furthermore, chronic stress has been shown to negatively impact reward processing and reduce reward responsiveness (Pizzagalli, 2014).

Although anhedonia is recognized as a core symptom of major depressive disorder (MDD), and is commonly investigated in depressed samples, it is a highly transdiagnostic symptom (Trøstheim et al., 2020). Anhedonia crosses diagnostic categories, affecting individuals with schizophrenia, posttraumatic stress disorder (PTSD), substance use disorders, and neurological conditions including Parkinson's disease and Alzheimer's disease (Der-Avakian & Markou, 2012). Thus, there is an urgent need for studies investigating anhedonia across traditional psychiatric diagnoses. In alignment with the Research Domain Criteria (RDoC) initiative set out by the NIMH, anhedonia has been identified as a core transdiagnostic construct (Pizzagalli, 2014). Specifically, anhedonia is described as one or more deficits within the Positive Valence System (PVS) domain of RDoC and is closely related to the underlying construct of reward responsiveness (i.e., reward wanting and liking). A transdiagnostic research framework like RDoC, aimed toward understanding the neurobiology underlying maladaptive behaviors and symptoms, may also contribute to the development of tailored treatments (Insel et al., 2010).

The Neurobiology of Anhedonia

Anhedonia and Mesocorticolimbic Reward Circuitry Functioning

Investigations probing the neural mechanisms of reward processes implicated in anhedonia, such as motivation and decision-making, have identified regions of interest in mesocorticolimbic dopamine (DA) circuitry. The mesocorticolimbic system, the brain's reward system, passes through the reward learning (-meso), cognitive control (-cortico), and emotional (-limbic) hubs of the brain (Berridge & Robinson, 2003). This system consists of several brain

structures, namely the nucleus accumbens (NAc) in the ventral striatum, the caudate nucleus and putamen in the dorsal striatum, ventral tegmental area (VTA), and prefrontal cortex (PFC) (Berridge & Robinson, 2016; Russo & Nestler, 2013). Regions of interest with strong connections to mesolimbic DA regions include the amygdala, hippocampus, anterior cingulate cortex (ACC), and insular cortex (Husain & Roiser, 2018). The mesocorticolimbic system is rich in DA receptors. Activation or excitability of the mesocorticolimbic system differs across psychopathologies that are marked by deficits in reward functioning or processing (i.e., altered responsiveness or motivation toward reward). For example, in disorders of drug addiction characterized by hyperactivation towards drug-related rewards, the mesocorticolimbic system becomes sensitized to drug rewards and responds more strongly to drug cues, contributing to dependence and higher tolerance (Schultz, 2011). Schizophrenia is also characterized by dysregulated mesocorticolimbic system reactivity, and in particular increased striatal DA; in fact, antipsychotic drugs work in part to relieve positive symptoms by diminishing dopaminergic hyperactivity (Weinstein et al., 2017). Conversely, mood disorders are characterized by reduced reactivity of the reward system, reflecting a higher threshold for rewarding stimuli (Russo & Nestler, 2013).

Anhedonia is associated with blunted mesocorticolimbic system functioning (Borsini et al., 2020; Pizzagalli, 2014). Most of the work investigating anhedonia and the reward system has been conducted in depressed samples, finding that anhedonia severity negatively correlates with ventral striatum activity during anticipation of reward in adults (Arrondo et al., 2015) and adolescents (Gabbay et al., 2013; Stringaris et al., 2015). A recent meta-analysis of neuroimaging findings of reward processing deficits in depression provides strong evidence for striatal hypoactivation as a neural mechanism of anhedonia, across reward wanting and liking (Borsini et al., 2020). Additionally, a study in a non-clinical sample of adults showed that decreased NAc

volume and reduced nucleus accumbens response to reward were uniquely related to anhedonia severity, and not depressive or anxious symptoms (Wacker et al., 2009). Hyperactivation in brain frontal cortices (i.e., medial PFC and dorsolateral PFC) and hypoactivation in the orbitofrontal cortex have been associated with both reward wanting and liking (Borsini et al., 2020). Hyperactivation has also been reported in cingulate cortices during reward anticipation in MDD samples, not specific to anhedonia (Gorka et al., 2014; W.-N. Zhang et al., 2013). Lastly, anhedonia severity in adolescents is correlated with increased intrinsic functional connectivity between striatal regions and the dorsomedial PFC (Gabbay et al., 2013). Together, these findings demonstrate distinct patterns of reward network activation and connectivity associated with anhedonia; and given that most studies have been conducted in MDD samples, further transdiagnostic work is needed.

Anhedonia and Mesocorticolimbic Dopamine

Anhedonia and reward sensitivity are multi-faceted constructs that have expanded from the original "anhedonia hypothesis", proposed to link DA and reward, which was specific to objectively measured reward function rather than the subjective clinical experience of anhedonia (Wise, 2008). The link between mesocorticolimbic dopaminergic functioning and reward processing is well documented: there is an extensive body of literature detailing how behavioral impairments in motivation and the anticipation of rewards are associated with alterations in tonic DA levels, phasic DA release, and DA signaling (Der-Avakian & Markou, 2012; Pizzagalli, 2014; Russo & Nestler, 2013; Schultz, 2019). Dopamine, commonly referred to as a "reward" neurotransmitter, is associated with reward processes, but also performs other functions (Berridge, 2006; Berridge & Robinson, 2016). Traditionally, striatal DA was hypothesized to be primarily involved in the reinforcement of reward and pleasure, but this has evolved with the introduction of competing findings. Instead, striatal DA's role is that of incentive salience

(Berridge & Robinson, 1998), transferring value from the reward to the cue that predicts the reward. Striatal DA release correlates with reward coding during anticipation (Borsini et al., 2020) and is related to reward wanting, decision-making, and the perception of effort, rather than the perception of pleasure (Der-Avakian & Markou, 2012; Salamone & Correa, 2012; Treadway et al., 2012). Similarly, anhedonia was originally proposed as a deficit in the capacity for pleasure (e.g., hedonic capacity) and has since been re-conceptualized (Olney et al., 2018; Treadway & Zald, 2011).

Much of our understanding about the relationship between anhedonia and DA comes from investigations into DA and reward processing across preclinical and human studies. Some positron emission tomography (PET) studies investigating striatal DA function have offered support for DA dysfunction in samples with core anhedonic symptoms (e.g., MDD). Although, this literature is inconsistent, with some finding that anhedonia is associated with decreased striatal DA release (J. Felger et al., 2013), increased striatal DA release in MDD non-remitters (Peciña et al., 2017), and others with no support for abnormal DA release capacity in MDD (Schneier et al., 2018). Perhaps the most compelling evidence in humans utilizes simultaneous magnetic resonance (MR) and positron emission tomography (PET) imaging to concurrently evaluate DA signaling and neural responses. Through the innovative application of PET-MR, at least two studies to-date using [^{11}C]raclopride, a radioligand that allows for the quantification of D2/D3 receptor-binding potential, have demonstrated that fMRI activation and functional connectivity in mesolimbic brain regions during reward anticipation correlate with ventral striatal DA release in clinical (Hamilton et al., 2018) and non-clinical samples (Schott et al., 2008).

Although the current PET study, using [^{11}C]raclopride, will evaluate the role of DA within the reward system, there are multiple neurotransmitters that are signaled along this circuit

and these regions of interest are made up of dopaminergic neurons as well as GABAergic and serotonergic neurons, among others (Russo & Nestler, 2013). Importantly, there is also evidence that dopaminergic neurons do not exclusively release DA, adding to the functional diversity of this system (Tritsch et al., 2012). The section below describes the ways that stress can negatively impact the mesocorticolimbic reward system, and more specifically dopaminergic function within regions of the reward system.

Chronic Stress and Mesocorticolimbic Dopamine Functioning

Stress and Mesocorticolimbic Reward Circuitry

The impact of stress on the brain is complex and not uni-directional. In response to stressors, the hypothalamic-pituitary-adrenal (HPA) axis is activated and gives rise to physiological sensations associated with stress and anxiety. While a comprehensive review of these biological processes and other important factors, such as the onset and timing of stressors, are beyond the scope of the current review, they are worth highlighting here. The resulting stress response induces a flood of glucocorticoids, or inflammatory mediators, that may instigate or account for abnormalities in reward-related brain function. These hormones pass the blood-brain-barrier and act on the mesocorticolimbic system (Sandi & Haller, 2015). The brain's reward system has a high density of glucocorticoid receptors, and Sandi and Haller (Sandi & Haller, 2015) argue that "glucocorticoid signaling at least partly mediates the behavioral effects of stress". Heightened glucocorticoid levels for extended periods of time (e.g., during a prolonged stress response) have been associated with altered functional connectivity between limbic and frontal brain regions within the reward system (Sheth et al., 2017).

Stress and Striatal Dopamine

Chronic and prolonged stress exposure is thought to cause widespread alterations in the mesocorticolimbic system, including but not limited to, dysfunctional DA signaling and

transmission, and dysregulated DA circuitry (Pizzagalli, 2014). Acute stressors lead to increased DA levels along the mesocorticolimbic pathway, originating from DA release in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), which is adaptive for the purpose of escaping or avoiding the stressor (Ironside et al., 2018; Kumar et al., 2015). Yet, following chronic stress, the NAc begins to inhibit DA release, which has been associated with learned helplessness and coping failure (Cabib & Puglisi-Allegra, 2012; Ironside et al., 2018). There also appears to be an important role for VTA DA neurons in the function of stress, whereby chronic stress alters DA neuron firing (Russo & Nestler, 2013). However, there is contradicting evidence from animal studies regarding the directionality of mesolimbic DA transmission (i.e., increase or decrease in DA release) in the relationship between stress and motivated behavior, depending on the intensity of the stressor (Hollon et al., 2015). Chronic mild stress in animals is associated with hypoactive ventral tegmental area (VTA) DA neurons (Chang & Grace, 2014), while social defeat stress in animals has been linked with an increased firing rate of VTA DA neurons (Krishnan et al., 2007). As with chronic mild stress paradigms, chronic cold stress exposure, designed to induce activation of the HPA axis, attenuates DA neuron firing in the VTA (Valenti et al., 2012). This effect has been shown to be specific to regions of the VTA that project to ventral striatal reward regions.

Together, these divergent findings in chronic stress support the idea that the mesocorticolimbic DA system becomes sensitized to novel stressors following chronic stress, potentially contributing to "the maintenance of anhedonic behavior" (Pizzagalli, 2014). Striatal dopaminergic functioning has been investigated in humans following induction of acute stress, finding that DA synthesis correlated with an acute stress response in healthy participants (Bloomfield et al., 2019). In this same investigation by Bloomfield and colleagues (2019), they observed blunted striatal dopaminergic functioning in adults with long-term exposure to

psychosocial adversity, a form of chronic stress. Additionally, a study of DA functioning in adults at elevated risk for developing schizophrenia found increased DA release in response to stress, which was unique to a group with physical anhedonia symptoms (Soliman et al., 2008). Abnormalities in the DA response to stress have been demonstrated following chronic stress in animal models and acute stress in clinical samples; thus, more studies of *in vivo* DA functioning in humans are needed to further elucidate the impact of chronic stress.

This is the first study of striatal dopaminergic functioning and reward circuitry in a transdiagnostic sample of adults with anhedonia, ranging in exposure to chronic stress. The goal of the current study was to use simultaneous functional magnetic resonance and positron emission tomography (PET-MR) imaging with the D2/D3 dopamine receptor antagonist [^{11}C]raclopride to investigate mesocorticolimbic network functioning during reward processing, in anhedonia. Here, we also sought to clarify the unique contribution of chronic stress, operationalized as the perception of stress as unpredictable and uncontrollable, on striatal dopamine (DA) and reward circuitry functioning.

Study Aims & Hypotheses

Aim 1 – Evaluate the role of striatal dopamine functioning during reward processing, using PET, in the association between chronic stress and anhedonia severity.

Hypothesis 1a: Striatal dopaminergic functioning, indexed by the non-displaceable binding potential (BP_{ND}) of [^{11}C]raclopride, will significantly predict anhedonia severity, demonstrating a direct effect of striatal DA release to rewards on anhedonia severity.

Hypothesis 1b: Striatal dopaminergic functioning will mediate the relationship between self-reported chronic stress and anhedonia severity, demonstrating a potential pathway through which chronic stress contributes to anhedonia severity.

Aim 2 – Evaluate the role of mesocorticolimbic network fMRI activation during reward processing in the association between chronic stress and anhedonia.

Hypothesis 2a: Mesocorticolimbic network fMRI activation, indexed by the blood-oxygen-level dependent (BOLD) signal in regions-of-interest during reward processing, will significantly predict anhedonia severity, demonstrating a direct effect of mesocorticolimbic activation on anhedonia severity.

Hypothesis 2b: Mesocorticolimbic network fMRI activation will mediate the relationship between self-reported chronic stress and anhedonia severity, demonstrating a potential pathway through which chronic stress contributes to clinical symptom severity.

Aim 3 – Evaluate the role of mesocorticolimbic network functional connectivity during reward processing, using simultaneous PET-MR imaging, in the association between chronic stress and anhedonia.

Hypothesis 3a: Mesocorticolimbic network connectivity, indexed by the functional connections between (a) ROIs that demonstrate significant phasic DA release to rewards

in Aim 1, and (b) atlas-derived ROIs, will significantly predict anhedonia severity, demonstrating a direct effect of mesocorticolimbic connectivity on anhedonia severity.

Hypothesis 3b: Mesocorticolimbic network connectivity will mediate the relationship between self-reported chronic stress and anhedonia severity, demonstrating a potential pathway through which chronic stress contributes to anhedonia severity.

CHAPTER 2: METHODS

Study Overview

The present study complements an ongoing 5-year NIMH-funded clinical trial (R61/R33 MH110027; co-PIs Dichter & Smoski) investigating the effects of a novel anhedonia treatment on neural responses to rewards and anhedonia symptoms (ClinicalTrials.gov Identifiers NCT02874534 and NCT04036136). The parent grant to this research supported the recruitment and characterization of anhedonia participants (n=25, ANH). A separate grant to this research (R21 MH110933; PI Dichter), investigating striatal dopamine binding in autism, supported the recruitment of control participants (n=12, CON) (Zürcher et al., 2021). The current study utilizes neuroimaging data (i.e., simultaneous PET-MR imaging data) from these two parent studies, as well as clinical assessment data from the anhedonia treatment clinical trial. The current research expands upon this work by investigating proposed mechanisms through which chronic stress impacts anhedonia severity.

Both parent studies met research standards for Institutional Review Board (IRB) approval at UNC Chapel Hill, and PET imaging protocols were approved by the UNC Radioactive Drug Research Committee. PET imaging protocols also received Investigational New Drug (IND) authorization from the Food and Drug Administration (FDA). Neuroimaging scan procedures were identical between the two studies. A bolus+infusion protocol (*Figure 1*) was implemented for PET-MR scanning, using the D2/D3 antagonist, [^{11}C]raclopride, which selectively binds to striatal DA receptors (Papenberg et al., 2019). ANH and CON participants completed neuroimaging scans at the UNC Biomedical Research Imaging Center (BRIC) at UNC Chapel Hill, and ANH participants completed symptom assessments at Duke University. PET-MR

imaging data acquisition occurred within 3 weeks of ANH participants' initial assessment appointments, which took place at Duke University. Written informed consent was obtained prior to inclusion in the study.

Participants

Eligibility Criteria

Eligible anhedonia participants (ANH) were 18 to 50 years old, treatment-seeking for clinically significant anhedonia (i.e., Snaith-Hamilton Pleasure Scale (SHAPS) scores greater than or equal to 30) (Franken et al., 2007), and had Clinician's Global Impression Scale Severity (CGI-S) scores greater than or equal to 3, indicating clinical impairment. Eligible control participants (CON) had no lifetime current or past history of psychiatric diagnoses, as assessed by the Structured Clinical Interview for DSM-5 (SCID-5-RV) (First et al., 2015). CON participants were recruited through a university email listserv.

Individuals who met any of the following criteria were excluded from participation: (1) those for whom medication management is the primary treatment approach (i.e. bipolar disorder or mania, schizophrenia, or other psychotic disorders), (2) those who have had prior treatment with behavioral activation or mindfulness-based approaches for depression (i.e., prior exposure to the experimental treatments used in the parent study), (3) those who may have difficulty understanding the cognitive components of treatment (i.e., an intellectual disability, neurocognitive disorder, dissociative disorder, or IQ score less than 90), (4) those with a feeding or eating disorder which may have confounding effects on the BOLD fMRI signal, (5) those with a severe current or lifetime substance use disorder (SUD) or alcohol use disorder (AUD) which may have confounding effects on the BOLD fMRI signal, (6) those with current suicidal intent or plan within the last month (i.e., those recommended for referral to more intensive clinical management services), (7) those with psychotropic medication use within the last month and/or

current psychotherapy, (8) those who are currently pregnant (i.e. measured via urine pregnancy screen immediately before MRI scans), (9) those with positive urinalysis screen for substance use at the time of the MRI scan, (10) those with neurological conditions (i.e., history of stroke, seizure, or traumatic brain injury), (11) those with contraindications for MRI imaging (i.e., metal in the body, prior metallic injury, or metallic dental work, (12) those who have had PET scans in the prior 12 months that exceed UNC IRB guidelines of 15 mSv radiation exposure, (13) those who have undergone radiation therapy or chemotherapy in the 2 months prior to scanning, and (14) those who are blind or unable to read and comprehend English.

Twenty-eight ANH participants and 23 CON participants completed a PET-MR scan with [^{11}C]raclopride at UNC Chapel Hill. Three ANH participants and 11 CON participants with unusable data were excluded due to problems with the PET injection or scanner (n=4; 4 CON participants), PET infusion (n=2; 2 ANH participants), and technical errors at the time of the scan (n=8; 1 ANH and 7 CON participants). The final sample included 25 anhedonia participants (ANH) and 12 control participants (CON).

Clinical Diagnostic & Symptom Measures

For all participants, the Structured Clinical Interview for DSM Disorders-5 Research Version (SCID-5-RV) was used for eligibility determination (i.e., to assess exclusionary diagnostic disorders) and clinical characterization. In addition to screening for psychiatric disorders (e.g., Major Depression, Generalized Anxiety Disorder, Bipolar Disorder), the SCID-5-RV also includes abbreviated questions pertaining to psychotherapy history and medication use (Shankman et al., 2018).

Additionally, participants in the ANH group completed self-report measures assessing perceived stress and anhedonia severity. These measures were not collected from CON participants. The Perceived Stress Scale (PSS-14) was the primary measure of chronic stress.

The PSS assesses self-reported unpredictable and uncontrollable stressors over the past month and contains 14 items rated on a 1 (never) to 4 (very often) scale (Hewitt et al., 1992). Total scores on the PSS range from 0 to 40, whereby higher scores indicate greater perceived stress (Bernstein et al., 1994). Participants respond to statements about the degree to which they are impacted by stressors in their life and can cope with these (e.g., "How often have you been upset because of something that happened unexpectedly?", "How often have you felt that you were unable to control the important things in your life?", "How often have you found that you could not cope with all the things that you had to do?")

The Snaith–Hamilton Pleasure Scale (SHAPS) was the primary measure of anhedonia; it was used to assess inclusion criteria for clinically significant anhedonia and served as the primary clinical outcome in the current study. The SHAPS is a well-validated 14-item questionnaire that assesses hedonic capacity. A SHAPS score of ≥ 20 corresponds to clinically significant anhedonia from a general population sample (Franken et al., 2007). On the SHAPS, participants respond to statements about how much they would enjoy specific activities (e.g., "I would be able to enjoy a beautiful landscape or view") (Snaith et al., 1995). SHAPS items are rated on a 1 (strongly agree) to 4 (strongly disagree) scale. Total scores on the SHAPS range from 14 to 56, whereby higher scores indicate greater anhedonia severity in the present state.

In post-hoc analyses, the Beck Depression Inventory (BDI-II) Anhedonia Subscale was used as a secondary measure of anhedonia. This subscale is comprised of four items from the BDI-II (i.e., loss of interest, loss of pleasure, loss of interest in sex, and loss of energy) (Pizzagalli et al., 2005). On the BDI-II Anhedonia subscale, participants choose statements about their loss of interest in daily activities over the past two weeks, asking them to consider the rewarding potential of activities and social interactions (e.g., "I have lost most of my interest in other people or things") (Joiner et al., 2003; Pizzagalli et al., 2005). Whereas the SHAPS

primarily assesses aspects of consummatory reward, or pleasure, the BDI-II Anhedonia Subscale captures aspects of both consummatory and *anticipatory* reward processing, or motivation and interest toward rewards (Pizzagalli et al., 2005). Although the BDI-II Anhedonia subscale is not widely used, its reliability is adequate (.60) (Pizzagalli et al., 2005).

Neuroimaging Data

Simultaneous PET-MR scan protocol

Participants completed a 75-minute simultaneous PET-MR scan on a Siemens Biograph mMR scanner at the UNC Biomedical Research Imaging Center (BRIC). Dynamic PET acquisition used a bolus+infusion protocol for [^{11}C]raclopride and a planned K_{bol} of 105 min, administered using a Medrad® Spectris Solaris® EP MR Injection System. List mode 3-D emission data were collected starting from bolus injection and continued over the 75 min scan. Radioactivity was limited to 15mCi in total over the bolus and infusion and mass dose did not exceed 10μg for the duration of the scan. In the first portion of scan acquisition, after the PET scan was initiated, participants underwent two 8-min fMRI resting state scans and one 6-min high resolution T1 scan. In the second portion, participants completed the monetary incentive delay (MID) task described below, during which BOLD fMRI data were acquired simultaneously. A structural T1 MR sequence (FOV=256 mm, 111 mm resolution, TR=2530ms, TE=1.69ms, flip angle=7 degrees) was used for anatomical localization, spatial normalization of imaging data, and generation of attenuation correction maps. Two identical resting-state scan sequences (echo planar imaging, FOV=212 mm, 3.312 x 3.312 x 3.3 mm resolution, TR=3000, TE=30ms, flip angle=90 degrees) were obtained to capture endogenous neural activity. The functional scan sequence (same parameters as resting-state), during which participants were engaged in the MID task, was collected over three task blocks. See *Figure 1* for timing of data collection by modality.

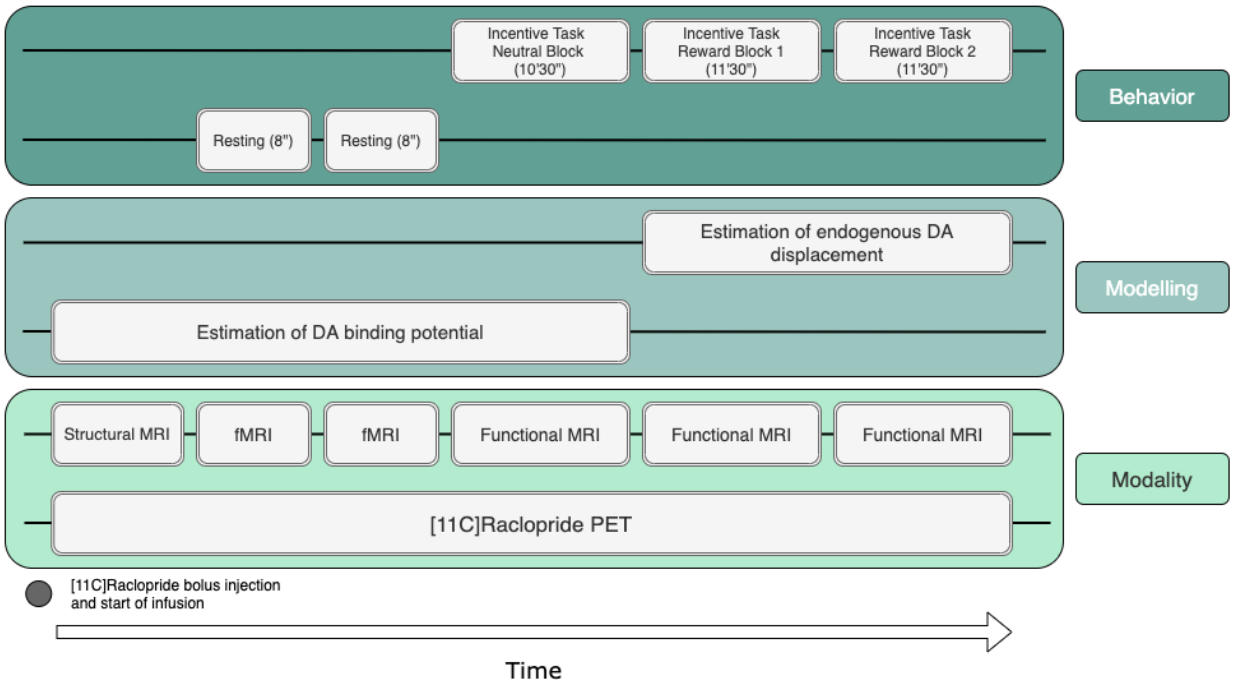

Figure 1. Scanning Procedure.
Timing of data collection, data modelling, and participant behavior during scanning.

Monetary Incentive Delay (MID) Task – Optimized Version for PET

Participants completed the monetary incentive delay (MID) task, a reward processing task shown to reliably elicit BOLD response and phasic DA release to rewards (Knutson et al., 2000; Weiland et al., 2014). The task was presented using PsychoPy software version 1.84.1 (Peirce et al., 2019). The MID task was optimized for the slow kinetics of [^{11}C]raclopride displacement (Schott et al., 2008) and has been used in prior investigations by the parent study (Zürcher et al., 2021). This optimized MID task includes novel features designed to maximize detection of DA release in the PET-MR environment. First, the initial reward block begins approximately 40 min after the [^{11}C]raclopride bolus injection, after the target-to-reference region ratio is stabilized. This long uptake period serves as a baseline scan. Second, about 75% of reward trials are followed by reward feedback, resulting in a success rate that is higher than traditional MID tasks to enhance incentive motivation. Third, while most MID versions use

explicit reward and neutral cues that make the potential outcome of each trial clear, the current design forces participants to learn which cues predict which reward magnitudes by experience. By adding associative learning, the current design aims to enhance sensitivity to positive prediction errors (and other learning-related signals) encoded by phasic DA release (Berridge & Robinson, 2003). This modified version of the MID task (*Figure 2)* was developed at McLean Hospital.

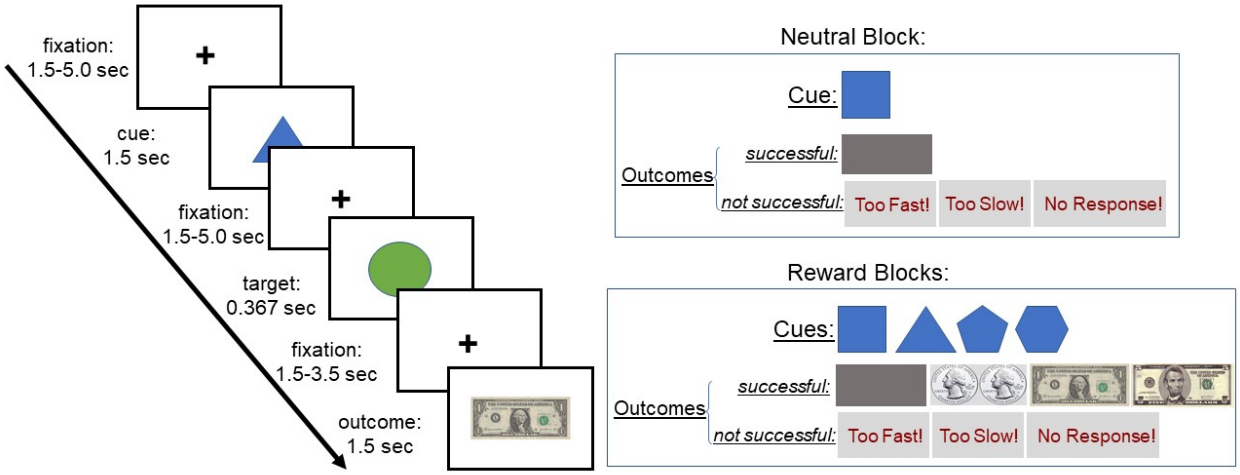

Figure 2. PET-MR Monetary Incentive Delay (MID) Task.
Each trial consisted of a cue phase and an outcome phase. Trials were presented first in a neutral block that consisted of only neutral trials and then in two reward blocks that consisted of neutral trials and reward trials of varying magnitudes (small, medium, or large).

On each trial (6.37–15.17 s), participants saw a blue polygon cue (1.5 s), followed by a green circle target (0.367 s) and an outcome (1.5 s). These stimuli were separated by jittered interstimulus and intertrial intervals during which a fixation cross was shown. The task required making a speeded button press with the right index finger upon seeing the target. The task was divided into one neutral (10'30") and two reward (11'30" x 2) blocks. The neutral and reward blocks were separated by a brief break.

During the neutral block, participants completed 63 trials that started with a square cue. No monetary rewards were delivered on these trials. Instead, sufficiently speeded button presses

resulted in the presentation of a gray rectangle as a "no-reward" outcome. The other outcomes indicated either no response ("No Response!"), the response was too quick (within 100 ms of the target presentation: "Too Fast!"), or it was made after an adaptive reaction time (RT) threshold ("Too Slow!") that was programmed such that ~75% of each participant's responses were successful.

In the reward blocks, comprised of 75% rewarded and 25% nonrewarded trials, participants won money if they responded quickly enough to the target stimuli on rewarded trials. In the reward blocks, different polygon cues (square, triangle, pentagon, and hexagon) indicated that trials could result in no-reward (gray rectangle) or a small (50 cents), medium (1 dollar), or large reward (5 dollars), respectively. The assignment of the four polygons to the four outcomes was stable across the reward blocks and counterbalanced across participants. Successful trials (i.e., trials with sufficiently speeded button presses) ended with images depicting the no-reward, small, medium, and large reward outcomes. Unsuccessful trials yielded the same feedback as in the neutral block ("Too Fast!", "Too Slow!", or "No Response!"). Each reward block contained two reward runs (number of trials per reward run: Block 1: 34/33, Block 2: 33/34). Following each neutral and reward block, participants rated cues and outcomes using a nine-point Likert scale with anchors of "very negative" and "very positive" at the ends and "neutral" in the center.

PET Image Preprocessing

List mode 3-D emission data were collected starting from bolus injection and continuing over the 75 min PET-MR scan. The list mode data, in 1-minute time frames, underwent post-scan reconstruction procedures, accomplished using MR-based attenuation maps with bone and sinus details that are created using the PseudoCT method (Ladefoged et al., 2017). Next, the PET images were corrected for motion using the Realign procedure of SPM12. This procedure was

followed by subject-to-MNI space transformation of the PET images using tools in Slicer and SPM12. Transformation to MNI space allows for (1) the mapping of atlases to individual subject PET images to allow us to obtain the time-activity curves (TAC) for several brain regions of interest, and (2) the creation of subject-specific voxel-wise maps in FSL using TACs for each voxel.

fMRI Image Preprocessing & Analysis

Functional data (i.e., MID task runs) for Aim 2 were preprocessed using FSL FEAT version 6.0 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, U.K.). The first four volumes of each functional run were discarded to allow for steady state equilibrium. Preprocessing in FSL included BET brain extraction for non-brain removal using the brain extraction tool (BET), motion correction using MCFLIRT, interleaved slice timing correction, spatial smoothing using a Gaussian kernel of FWHM 6mm, pre-whitening with the FILM tool (Woolrich et al., 2001), co-registration of functional and anatomical images using the boundary based registration (BBR) algorithm (Greve & Fischl, 2009), registration to a standard stereotaxic space (Montreal Neurological Institute; MNI152 2mm) using linear transformation (FLIRT; 12 DOF, 10mm warp field resolution), and high-pass filtering (cutoff of 100 sec). To control for excessive motion, we censored volumes that exceeded a framewise displacement threshold of 0.5mm (Siegel et al., 2014).

Functional connectivity data (i.e., resting-state and MID task runs) for Aim 3 were preprocessed with the default preprocessing pipeline in the SPM12 CONN functional connectivity toolbox, version 19c. The default preprocessing pipeline consists of (a) resampling the scan data to 222-mm voxels and unwarping, (b) centering, (c) slice time correction, (d) normalization to MNI template, (e) outlier detection (ART-based scrubbing), and (f) spatial smoothing. Motion parameters were entered as multiple regressors and used for the identification

of potential outliers that exceeded framewise displacement thresholds. For most of the sample (n = 35), all five runs of functional data were analyzable and all participants had at least three analyzable runs. Reasons for excluded runs were technical errors (n=2), and striation artifacts (n=1). There were no significant differences between groups on average motion, $t(35) = -0.86$, $p = 0.396$ (two-sided), or average global BOLD signal changes, $t(35) = 0.78$, $p = 0.441$ (two-sided).

Estimating Striatal Dopaminergic Functioning (Aim 1)

The use of [^{11}C]raclopride enables two key design features that were utilized in the current study: 1) the use of a highly validated reference tissue model for quantifying binding potential changes; and 2) the use of a bolus+infusion radiotracer administration protocol to increase sensitivity towards measuring DA release. [^{11}C]Raclopride is a D2/D3 receptor antagonist, and therefore competes with endogenous DA for receptors. Binding potential (BP_{ND}), the ratio of selectively bound ligand to non-displaceable ligand in the tissue at equilibrium, was estimated from dynamic PET images for the neutral and reward blocks of the MID task per subject. Here, reward blocks encompass trials during which participants both anticipated and received rewards. We used baseline BP_{ND} and change in BP_{ND} following reward task onset (Δ BP_{ND} %) to measure dopaminergic functioning during baseline (tonic) and activation (phasic) states. This approach allows us to compare the extent to which endogenous DA displaces the radiotracer. A typical, or adaptive, DA response to rewards in the striatum would be indicated by lower BP_{ND} values during reward, relative to neutral, indicating that DA has increased and competed out the tracer for binding sites (Peciña et al., 2017). Moreover, a decrease in BP_{ND} indicates an increase in dopamine (DA) release.

In order to identify regions that showed between-group differences in BP_{ND} from neutral to reward phases of the MID, we estimated striatal dopamine functioning during each condition

of the task for each subject. A *z*-score statistical map representing the difference between groups and conditions (ANH > CON; Reward>Neutral) was created from subject images by contrasting voxel-wise BP_{ND} (Reward > Neutral) maps. This *z*-score statistical map was then thresholded at *z* > 2.58 and anatomically constrained to the striatum (i.e., bilateral caudate, putamen, and nucleus accumbens) using masks from the Harvard-Oxford probabilistic atlas. Results for the contrast of ANH > CON, Reward > Neutral signify increased BP_{ND} or decreased phasic DA release to the reward condition, relative to the neutral condition, in the ANH group compared to controls. For each significant cluster, condition-specific BP_{ND} values were extracted from each participant and analyzed using group (ANH, CON) × condition (reward, neutral) ANOVAs. Finally, for clusters that showed between-group differences, we then examined associations between striatal BP_{ND} values and anhedonia and stress measures within the ANH group (because anhedonia and stress measures were only collected in the ANH group).

Estimating Mesocorticolimbic Network Activation (Aim 2)

To examine fMRI responses during reward anticipation, the contrast between neutral and reward trials of all magnitudes (small, medium, and large) from the onset of the cue to the end of the fixation period (i.e., during the cue and the target) was examined. To examine fMRI responses during reward outcomes, the contrast between successful and unsuccessful outcomes (i.e., successful vs. unsuccessful reward outcomes on reward trials of all magnitudes (small, medium, and large)) was examined.

A *priori* hypothesis testing was conducted using a region of interest (ROI) approach. During reward anticipation, ROIs included the bilateral nucleus accumbens, caudate, and putamen (Berridge & Robinson, 2016; Russo & Nestler, 2013). During reward outcomes, ROIs included the medial prefrontal cortex and anterior cingulate cortex (Husain & Roiser, 2018). These ROIs were defined using the Harvard-Oxford subcortical and cortical structural

probabilistic atlases. For each participant and condition, BOLD percent-signal change values were calculated and extracted from ROIs using FSL Featquery. We then conducted independent samples (ANH, CON) t-tests to explore group differences in BOLD percent-signal change. ROI analyses were supplemented with a general linear model approach, fitted to generate whole-brain images, allowing us to examine activation in other reward processing regions. Group-wise activation images were calculated using Bayesian estimation (FMRIB Local Analysis of Mixed Effects), and were cluster corrected with a cluster-defining threshold of $z = 2.58$, and cluster p-threshold of $p < 0.05$.

Estimating Mesocorticolimbic Network Connectivity (Aim 3)

A general functional connectivity (GFC) approach was used to examine whole-brain connectivity with striatal PET-derived seed regions that displayed significant differences in BP_{ND} between neutral and reward blocks of the MID task. GFC, a method that combines resting-state and task fMRI data, offers better test-retest reliability and higher estimates of heritability than intrinsic connectivity estimates from the same amount of resting-state data alone (Elliott et al., 2019). In the current study, the combination of two resting-state runs and three task blocks of the MID yielded approximately 45 minutes of fMRI data for connectivity analyses, and an advantage of GFC is the ability to improve reliability by analyzing longer durations of fMRI data. This is critical given that >25 min of fMRI data is needed to reliably detect individual differences in connectivity (Anderson et al., 2011). Voxel-wise whole-brain connectivity was evaluated using the CONN Toolbox's seed-to-voxel analysis, using (1) PET-derived seeds and (2) atlas-derived seeds. *A priori* seeds included atlas-derived brain regions within the mesocorticolimbic reward network, including the medial prefrontal cortex, anterior insula, anterior cingulate cortex, amygdala, ventral tegmental area, and hippocampus. All atlas-derived seeds, with the exception of the ventral tegmental area, were derived from the Harvard-Oxford cortical and subcortical

structural probabilistic atlases. The ventral tegmental area (VTA) seed was derived from the CIT168 brain atlas, which includes subcortical nuclei (Pauli et al., 2018). All analyses corrected for multiple comparisons using a false-discovery rate (FDR) approach, at the familywise error rate of $p < .05$.

Statistical Analyses

Exploring Direct Effects - Linear Regression

To examine whether anhedonia severity was predicted by striatal dopaminergic function (Hypothesis 1a), mesocorticolimbic network fMRI activation (Hypothesis 2a), and mesocorticolimbic network functional connectivity (Hypothesis 3a), we conducted statistical regression models in R, version 4.0.3 (2020). Here, PET-derived striatal binding potential (BP_{ND}) (Hypothesis 1a), fMRI-derived BOLD signal (Hypothesis 2a), and fMRI-derived correlations between network regions with correlated BOLD signal change (Hypothesis 3a) were used as individual predictors in separate regressions. All analyses were corrected for multiple comparisons using the false-discovery rate (FDR) method (Benjamani & Hochberg, 1995).

Exploring Indirect Effects - Mediation

To examine whether the relationship between chronic stress and anhedonia was mediated by striatal dopaminergic function, mesocorticolimbic network fMRI activation, and mesocorticolimbic network functional connectivity, we tested mediation models in *PROCESS macro* for each hypothesis. PROCESS is an observed variable ordinary-least-squares (OLS) and logistic regression path analysis modeling tool (Preacher & Hayes, 2008). Mediation models tested the (1) total effect (i.e., all direct and indirect effects), (2) direct effects (i.e., the independent variable (IV) on the dependent variable (DV), IV on the mediator, and the mediator on the DV), and (3) indirect effects of the IV on the DV through the mediator. For all models, the IV was chronic stress and the DV was anhedonia. The *PROCESS* software generated the

individual beta coefficients (unstandardized weights), standard error (SE), t-value, and p-values for each estimated direct effect. An R^2 value was also generated, to be interpreted as the amount of variance in anhedonia accounted for by chronic stress and mediator variable of interest. Bootstrapping methods, for bias-correction, were used to test the significance of indirect effects in our mediation models and compute 95% confidence intervals (CI). CIs were also estimated using *PROCESS*. Given that indirect effects are estimated using bootstrapping methods, *p*-values are not available for the interpretation of the indirect effect. Rather than a significant (<.05) *p*-value, criteria for mediation requires that the confidence interval does not include 0. If the confidence interval includes 0, the true value of the parameter of interest could be 0, and mediation cannot be concluded. Here, PET-derived striatal binding potential (BP_{ND}) (Hypothesis 1b), fMRI-derived BOLD signal (Hypothesis 2b), and fMRI-derived correlations between network regions with correlated BOLD signal change (Hypothesis 3b) were used as mediators in separate models.

CHAPTER 3: RESULTS

Patient Characteristics

Table 1 reports demographic information and descriptive statistics for the samples, including clinical symptom score averages.

	Anhedonia Group (n=25)			**Control Group** (n=12)			**Total Sample** (n=37)		
Variable	*M*	*SD*	*Range*	*M*	*SD*	*Range*	*M*	*SD*	*Range*
Age	26.32	6.01	19-42	25.67	4.30	21-36	26.40	5.49	19-42
Variable	*Count*		*Percent*	*Count*		*Percent*	*Count*		*Percent*
Sex									
Female	15		(60%)	2		(16.7%)	17		(45.9%)
Male	10		(40%)	10		(83.3%)	20		(54.1%)
Race									
White	13		(52%)	8		(66.7%)	21		(56.8%)
Black / African American	3		(12%)	2		(16.7%)	5		(13.5%)
Asian	7		(28%)	1		(8.3%)	8		(21.6%)
American Indian / Alaska Native	1		(4%)	-		-	1		(2.7%)
Other (Not Listed)	2		(8%)	-		-	2		(5.4%)
Not Reported	-		-	1		(8.3%)	1		(2.7%)
Ethnicity									
Hispanic	4		(16%)	2		(16.7%)	6		(16.2%)
Non-Hispanic	21		(84%)	10		(83.3%)	31		(83.8%)
Education									
High School	-		-	1		(8.3%)	1		(2.7%)
Some College	4		(16%)	-		-	4		(11%)
Associate Degree	1		(4%)	1		(8.3%)	2		(5.4%)
Bachelor's Degree	13		(52%)	6		(50%)	19		(51%)
Master's Degree	7		(28%)	2		(17%)	9		(24%)
Doctoral or Professional Degree	-		-	2		(17%)	2		(5.4)
Annual Income									
Up to $10,000	2		(8%)	2		(17%)	4		(11%)
$10,001 to $40,000	7		(28%)	3		(25%)	10		(27%)
$40,001 to $70,000	6		(24%)	5		(42%)	11		(30%)
$70,001 to $100,000	5		(20%)	1		(8.3%)	6		(16%)
$100,001 to $130,000	3		(12%)	-		-	3		(8.1%)
$130,001 to $160,000	1		(4%)	-		-	1		(2.7%)
$230,001 to $260,000	1		(4%)	-		-	1		(2.7%)
Not provided	-		-	1		(8.3%)	1		(2.7%)

Table 1. Sample Characteristics.
Note – Participants were able to endorse one or more race categories.

ANH and CON groups did not differ based on age ($t(28.7) = -0.14$, $p = .887$). There were significantly more males than females in the CON group, relative to the ANH group ($\chi^2(1) = 6.13$, $p = .013$). [^{11}C]Raclopride dose differed between groups; for the ANH and Control groups, the average dose was 13.27 mCi (*SD* = 1.28) and 11.73 mCi (*SD* = 2.14), respectively ($t(14.9) = 2.31$, $p = .036$).

For ANH participants, the mean Perceived Stress Scale (PSS) score was 20.8 (*SD* = 3.64) (range 13 to 27), reflecting moderate levels of stress (Cohen & Janicki-Deverts, 2012). Within the ANH group, males reported significantly greater perceived stress on the PSS than females ($t(22.7) = -2.73$, $p = .011$). Additionally, ANH participants reported moderate levels of anhedonia, as assessed by both the Snaith-Hamilton Pleasure Scale (SHAPS) and BDI-II Anhedonia subscale. The mean SHAPS score was 36.6 (*SD* = 4.37) (range from 30 to 45) and the mean BDI-II Anhedonia subscale score was 5.04 (*SD* = 2.03) (range from 2 to 9). Scores on the SHAPS and BDI-II Anhedonia subscale were highly positively correlated ($r = 0.65$, $p = .0005$). Scores on the PSS and BDI-II Anhedonia subscale were highly positively correlated ($r = 0.47$, $p = .0179$). Anhedonia severity ratings did not differ based on sex. A majority of the ANH sample had a primary diagnosis of Major Depressive Disorder (MDD), assessed by the SCID-5. The next largest proportion of ANH participants did not meet criteria for any current diagnoses; however, each of these subjects had a CGI-S score of 3, indicating clinical impairment. *Table 2* reports clinical characteristics for the ANH group.

	Anhedonia Group (n=25)		
Variable	*M*	*SD*	*Range*
PSS	20.84	3.64	13 - 27
SHAPS	36.64	4.37	30 - 45
BDI-II Anhedonia Subscale	5.04	2.03	2 - 9
Primary Diagnosis (SCID-IV)			
No Current Diagnosis	6	(24%)	
Major Depressive Disorder (MDD)	9	(36%)	
Persistent Depressive Disorder (PDD)	3	(12%)	
Generalized Anxiety Disorder	3	(12%)	
Attention-Deficit Hyperactivity Disorder (ADHD)	2	(8%)	
Specific Phobia	1	(4%)	
Other Specified Anxiety Disorder	1	(4%)	

Table 2. Anhedonia Group Clinical Characteristics.
PSS – Perceived Stress Scale; SHAPS – Snaith-Hamilton Pleasure Scale; BDI-II – Beck Depression Inventory.

Striatal Dopaminergic Functioning (Aim 1)

Group Differences in BP_{ND} during the MID Task (Reward – Neutral Conditions)

We first compared striatal dopamine functioning in the ANH group to the CON group. Four striatal clusters located in the left putamen, right putamen and pallidum, left caudate, and left nucleus accumbens (NAc) and putamen demonstrated between-group differences in BP_{ND} values for the contrast of (ANH > CON; Reward > Neutral). See *Table 3* for striatal cluster statistics. On average, CON participants showed lower [^{11}C]raclopride binding potential (BP_{ND}) during the reward condition of the MID relative to the neutral condition, across striatal clusters. Decreased binding potential represents increased phasic DA release to rewards. Relative to CON participants, ANH participants tended to exhibit increased $BP_{ND,}$ or reduced phasic DA release, to rewards. *Figure 3* displays [^{11}C]raclopride BP_{ND} values for each subject, by condition and group. In each of these four clusters, there was a significant group × condition interaction, F's(1,20) > 7.38, p's < .010 (see *Table 4 and Figure 3*).

Cluster Label	*Cluster Size*	*Max Z value*	*Max X*	*Max Y*	*Max Z*
Left putamen	88	4.7	-22	4	12
Right putamen/pallidum	23	3.63	18	6	-4
Left caudate	23	3.33	-16	4	14
Left NAc and putamen	19	3.45	-12	6	-8

Table 3. Striatal Clusters demonstrating ANH > CON Group Differences at a cluster-corrected threshold of z > 2.58.
Contrast of ANH > CON; Reward > Neutral BP_{ND} values. MNI Coordinates. NAc, Nucleus Accumbens. ANH, Anhedonia participants. CON, Control participants.

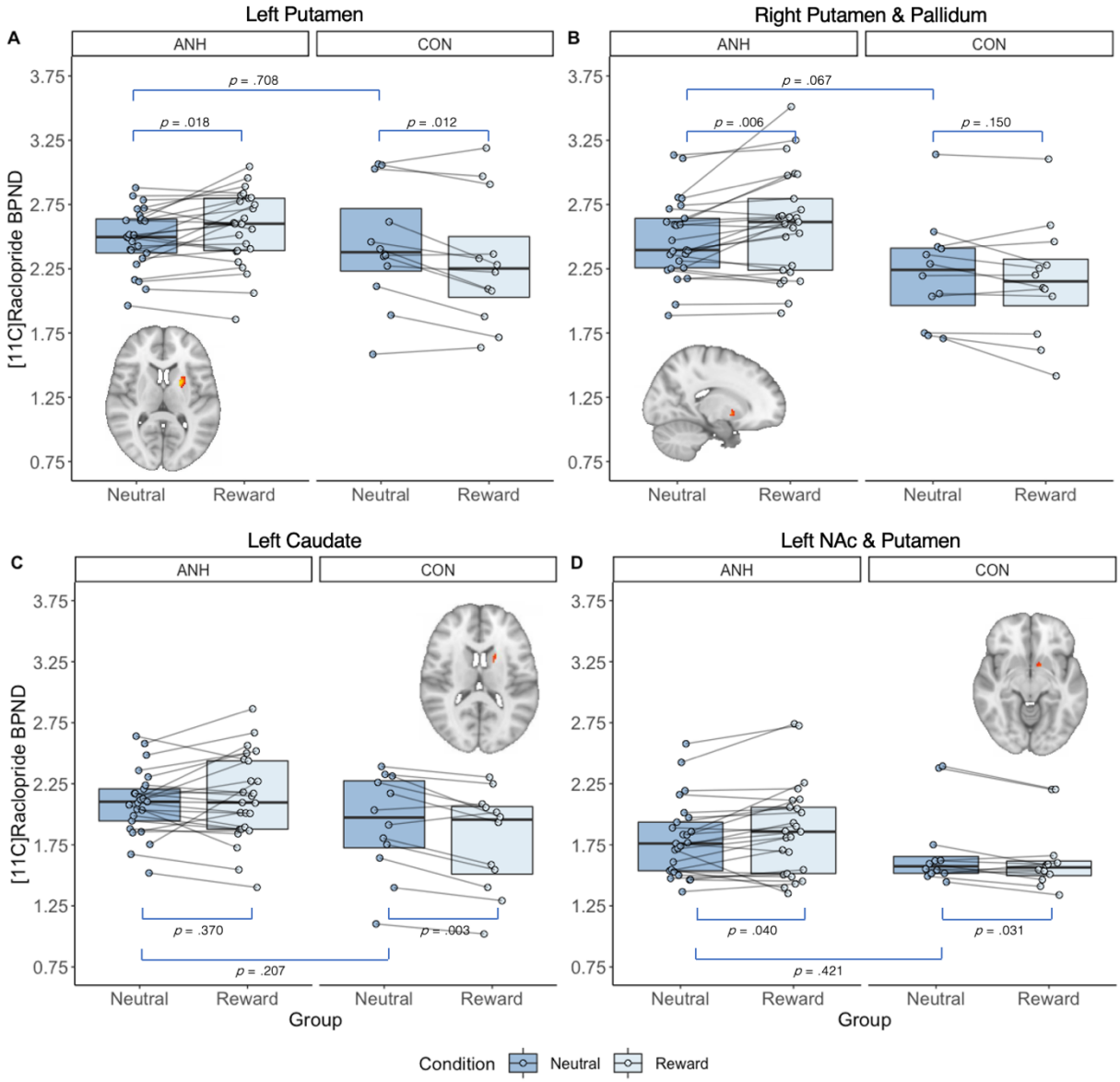

Figure 3. [^{11}C]Raclopride binding potential in striatal clusters demonstrating group differences for the contrast of (ANH > CON; Reward > Neutral).
T-tests are within-group comparisons of BP_{ND} values (Reward > Neutral) and between-group comparisons of BP_{ND} values (Neutral). In each of these four clusters, there was a significant group x condition interaction, F's(1,20) > 7.38, p's < .010. The neutral phase depicted here encompasses the first 42 minutes of scanning (i.e., a measure of tonic DA at baseline).

Cluster	*Sums of Squares*	*F value*	*p-value*
Left putamen			
Group	0.408	1.81	.187
Condition	0.004	0.33	.572
*Group*Condition*	0.178	14.14	.0007***
Right putamen/pallidum			
Group	1.972	7.06	.012*
Condition	0.064	4.09	.051
*Group*Condition*	0.129	8.21	.007**
Left caudate			
Group	1.060	4.83	.035*
Condition	0.007	0.41	.526
*Group*Condition*	0.123	7.38	.010*
Left nAcc and putamen			
Group	0.408	1.93	.173
Condition	0.011	1.14	.293
*Group*Condition*	0.070	7.46	.009**

Table 4. Analysis of Variance Results
For all clusters, the Group (ANH, CON) × Condition (Reward, Neutral) interaction effect on [^{11}C]raclopride BP_{ND} values were significant. *p*-values <.05*, <.01**, <.001***

Relations between Anhedonia and Reduced Phasic DA Release in Striatal Clusters

To evaluate the impact of striatal dopaminergic functioning on anhedonia severity, we examined associations between BP_{ND} values in the striatal clusters that demonstrated group differences, described above, and anhedonia severity scores on the SHAPS and BDI-II Anhedonia subscale. SHAPS scores were not significantly associated with phasic DA release in any of these four clusters (*p*'s > .05). However, reduced phasic DA release to rewards in the left putamen cluster significantly predicted BDI-II Anhedonia subscale scores (β_{STD} = .53, *SE* = 0.20, *t* = 2.63, *p* = .015), controlling for age and sex (*Figure 4*). Moreover, there was a significant positive correlation between BP_{ND} values in the left putamen cluster and BDI-II Anhedonia subscale scores, (*r* = .47, *p* = .017, *pFDR* = .094). Results showed that increased BP_{ND} , or decreased phasic DA to rewards, in the left putamen was associated with greater self-reported anhedonia. BDI-II Anhedonia subscale scores were not significantly associated with phasic DA in the other three striatal clusters (*p*'s > .05).

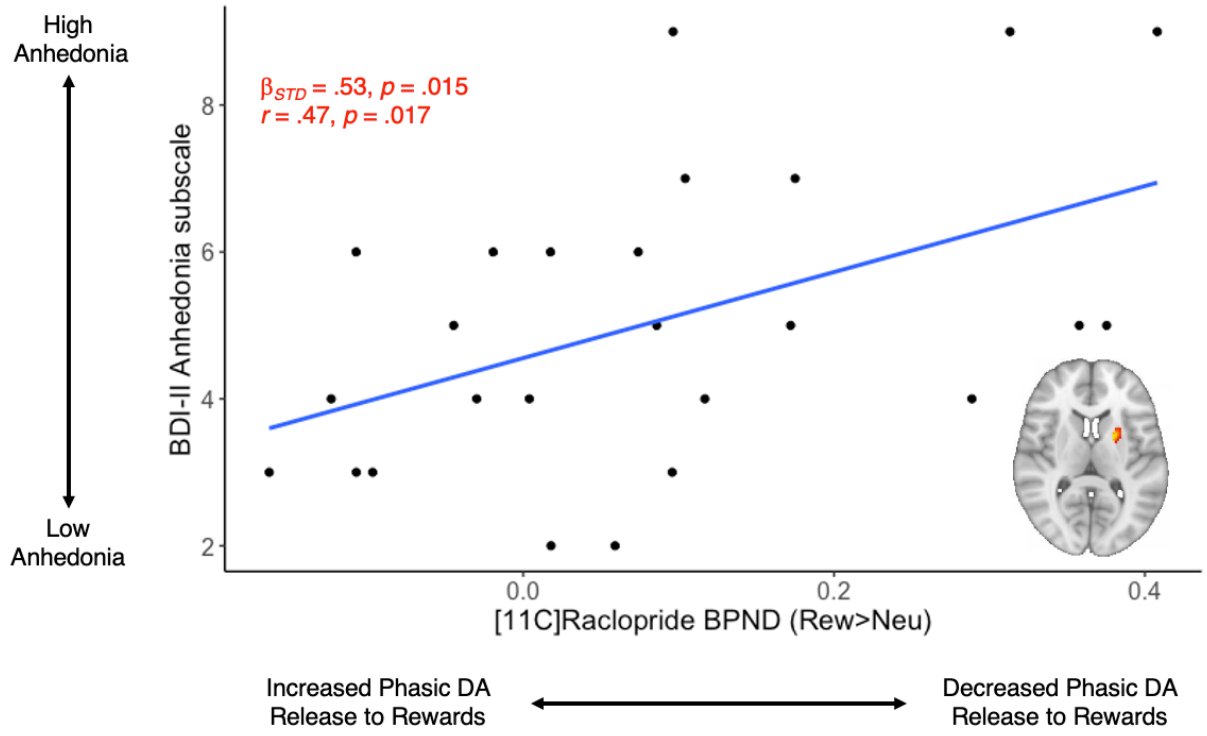

Figure 4. Phasic DA release to rewards in the left putamen striatal cluster correlated with BDI-II Anhedonia subscale scores.
In ANH participants, greater [^{11}C]raclopride binding potential (BP_{ND}) was associated with greater anhedonia severity on the BDI-II Anhedonia subscale (BDI-II, Beck Depression Inventory). Positive BP_{ND} values represent decreased phasic DA release to rewards, relative to neutral stimuli, on the MID task.

Prediction of Anhedonia through Striatal Dopamine Release and Perceived Stress

To test for mediation of the effect of chronic stress on anhedonia through striatal DA functioning, we entered perceived stress (X), anhedonia severity on the BDI-II Anhedonia subscale (Y), and BP_{ND} values in the left putamen cluster (ANH > CON; Reward > Neutral) (M) into a nonparametric bootstrapped model in R's PROCESS macro. The direct association between stress and anhedonia was significant (β = 0.29, *SE* = .11, *p* = .021). Mirroring the results reported above, reduced phasic DA release to rewards in the left putamen cluster (i.e., higher BP_{ND} values) was positively associated with anhedonia (b Path), although this effect was non-significant (β = 4.54, *SE* = 2.37, *p* = .07). The indirect effect (ab Path) was non-significant in the model, containing the direct path from perceived stress to striatal dopamine release and from

striatal dopamine release to anhedonia (β=0.08, CI 95% = -0.036-0.21, as shown in *Figure 5*). The standardized indirect effect of left putamen DA release to rewards on the path between perceived stress and anhedonia was β=0.135 (CI 95% = -0.07-0.363). Together, perceived stress and striatal dopamine release to rewards in the left putamen explained 42% of the variance in anhedonia ($F(4,20) = 3.77$, $R^2 = .429$, $p = .019$). Perceived stress alone explained 22% of the variance in striatal dopamine release to rewards in the left putamen ($F(3,21) = 1.99$, $R^2 = .222$, $p = .145$. This model was adjusted for age and sex. These results indicate that mediation was not supported.

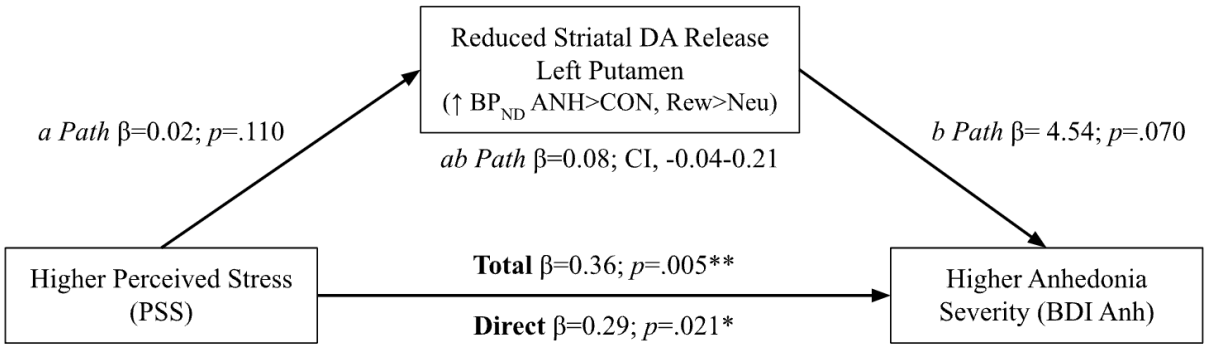

Figure 5. Reduction in striatal DA release to rewards in the left putamen cluster did not mediate the relation between perceived stress and anhedonia.

Mesocorticolimbic fMRI Activation (Aim 2)

Whole-Brain General Linear Model Approach

We examined whole-brain BOLD fMRI responses during reward anticipation and reward outcomes on the MID task. Cluster-corrected results yielded no significant clusters that differentiated groups at a threshold of $z > 2.58$ during reward anticipation or reward outcome phases.

Regions-of-Interest Approach

We examined BOLD percent-signal change in mesocorticolimbic network regions-of-interest (ROIs) during reward anticipation and reward outcomes on the MID task. We found

significant between-group differences in right caudate activation; however, these results did not withstand an FDR-correction for multiple comparisons ($p > .05$). First, across cue phases of the MID task, contrasting Reward > Neutral cues, the ANH group showed increased activation relative to the CON group in the right caudate ($t(26.8) = 2.58$, $p = .016$, $pFDR = .144$). Additionally, across cue phases and fixation phases (i.e., a broader anticipation window than cue phase alone, see *Figure 2*) of the MID task, contrasting Reward > Neutral anticipation trials, the ANH group showed increased activation relative to the CON group in the right caudate ($t(21.0) = 2.26$, $p = .035$, $pFDR = .315$). There were no group differences in activation during reward outcomes.

Relations between Anhedonia and Mesocorticolimbic Activation during Reward Anticipation

To evaluate the impact of mesocorticolimbic activation on anhedonia severity, we examined associations between BOLD activation in the right caudate during reward anticipation (Reward > Neutral) during the MID task, and anhedonia severity scores on the SHAPS and BDI-II Anhedonia subscale. Neither SHAPS nor BDI-II Anhedonia subscale scores were significantly associated with BOLD activation in the right caudate during reward anticipation ($p > .05$).

Prediction of Anhedonia through Mesocorticolimbic Activation and Chronic Stress

Given that mesocorticolimbic activation did not predict anhedonia, and thus, Hypothesis 2A was not supported, we did not test for mediation of the effect of chronic stress on anhedonia through mesocorticolimbic activation as hypothesized.

Mesocorticolimbic fMRI Connectivity (Aim 3)

PET-derived Seed-based General Functional Connectivity

A general functional connectivity (GFC) approach was used to examine whole-brain connectivity with striatal PET-derived seed regions that displayed significant differences in BP_{ND} (i.e., phasic DA release to rewards) between neutral and reward blocks of the MID task. Whole-

brain GFC analysis revealed several significant group differences in connectivity using the PET-derived striatal clusters. In general, PET-derived seeds demonstrated decreased connectivity with subcortical and cortical regions in the ANH group, relative to the CON group. Target regions of these seeds included structures commonly implicated in reward processing, including bilateral caudate, putamen, and pallidum, as well as the medial prefrontal cortex. Associated regions in the anterior cingulate cortex and the thalamus were also identified as target regions. See *Table 5* for striatal cluster connectivity statistics. *Figure 6* illustrates group differences in connectivity between the PET-derived seeds and their respective target regions.

Seed *Target Label*	Cluster Size (voxels)	Size *p*-FEW	Size *p*-FDR	Size *p*-unc	Peak *p*-FEW	Peak *p*-unc
Left Putamen						
Bilateral Striatum (-22, 0, 6)	786	.000	.000	.000	.001	.000
Right Striatum (18, 6, 8)	603	.000	.000	.000	.009	.000
Right Superior Frontal Gyrus (22, -4, 62)	87	.010	.006	.000	.997	.000
Right Putamen / Pallidum						
Right Striatum (18, 8, -8)	268	.000	.000	.000	.003	.000
Right Paracingulate Gyrus / Anterior Cingulate Gyrus (2, 36, 26)	78	.014	.008	.000	.159	.000
Right Caudate (12, 6, 12)	54	.085	.033	.001	.975	.000
Left Caudate						
Bilateral Striatum / Left Thalamus (18, 18, -4)	515	.000	.000	.000	.397	.000
Left Caudate (-16, 10, 20)	324	.000	.000	.000	.001	.000
Left Striatum (-24, 2, -12)	99	.005	.002	.000	.987	.000
Left Caudate / Thalamus (-10, -12, 16)	69	.035	.011	.000	.148	.000
Left Nucleus Accumbens and Putamen						
Left Striatum (-14 6, -12)	268	.000	.000	.000	.003	.000
Medial Frontal Cortex (-8, 50, -16)	57	.065	.038	.001	.978	.000

Table 5. Statistics for clusters demonstrating ANH > CON group differences in GFC seed-to-voxel analysis with PET-derived seeds.
Size p-values indicate the significance of the size of the target cluster (voxels). Peak p-values indicate the significance of the signal of the target cluster, at its peak, or strongest point of connectivity. FEW, family-wise error. FDR, false-discovery rate. Unc, uncorrected. FEW and FDR are two common methods for correction of multiple comparisons. Unc p-values have not been corrected for multiple comparisons. ANH, Anhedonia participants. CON, Control participants.

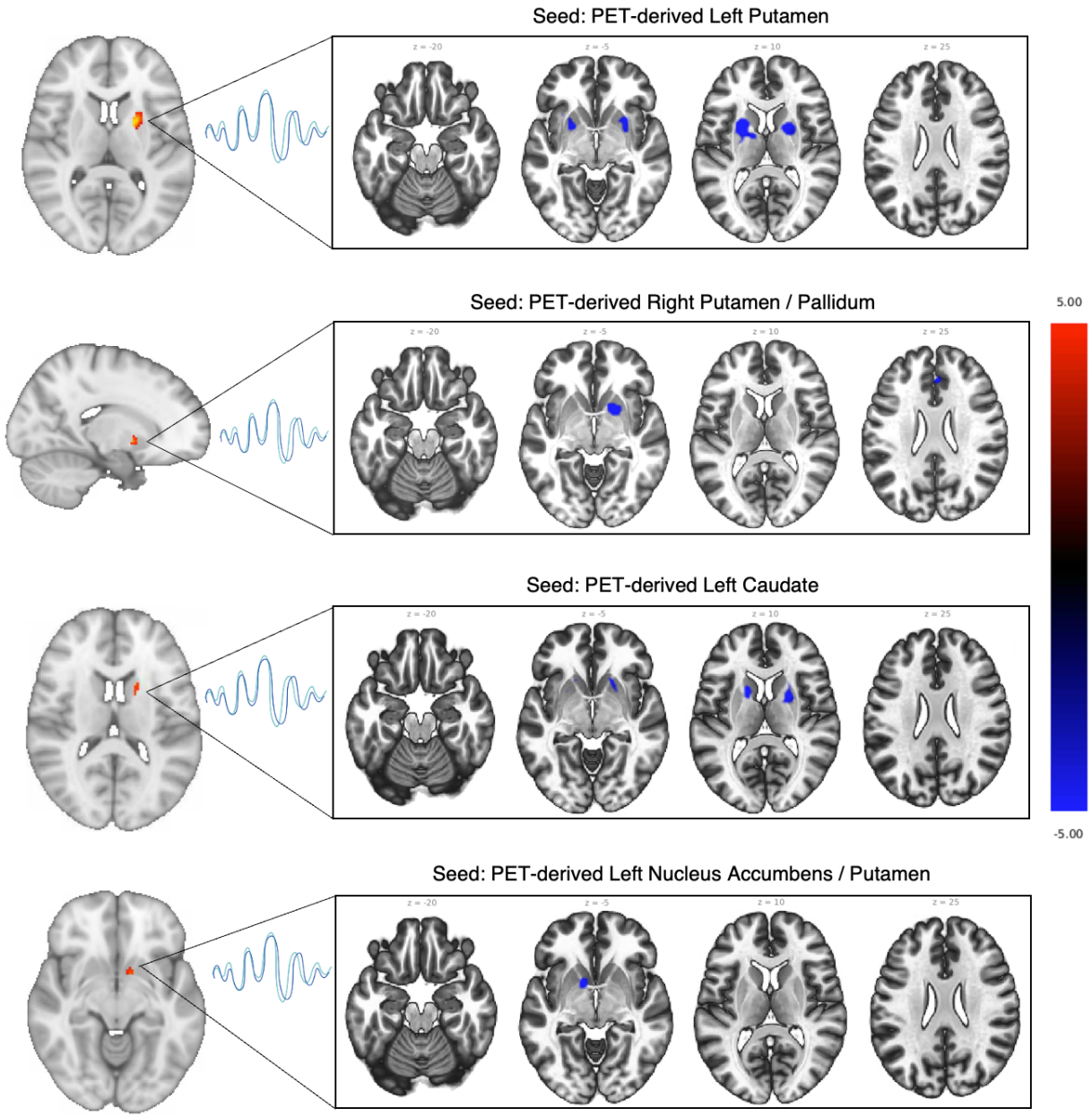

Figure 6. Group differences in general functional connectivity of PET-derived seeds. Seed-to-voxel analysis (ANH>CON) controlling for age and sex. Negative connectivity values are represented in blue. PET striatal seeds are presented in radiologic view, so the left and right are reversed. ANH, Anhedonia participants. CON, Control participants.

Atlas-derived Seed-based General Functional Connectivity

A general functional connectivity (GFC) approach was used to examine whole-brain connectivity with mesocorticolimbic network atlas-derived seed regions. Relative to CON participants, the ANH group exhibited decreased GFC between mesocorticolimbic network seeds

and the rest of the brain. *Figure 7* illustrates group differences in connectivity between the PET-derived seeds and their respective target regions.

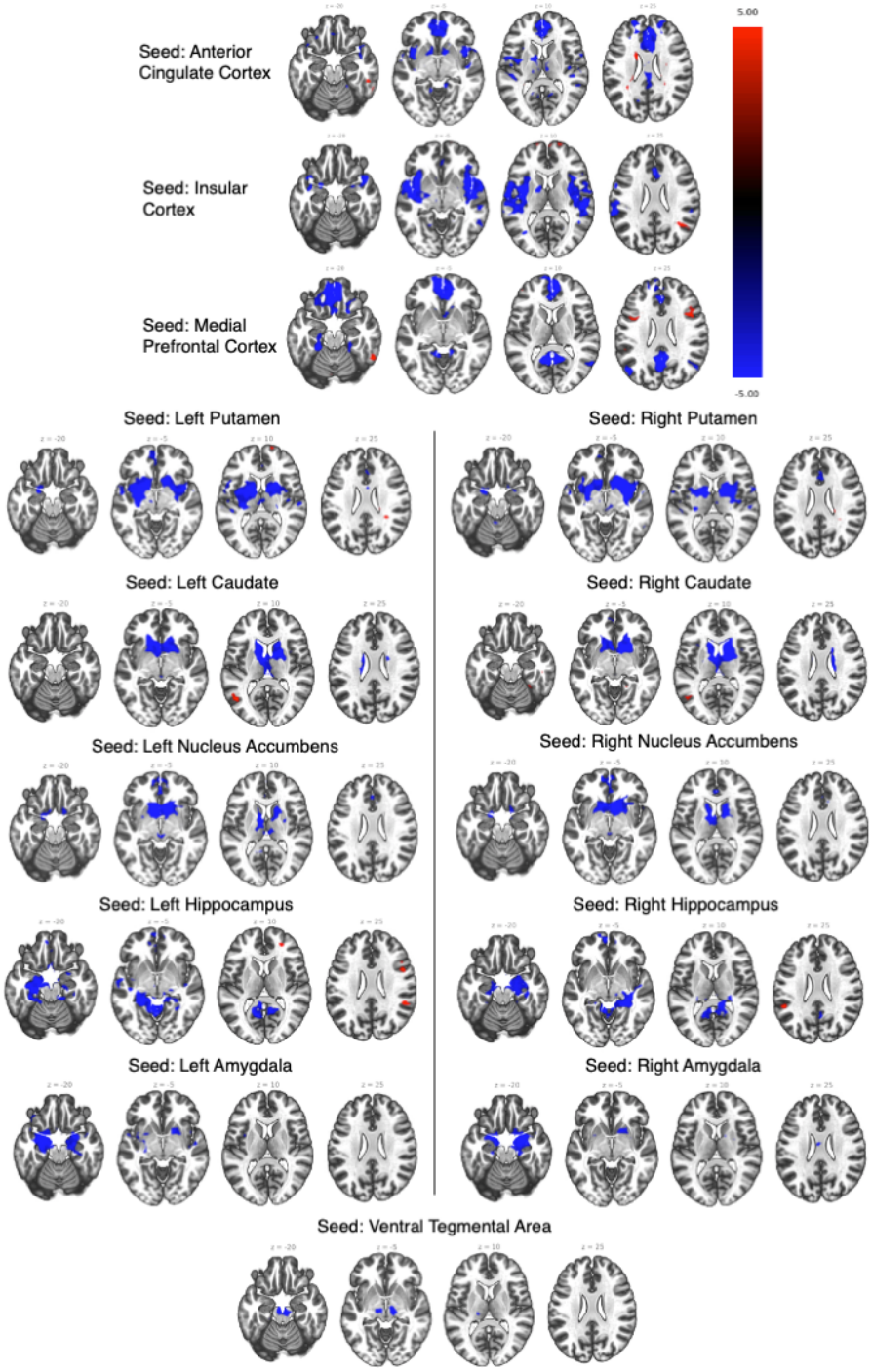

Figure 7. Group differences in general functional connectivity of atlas-derived seeds of the mesocorticolimbic network.
Seed-to-voxel analysis (ANH>CON) controlling for age and sex. pFWE-corrected. Negative connectivity values are represented in blue. Positive connectivity values are represented in red. ANH, Anhedonia participants. CON, Control participants.

Relations between Anhedonia and Mesocorticolimbic Connectivity

To evaluate the impact of mesocorticolimbic network connectivity on anhedonia severity, we examined associations between seed- and atlas-based GFC values and anhedonia severity scores on the SHAPS and BDI-II anhedonia subscale. There were no significant associations between SHAPS and BDI-II Anhedonia subscale scores and PET-derived GFC strength for any region pairs ($p > .05$) (see *Figure 8*), nor for atlas-derived GFC strength for any region pairs ($p > .05$). All analyses were corrected for multiple comparisons using a false-discovery rate (FDR) approach.

Prediction of Anhedonia through Mesocorticolimbic Connectivity and Chronic Stress

Given that mesocorticolimbic connectivity did not predict anhedonia, and thus, Hypothesis 3A was not supported, we did not test for mediation of the effect of chronic stress on anhedonia through mesocorticolimbic network connectivity as hypothesized.

Correlations between [^{11}C]Raclopride Binding Potential, Mesocorticolimbic Network Connectivity, and Clinical Measures

Figure 8 summarizes bivariate Pearson correlations for clinical measures of stress and anhedonia, [^{11}C]raclopride binding potential in striatal clusters demonstrating group differences, and general functional connectivity of these striatal clusters with their respective whole-brain target regions, in the ANH group. As expected, greater [^{11}C]raclopride binding potential (i.e., reduced striatal DA release to rewards) in striatal clusters tended to be negatively associated with general functional connectivity values of these seeds and their target regions (see *Figure 8, lower triangle*). However, not all of these correlations remained after an FDR-correction for multiple comparisons (see *Figure 8, upper triangle*).

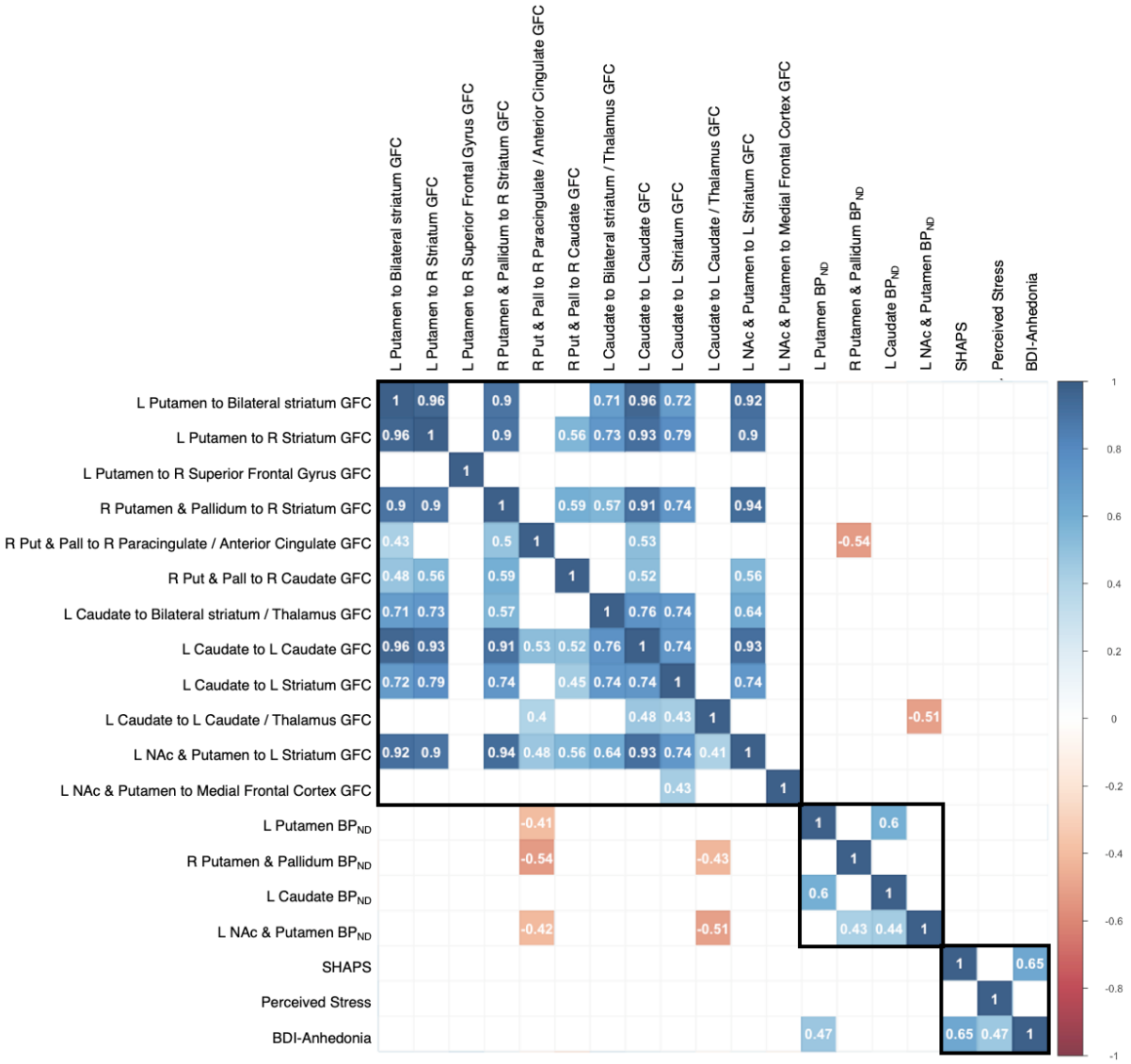

Figure 8. Pearson correlation matrix for variables of interest.
Pearson correlation values range from -1 to 1. Only significant correlations ($p < .05$) are displayed. Correlations presented in the upper triangle of the matrix are corrected for multiple comparisons, using the false-discovery rate (FDR) method. Correlations in the lower triangle are uncorrected. L, left. R, right. GFC, general functional connectivity. Put, Putamen. Pall, Pallidum. NAc, Nucleus Accumbens. BP_{ND}, binding potential non-displacement. SHAPS, Snaith-Hamilton Pleasure Scale. BDI, Beck Depression Inventory.

CHAPTER 4: DISCUSSION

The present investigation explored associations between chronic stress, anhedonia, striatal dopamine (DA), and reward circuitry functioning in a transdiagnostic sample with clinically elevated anhedonia. We sought to clarify the unique contributions of phasic striatal DA release to rewards and mesocorticolimbic network activation and connectivity on anhedonia severity. Our findings, discussed below, provide support for the association between blunted striatal DA functioning and anhedonia. Given prior research indicating that chronic stress negatively impacts reward sensitivity (Hollon et al., 2015; Ironside et al., 2018), we also sought to evaluate the global effects of perceived stress on mesocorticolimbic function. We did not find evidence for the contribution of perceived stress on mesocorticolimbic DA system functioning (see *Figure 5* and *Figure 8)*. Thus, we present alternative avenues for future research into the role of chronic stress.

Striatal Dopamine and Anhedonia

Consistent with major theories of anhedonia and depression, we found decreased striatal DA release to rewards in ANH participants, providing evidence for one mechanism by which rewarding stimuli are less motivating in anhedonia. Relative to the CON group, ANH participants exhibited increased [^{11}C]raclopride binding potential (BP_{ND}) in the left and right dorsal striatum and left ventral striatum (see *Figure 3*). Increased BP_{ND} is indicative of decreased DA release. These findings represent the first report of decreased phasic DA release to rewards in a transdiagnostic sample with clinically impairing anhedonia. These results are consistent with previous findings of decreased striatal DA release to rewards in Major Depressive Disorder (MDD) (Hamilton et al., 2018; Peciña et al., 2017). Altered striatal DA responses to reward

incentives have also been demonstrated across clinical disorders marked by anhedonia, including MDD, schizophrenia, and Parkinson's disease (J. C. Felger & Treadway, 2017; Olney et al., 2018).

Reduced striatal DA release to rewards in ANH participants relative to controls may be due to impaired reward learning in anhedonia. Reward learning is a subtype of reward processing shown to be compromised in anhedonia (Borsini et al., 2020). The optimized MID task used here elicited the learning of which cues predicted which reward magnitudes, enhancing the sensitivity of the task toward positive prediction errors encoded by phasic DA release (Berridge & Robinson, 2003). Though we did not evaluate prediction errors *per se*, prior work has demonstrated that impaired ability to modulate behavior toward rewards, during a probabilistic reward task, is characteristic of anhedonia in depressed individuals (Pechtel et al., 2013; Vrieze et al., 2013). This work is clinically relevant, given that reduced reward learning also predicted persistent depressive symptoms following eight weeks of psychotherapy or pharmacological treatment for MDD (Pechtel et al., 2013; Vrieze et al., 2013). Moreover, impaired reward learning has been demonstrated in animal models of depression, specifically following implementation of social defeat stress paradigms (Der-Avakian et al., 2017).

Another possible explanation for reduced striatal DA response to rewards in the ANH group is that anhedonic participants, on average, have lower tonic levels of DA (i.e., lower availability of DA than CON participants). Lower tonic levels of DA have been demonstrated in depressed samples, specifically in the bilateral ventral striatum and right dorsal striatum (Hamilton et al., 2018). Our approach allowed us to measure both tonic (i.e., baseline) DA and phasic DA release to rewards. Tonic DA was defined for the time period from when the tracer was injected at the start of scanning through the neutral block of the MID task. Phasic DA release to rewards was measured across the two reward blocks of the MID task. For the contrast

of ANH > CON [^{11}C]raclopride binding potential, we did not find evidence that ANH participants have significantly lower tonic DA (i.e., higher binding potential) relative to CON participants (see *Figure 3*) suggesting that lower tonic levels were not the primary driver of results.

Regarding associations between striatal BP_{ND} and self-report measures of anhedonia, we found that increased BP_{ND} in the left dorsal striatum (i.e., putamen), indicative of decreased phasic DA reward signaling, was also positively associated with anhedonia severity on the BDI-II Anhedonia subscale. However, SHAPS scores were not significantly related to phasic DA reward signaling, which is consistent with at least one recent [^{11}C]raclopride PET study in MDD (Peciña et al., 2017). These contrasting results are likely due to differences in the aspects of reward processing that these two scales best capture. Whereas the SHAPS assesses hedonic capacity (Snaith et al., 1995) and is thought to capture aspects of consummatory reward (i.e., pleasure), the BDI-II Anhedonia subscale may capture aspects of both consummatory and *anticipatory* reward processing, or the motivation and interest toward rewards (Joiner et al., 2003; Pizzagalli et al., 2005; Snaith et al., 1995).

Impact of Chronic Stress on Anhedonia via Striatal Dopamine

Chronic stress is thought to sensitize the mesocorticolimbic DA system and contribute to the maintenance of anhedonic behavior (Hollon et al., 2015; Pizzagalli, 2014; Valenti et al., 2012). We hypothesized that chronic stress, assessed using the Perceived Stress Scale (PSS), would predict anhedonia severity and that striatal DA release to rewards would mediate the relationship between chronic stress and anhedonia. The PSS was used as our primary measure of chronic stress because it is a retrospective measure that assesses the extent to which stress is unpredictable and uncontrollable. There are more comprehensive scales for the assessment of chronic stress, which better evaluate different types and chronicity of stressors (Slavich &

Shields, 2018). It is possible that other scales may be better suited to illuminate the role of chronic stress in DA function and reward processing more broadly.

Consistent with previous work (Pizzagalli, 2014; Slavich & Irwin, 2014), perceived stress and anhedonia symptom scores on the BDI-II Anhedonia subscale were highly correlated. Perceived stress also significantly predicted anhedonia in our mediation model (see *Figure 5*). Further, greater perceived stress was associated with reduced striatal DA release to rewards, though this trend was not statistically significant (see *Figure 5*). However, our hypothesis that striatal DA function would mediate the relation between chronic stress and anhedonia was not supported (see *Figure 3*). We may not have found evidence for the mediating role of striatal DA functioning since the current study was inadequately powered to detect small effects. A power analysis revealed the statistical power for the proposed research was .08 for the detection of a small effect, .32 for a medium effect size, and .80 for a large effect size. The effect size of the indirect effect of left putamen DA release to rewards on the path between perceived stress and anhedonia was β_{STD}=0.135 (CI 95% = -0.07-0.363). This indicates that an ANH participant with one standard deviation (SD) more perceived stress was estimated to have 0.135 SDs greater anhedonia severity as a result of the positive effect of perceived stress on [^{11}C]raclopride BPND to rewards, which in turn affects anhedonia severity. General effect size boundaries are .02 (small), .15 (medium), and .35 (large) (J. Cohen, 1992). Therefore, the present null findings for mediation may be a reflection of low statistical power to detect small effects (0.135) in the current sample, rather than the absence of a true effect. In future investigations, a sample size of n=85 would be necessary to detect the effect size we found in the current study, as estimated by an *a priori* power analysis with statistical power of 0.80.

Mesocorticolimbic Activation during Reward Anticipation and Reward Outcome

Anhedonia severity is associated with altered reward-network function (Admon & Pizzagalli, 2015; Gabbay et al., 2013; Gradin et al., 2011). Despite examining mesocorticolimbic activation using both whole-brain and ROI-based analytic approaches, we did not find evidence of altered mesocorticolimbic activation during reward anticipation or reward outcome phases in ANH participants. This is inconsistent with prior fMRI research showing hypo-responsivity of striatal regions during anticipatory (Borsini et al., 2020; Leroy et al., 2020; Luijten et al., 2017; Plichta & Scheres, 2014; B. Zhang et al., 2016) and consummatory processing (Borsini et al., 2020; Luijten et al., 2017; Nawijn et al., 2015; Ng et al., 2019; B. Zhang et al., 2016) in psychiatric populations where anhedonia is a central feature. As mentioned above, one possibility for our divergent findings (i.e., the lack of group differences in mesocorticolimbic activation) is that the current study was inadequately powered to detect small effects.

Anhedonia and Mesocorticolimbic General Functional Connectivity

The present study investigated functional connectivity between regions exhibiting blunted striatal DA release to rewards (PET-derived seeds) and the broader mesocorticolimbic network using a whole-brain general functional connectivity (GFC). Broadly, compared to CON participants, ANH participants showed decreased GFC between PET-derived seeds and several regions implicated in reward processing (e.g., bilateral caudate, putamen, and pallidum), as well as cognitive control (e.g., anterior cingulate gyrus) and control of attention (e.g., thalamus). Overall, these results are consistent with reports of altered functional cortico-striatal connectivity in MDD (Gabbay et al., 2013; Kang et al., 2018; Walsh et al., 2017) and a previous [^{11}C]raclopride PET-MR study of functional connectivity in MDD (Hamilton et al., 2018). Hamilton and colleagues (2018) demonstrated that increased BP_{ND} in the ventral striatum predicted decreased functional connectivity between PET-derived seeds and "their respective

default-mode and salience network targets" (Hamilton et al., 2018). Among these resulting network targets was the left superior frontal gyrus, and our results in anhedonia presented here showed decreased connectivity with the right superior frontal gyrus (see *Table 5 and Figure 6*). However, these observed group differences in GFC were not significantly associated with clinical measures of anhedonia. This was unexpected, as decreased functional connectivity within the reward network in MDD patients has been shown to predict anhedonia symptoms (Gong et al., 2018).

This pattern of decreased connectivity was also evident with atlas-derived seeds. Importantly, the left and right nucleus accumbens showed decreased connectivity with some areas of the prefrontal cortex (see *Figure 7*). Decreased ventral striatum (VS) to medial prefrontal cortex (mPFC) connectivity has been reported in anhedonic and depressed samples (Gabbay et al., 2013; Yin et al., 2019) and shown to be associated with stress-related psychopathology more broadly (Mehta et al., 2020; Pessin et al., 2021). Using a seed-to-voxel approach allowed us to explore neural connectivity between our regions of interest in the mesocorticolimbic network and the whole brain.

Limitations and Future Directions

This study adds to the growing literature of the neural and molecular mechanisms underlying the association between chronic stress and anhedonia, through the application of simultaneous positron emission tomography and magnetic resonance imaging (PET-MR). Strengths of this study include the use of multi-modal imaging techniques to compare key aspects of mesocorticolimbic network functioning in a transdiagnostic sample. Nevertheless, there are a few limitations to be considered in the present study.

First, it is important to recognize that modest sample sizes are a limitation for most PET imaging studies (Baumgartner et al., 2018), and the current research is no exception. Second,

given that this is a cross-sectional study, we cannot determine causal relationships between reduced striatal DA release to rewards and anhedonia. Avenues for future research may investigate whether reduced striatal DA release to rewards precedes anhedonia or whether anhedonia impacts striatal DA functioning.

Third, another limitation is that the ANH sample was not recruited based on severity of chronic stress symptoms. This aspect of the study design is important to note given that we examined the extent to which chronic stress contributes to anhedonia via alterations in reward circuitry functioning and striatal dopaminergic functioning. Although patient characteristics of the ANH sample (see *Table 2*) demonstrate moderate levels of chronic stress in this transdiagnostic sample (see *Table 1*), the variability of PSS scores was limited. In an early study of the PSS in a psychiatric sample with depressive symptoms, the mean PSS score was 29.07 (SD=8.81), which is somewhat higher than the current sample (Hewitt et al., 1992). Community samples from the same study were more similar in mean PSS scores to the current sample (M=23.18 and 23.67) (Hewitt et al., 1992).

The timing, severity, and type of stress may differentially impact striatal dopamine functioning and increase risk for depression and anhedonia (Danese & Lewis, 2017; A. B. Miller et al., 2018; Smith & Pollak, 2020). Stressors early in life are particularly relevant to transdiagnostic research, given that these have been broadly linked to increased risk for adult psychopathology (Danese et al., 2009). Recent investigations into structural connectivity of the corticostriatal circuit have begun to elucidate the impact of early life adversity on brain regions involved in reward learning, finding relations between ventral striatum to frontal brain tract integrity and childhood adversity (Kennedy et al., 2021). Future studies should explore the impact of different stressor types, with consideration toward stress during vulnerable periods of development, and utilize various available methods for understanding mesocorticolimbic activity

and connectivity. Specific chronic stressors such as psychosocial and even financial stress are thought to have differential effects on wellbeing and may be important to consider alongside anhedonia as well (Sturgeon et al., 2016). Given that the ratio of females to males significantly differed across groups, it would also be valuable to explore differences in chronic stress and anhedonia across participants grouped by gender. This is especially important considering gender differences in rates of depression (Hammen, 2005; Hammen et al., 2009).

Furthermore, there is evidence to suggest that inflammation may play a critical role in disrupting communication between prefrontal and subcortical regions of reward- and threat-processing networks to influence reward processing and mood (Eisenberger et al., 2010; Hanson et al., 2018; Lucido et al., 2021; Mehta et al., 2020; Yin et al., 2019). Given that the measures of subjective stress utilized in the current study are not specific to physiological or oxidative stress related to inflammation, they may be less predictive of altered neurocircuitry. Future research ought to simultaneously evaluate physiological (i.e., inflammatory markers) and psychological markers of chronic stress.

Conclusion

The present study fills a gap in our understanding of phasic striatal DA release and anhedonia, which has been limited to MDD samples, rather than transdiagnostic samples. We found reduced striatal DA response to rewards and decreased general functional connectivity in anhedonia participants, but these group differences were not associated with symptom severity. Contrary to predictions, we did not find evidence of altered neural activation within the mesocorticolimbic network and anhedonia. We demonstrated that symptoms of chronic stress were strongly associated with anhedonia; however, mediation hypotheses were not fully supported. Collectively, these findings provide support for the association between chronic stress

and anhedonia, and highlight a molecular mechanism that may address, in part, the pathogenesis of impaired DA functioning in anhedonia and stress-related psychopathologies.

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