Abstract of the Dissertation

Neuromelanin, Reinforcement Learning, and Anhedonia:

Identifying Associations, Antecedents, and Consequences

by

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Doctor of Philosophy

in

Clinical Psychology

Stony Brook University

2023

Reward processing plays a transdiagnostic role in the etiopathogenesis of psychopathology. Reinforcement learning deficits, driven by dopamine dysregulation, are hypothesized to explain key aspects of such abnormalities. Therefore, this proposal seeks to examine whether dopamine, assessed using neuromelanin-sensitive magnetic resonance imaging (NM-MRI), a novel imaging technique for assessing long-term midbrain dopamine function in the Substantia Nigra (SN) and Ventral Tegmental Area (VTA), contributes to reinforcement learning performance. Additionally, I aim to elucidate the relationship between dopamine dysfunction and anhedonia. Finally, due to evidence suggesting that life stress may interrupt dopaminergic and learning processes, I investigate the influence of prospective measures of early childhood adversity (ECA) and chronic life stress on reinforcement learning and dopamine dysfunction. Importantly, each of these questions have bearing on the construct validity of NM-MRI as an individual-difference measure of dopamine function.

Participants (N = 81) were recruited from the Stony Brook Temperament Study (SBTS), an ongoing longitudinal study, shortly after their 18th birthday to complete NM-MRI imaging, a behavioral reinforcement learning task, and anhedonia questionnaires. Associations were examined between NM-MRI-assessed dopamine, multiple measures of reinforcement learning performance, multiple assessments of anhedonia, and ECA and chronic life stress. Results from the current investigation indicate that NM-MRI-assessed dopamine was significantly associated with certain measures of reinforcement learning, but not others. Additionally, other measures of impaired reinforcement learning were related to increased concurrent anhedonic symptoms. Finally, higher levels of chronic life stress, but not ECA, were associated with impairments in reinforcement learning performance. Taken together, there are links between dopaminergic function, reinforcement learning, life stress, and anhedonia, but these associations vary across measures. Future work should continue to elucidate potentially important etiological processes in the development of reinforcement learning and anhedonia.

Dedication Page

This dissertation is dedicated to my wife, Fran, who has been a constant source of support and encouragement throughout all the challenges of graduate school and life. I am truly grateful for having you in my life and you continue to inspire me to better myself.

This work is also dedicated to my parents, Mark and Lisetta, who have always loved me unconditionally and set an example to work hard for the things that I aspire to achieve.

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List of Abbreviations

αG – Positive learning rate

αL – Negative learning rate

β – Stochastic parameter

BOLD – Blood oxygen level dependent

ERP – Event-related potential

fMRI – Functional magnetic resonance imaging

IDAS-II – Expanded Version of the Inventory of Depression and Anxiety Symptoms

MRI – Magnetic resonance imaging

PET – Positron emission tomography

PPM – Preschool Parenting Measure

PSDQ – Parenting Styles and Dimensions Questionnaire

PVSS – Positive Valence Systems Scale

RewP – Reward positivity

SBTS - Stony Brook Temperament Study

SPECT – Single-photon emission computed tomography

Acknowledgments

Firstly, I would like to express my deepest appreciation to Dr. Dan Klein. I remember being accepted to work with you during graduate school after working towards that goal for years. Your mentorship throughout my time at Stony Brook has far surpassed my expectations, and I am eternally grateful for the role you have played in my professional development. I am confident that I am prepared for the next step in my career largely due to what I have learned while working with you. Also, your continuous guidance and feedback throughout multiple iterations of the current project were critical to its execution. Thank you for everything you have done over the years.

Additionally, I am extremely grateful my dissertation committee members, Drs. Brady Nelson, Greg Perlman, and Christian Luhmann. Dr. Brady Nelson, thank you for chairing my dissertation committee and for providing thoughtful suggestions on how to improve my project. Also, thank you for your mentorship and collaboration on multiple projects throughout my time in graduate school. Dr. Perlman, thank you for your willingness to provide training on the acquisition and analysis of NM-MRI data, and for facilitating additional data collection, which allowed me to pursue this project. I have thoroughly enjoyed each opportunity I have had to work with you, and I am grateful for your willingness to oversee my first academic project back when I was a research assistant getting started in the field of psychology. Dr. Luhmann, thank you for helping guide me through learning an entirely new literature and for prompting me to think critically about computational modeling and reinforcement learning. Your guidance helped to foster my interest in a new area of research and has led to the development of several additional projects which build upon what I have learned working with you.

I am also thankful to my lab mates who provided thoughtful comments during the development of this project, to my graduate school colleagues who helped by piloting the task

included in my project, to the staff members who helped to recruit and collect these data, and to my cohort who was there to experience the long journey towards a Ph.D. with me.

Finally, I would like to thank my family for their unconditional support in my graduate school pursuits. Notably, thank you to my wife, Fran, and my parents, Mark and Lisetta. You have all supported my pursuits, which has been critical to my personal and professional development and has culminated in this work. Lastly, thank you to Kado for the entertainment and emotional support.

Introduction

Reinforcement Learning and Dopamine Function

Reinforcement learning is critical for updating beliefs and behavior based on experience (Berridge, 2000; Cox & Witten, 2019; Schultz, 2016; Schultz, Dayan, & Montague, 1997), and is implicated in mental disorders characterized by anhedonia (Barch, Pagliaccio, & Luking, 2015; Huys, Daw, & Dayan, 2015; Huys, Pizzagalli, Bogdan, & Dayan, 2013; Zald & Treadway, 2017). Midbrain dopamine dysregulation may underlie reinforcement learning deficits (Cox & Witten, 2019; Schultz, 2016), however, very few studies have specifically examined the association between dopamine and reinforcement learning in humans due to methodological limitations of imaging dopamine function (Kasanova et al., 2017). Electrophysiological studies in non-human primates have demonstrated that midbrain dopamine neurons encode a "prediction error" reflecting the difference between expected and actual outcomes (Schultz, 1998). This prediction error is indexed by an increased phasic dopamine release when the outcome is better than expected, increasing similar future behavior, or pauses in tonic dopamine release when an outcome is worse than expected, decreasing similar future behavior (Chang et al., 2016; Hamid et al., 2016; Schultz, 1998). Over time, expectations converge with outcomes, minimizing prediction errors and maximizing rewards (McClure, Berns, & Montague, 2003). Previous work indicates that dopamine firing and prediction error signals are closely coupled (Cox & Witten, 2019; Schultz, 2016; Schultz et al., 1997). This suggests that dopamine neuronal firing acts as a "teaching signal" that mediates the learning of stimulus–outcome and stimulus–response–outcome associations (Montague, Dayan, & Sejnowski, 1996), and that dopamine function contributes to the process by which a stimulus motivates goal-directed behavior by creating associations with reinforcing events (Berridge, 2007; Berridge & Robinson, 1998). This is

further supported by evidence showing that inhibition of dopamine receptors (e.g., via drug administration) contributes to poor reinforcement learning in humans (Chowdhury et al., 2013; Frank & O'Reilly, 2006; Huys et al., 2013).

In humans, dopamine neurons in the Substantia Nigra (SN) and Ventral Tegmental Area (VTA), together the SN-VTA complex, produce these dopamine-encoded prediction errors responsible for learning (Cox & Witten, 2019; Schultz, 2016; Schultz et al., 1997). VTA dopamine neurons primarily project to nucleus accumbens, the major structure of the ventral striatum, which responds to the hedonic value of rewards and encodes stimulus-outcome associations (Berridge, 2000; Cox & Witten, 2019). Conversely, SN dopamine neurons primarily project to the dorsal striatum, which is implicated in stimulus-response and stimulus-action associations responsible for goal-directed behaviors (Cox & Witten, 2019). Both the VTA-ventral striatum and SN-dorsal striatum pathways are critical for reinforcement learning.

Development of Neuromelanin-Sensitive Magnetic Resonance Imaging Technology

Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) is a novel, non-invasive imaging technique that detects neuromelanin in SN and VTA dopamine neurons (Chen et al., 2014; Ito et al., 2017; Langley, Huddleston, Liu, & Hu, 2017; Sasaki, Shibata, Kudo, & Tohyama, 2008; Wengler et al., 2020). Neuromelanin is characterized by a signature dark pigment of that reflects the iron-dependent oxidation of cytosolic dopamine and other cellular processes in midbrain dopamine neurons (Zecca et al., 2008; Zucca et al., 2014). This is supported by studies showing that L-DOPA-induced dopamine synthesis in rodents leads to neuromelanin accumulation in the SN (Sulzer et al., 2000). Neuromelanin accumulates in the SN and VTA over the lifespan as a biproduct of dopamine synthesis and it is not cleared from dopamine neurons except in the case of dopamine cell death (Zucca et al., 2014; Zucca et al.,

2018). Importantly, iron deposits in neuromelanin accumulations are paramagnetic, making them detectable by specialized MRI sequences (Sasaki et al., 2006; Tosk et al., 1992; Trujillo et al., 2017; Zucca et al., 2017). Therefore, NM-MRI provides a lifelong measure of dopamine function. This technique is increasingly used to study neurodegenerative diseases such as Parkinson's Disease, which is associated with a low neuromelanin signal (Fabbri et al., 2017; Isaias et al., 2016; Sasaki et al., 2006; Sulzer et al., 2018; Zucca et al., 2017; Zucca et al., 2018). NM-MRI sequences have also been utilized to study schizophrenia (Cassidy et al., 2019; Shibata et al., 2008; Yamashita et al., 2016), substance use disorders (Bradberry, 2020; Cassidy et al., 2020), and sleep disorders (Boeve, St. Louis, & Kantarci, 2016), demonstrating that NM-MRI can also be used to assess dopamine dysfunction in psychiatric disorders.

Recently, an improved NM-MRI sequence was refined and validated using positron emission tomography (PET) imaging (Cassidy et al., 2019). This work demonstrated that the NM-MRI signal in the SN is strongly correlated ($r = 0.69$) with the magnitude of amphetamine-induced dopamine release in the striatum, the area of projection of SN and VTA dopamine neurons. This combination of parameters maximized the strength and reliability of the NM-MRI signal (Wengler et al., 2020). Additionally, using a high-resolution probabilistic atlas identifying dopamine nuclei (Pauli, Nili, & Tyszka, 2018), it is possible to reliably assess the NM-MRI signal in the SN and VTA nuclei (Wengler et al., 2020).

NM-MRI offers several advantages compared to PET imaging, mainly lower cost, non-invasiveness, and no radiation exposure. NM-MRI is the first viable and validated alternative to PET for quantifying dopamine function and it can be used in youth and other vulnerable samples. This technological advance is underutilized but has immense potential for addressing critical issues such as the relationship between dopamine and reinforcement learning, and their role in

psychopathological symptoms such as anhedonia.

Computational Modeling of Reinforcement Learning Data

Reinforcement learning describes a family of mathematical models that characterize reinforcement-based learning and decision-making. These models can decompose an individual's performance on a reinforcement learning task into several components, generating parameter estimates that inform neurobiological models of brain function (Daw & Doya, 2006; Doll, Simon, & Daw, 2012; Frank & Claus, 2006; O'Doherty, 2012) in ways that raw behavioral data cannot (Daw, O'doherty, Dayan, Seymour, & Dolan, 2006). Reinforcement learning models thus provide a quantitative framework for modeling dopamine responses to stimuli/feedback to inform predictions of future outcomes (Dayan & Abbott, 2001; Montague et al., 1996). These models are fit to the trial-level responses for individual subjects and allow for examination of individual differences in specific model parameters, including whether differences are accounted for by other variables (e.g., NM-MRI-assessed dopamine function).

Several parameters are estimated in Q-learning models, the type of reinforcement learning model employed in the current project. This includes prediction errors, which are computed on each trial. Positive prediction errors, which provide information on the difference between expected and actual outcomes following results that are better than expected, are closely related to midbrain dopamine firing rates and drive approach learning (Cox & Witten, 2019; Daw & Doya, 2006; Montague et al., 1996; O'Doherty et al., 2004; Schultz, 1998, 2016). Conversely, negative prediction errors, computed in situations where outcomes are worse than expected, are associated with pauses in dopamine firing and drive avoidance learning (Chang et al., 2016; Frank, 2005; Frank, Seeberger, & O'reilly, 2004; Hamid et al., 2016; Ungless, Magill, & Bolam, 2004). A hallmark feature of learning is the adaptive employment of prediction errors

to adjust prediction of future outcomes. The rate of these adjustments in prediction, which are reflected by behavioral changes on subsequent trials, are controlled by learning rates. Learning rates, which are estimated for each participant over the duration of the task by fitting data to computational reinforcement learning models, reflect how learning shifts following changes in the environment (e.g., task-related feedback; Behrens, Woolrich, Walton, & Rushworth, 2007; Jiang, Heller, & Egner, 2014; McGuire, Nassar, Gold, & Kable, 2014; Nassar, Wilson, Heasly, & Gold, 2010; Payzan-LeNestour & Bossaerts, 2011; Wu et al., 2017). Positive and negative learning rates are defined as the rate of behavioral updating following better or worse than expected outcomes, respectively. In stable environments where rules do not change (e.g., the proposed task), learning rates should be low-moderate to allow for the smooth integration of information over an extended period of time, so that learning is robust to noise (Behrens et al., 2007; Jiang et al., 2014; McGuire et al., 2014; Nassar et al., 2010; Payzan-LeNestour & Bossaerts, 2011; Wu et al., 2017). Very low learning rates are maladaptive and indicate poor acquisition of new information; low learning rates are observed in disorders characterized by reward insensitivity and low dopamine levels, such as depression and Parkinson's Disease (Behrens et al., 2007; Chase et al., 2010; Chen, Takahashi, Nakagawa, Inoue, & Kusumi, 2015; Frank et al., 2004; Jiang et al., 2014; Klimke et al., 1999; McGuire et al., 2014; Meyer et al., 2001; Nassar et al., 2010; Payzan-LeNestour & Bossaerts, 2011; Wu et al., 2017). Conversely, learning rates that are too large can contribute to overweighting recent experience, eliminating prior learning. Substance abuse and ADHD are characterized by excess dopamine and associated with elevated learning rates (Busemeyer, Stout, & Finn, 2003; Parvaz, Kim, Froudist-Walsh, Newcorn, & Ivanov, 2018; Spencer et al., 2005; Volkow, Fowler, Wang, & Swanson, 2004). The Q-learning model uses the estimated parameters to produce estimated values, or "Q-values", for

each stimulus presented during the reinforcement learning task at the participant-level. The Q-values reflect the subjective value each participant assigns to that stimulus, derived based on their behavior (i.e., stimulus selection) and the feedback they receive throughout the task.

The current project focuses on two major components from our Q-learning models: learning rates and Q-values. Learning rates are associated with dopamine function and are computed using several parameters derived from trial-by-trial behavior, including prediction errors, which are known to be driven by dopamine function. In the proposed model, learning rates are calculated for each individual participant based on their behavioral updating following feedback on the prior trial, over the duration of the task and across all stimuli. Separate learning rates will be estimated for positive and negative feedback, which reflect disparate striatal mechanisms (Yin, Knowlton, & Balleine, 2004), and provide measures of approach and avoidance learning, respectively. Q-values, which are also associated with dopamine (Huys et al., 2013), represent the expected reward associated with each stimulus (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Sutton & Barto, 1998). In a probabilistic reinforcement learning task, subjects should assign stimuli rewarded more frequently a higher Q-value to reflect the greater expectation of reward. In the proposed task, participants can learn to select the more frequently rewarded or avoid less frequently rewarded stimuli. Therefore, Q-values of the more and less frequently rewarded stimuli can be conceptualized as providing measures of approach and avoidance learning, respectively. While learning rates are used to calculate the Q-value for each stimulus (see Data Analytic Strategy, *Computational Modeling of Reinforcement Learning Data*), they are empirically and conceptually distinct. Empirically, there are multiple parameters estimated by the model based on participant behavior including, but not limited to, the two learning rates. Therefore, behavioral selections made over the entire task are used to estimate the

learning rates, which subsequently influence the calculation of the Q-value for each stimulus; however, the learning rates are calculated separately from one another and reflect only a portion of what influences the estimation of the Q-value. Therefore, the learning rates and Q-values may relate differently to extraneous variables. Conceptually, the learning rates reflect the rate at which participants update their decision making, whereas Q-values reflect how much relative value the participants assign to a given stimulus. Importantly, the learning rates and Q-values obtained from Q-learning models provide richer, more nuanced information than basic task performance.

Dopamine Dysfunction, Reinforcement Learning, and Anhedonia

Anhedonia is a common and impairing symptom that is central to depression (Treadway & Zald, 2011), but also implicated in other internalizing and psychotic disorders (Conway, Li, & Starr, 2019; Craske, Meuret, Ritz, Treanor, & Dour, 2016; Lambert et al., 2018; Treadway & Zald, 2013). It is characterized by reduced interest in appetitive stimuli, and/or diminished pleasure in response to stimuli previously considered rewarding (Treadway & Zald, 2013). Importantly, dopamine dysfunction is hypothesized to contribute to anhedonia (Der-Avakian & Markou, 2012; Huys et al., 2013; Pizzagalli, 2014; Treadway & Zald, 2013). The most direct evidence for the dopamine-anhedonia association in humans comes from PET and single photon emission computed tomography (SPECT) imaging studies. Findings from PET studies show that dopamine receptor availability in the ventral striatum is negatively correlated with anhedonia severity (Peciña et al., 2017). Similarly, SPECT studies indicate that dopamine receptor binding is reduced in anhedonic depressed patients compared to healthy controls (Sarchiapone et al., 2006). These studies provide preliminary evidence in humans suggesting that reduced dopamine function is associated with increased symptoms of anhedonia.

Additional indirect evidence for the role of dopamine contributing to anhedonia come from event-related potential (ERP) and functional magnetic resonance imaging (fMRI) studies. ERPs provide precise temporal resolution of electrophysiological recordings on the scalp in response to stimuli, thus providing a measure of neural activity on the order of milliseconds. The reward positivity (RewP; also called the Feedback Negativity [FN] and Feedback-Related Negativity [FRN]) is an ERP component elicited in response to rewards. Importantly, reinforcement learning theory suggests that the RewP is generated in response to phasic changes in dopamine release that reflect prediction errors, with larger magnitude RewP components reflecting greater phasic dopamine release/prediction errors (Baker & Holroyd, 2011; Gehring & Willoughby, 2002; Holroyd & Coles, 2002; Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Miltner, Braun, & Coles, 1997; Satoh, Nakai, Sato, & Kimura, 2003; Schultz, 2002). This is further supported by evidence from source localization studies indicate that the RewP is generated by the striatum, a key region in the midbrain dopaminergic system (Foti, Weinberg, Dien, & Hajcak, 2011), and is correlated with fMRI BOLD activation in the striatum (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Accumulating evidence suggests that the RewP is an important biological marker of risk for depression (Mackin, Nelson, & Klein, 2021). Indeed, a blunted RewP is concurrently and prospectively associated with depressive symptoms and episodes among youth and adults (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Bress, Smith, Foti, Klein, & Hajcak, 2012; Foti, Carlson, Sauder, & Proudfit, 2014; Foti & Hajcak, 2009; Keren et al., 2018; Liu et al., 2014; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). Critically, the relationship between the RewP and depression may be strongest for melancholic depression, a subtype of depression that is characterized by pervasive anhedonia and lack of reactivity to positive events. Consistent with

this possibility, prior investigations have demonstrated that a blunted RewP in response to monetary rewards are specific to with current or remitted melancholic depression, not to other forms of current or remitted depression (Weinberg & Shankman, 2017). Similarly, another study demonstrated that a reduced RewP amplitude is associated with the severity of self-reported anhedonia, even after adjusting for depression severity (Liu et al., 2014).

Studies that have used fMRI to examine the association between prediction errors and anhedonia in adults have also identified strong associations. For example, one study utilizing a reward learning task to examine the influence of reward-prediction errors on depression demonstrated that depressed patients exhibited reduced prediction errors in the striatum and midbrain compared to healthy controls; critically, the extent of signal reduction in the bilateral caudate, nucleus accumbens, and midbrain correlated with increased anhedonia severity (Gradin et al., 2011). These findings are further supported by results demonstrating associations between reduced prediction errors in the striatum during reinforcement learning tasks (indicating impaired reinforcement learning) and anhedonia severity (Greenberg et al., 2015; Vrieze et al., 2013). Other fMRI studies have reported associations between activation in subcortical reward regions (e.g., dorsal and ventral striatum) during reward-related tasks and symptoms of anhedonia in children, adolescents, and adults (Admon et al., 2015; Forbes et al., 2010; Morgan, Olino, McMakin, Ryan, & Forbes, 2013; Pizzagalli et al., 2009; Sharp et al., 2014; Stringaris et al., 2015). For example, reduced bilateral ventral striatal activation was concurrently associated with the presence of anhedonia in a sample of adolescents, and prospectively predicted the presence of anhedonia at the 2-year follow-up, again suggesting that dopamine-related deficits that drive reinforcement learning might be especially relevant to anhedonia (Stringaris et al., 2015).

Reinforcement learning deficits are also hypothesized to influence the development of

anhedonia. Findings from behavioral studies indicate that, relative to healthy subjects, individuals with high levels of depression symptoms or with major depressive disorder (MDD) are less likely to learn to select a more highly rewarded stimuli (Pizzagalli et al., 2009; Pizzagalli, Jahn, & O'Shea, 2005). Individuals with MDD respond more slowly and receive fewer rewards on reinforcement learning tasks due to an impaired ability to accumulate and incorporate evidence, not slowed perception or response, indicating that learning rates (i.e., the rate at which information is integrated and behavior is updated) may be impaired in depression (Lawlor et al., 2019). Additionally, anhedonia has been hypothesized to be the feature of depression most directly influenced by impaired reinforcement learning. This is supported by a prior study using computational modeling of a reinforcement learning task which demonstrated that reduced learning rates in a reinforcement learning task are associated with anhedonia (Chase et al., 2010).

Thus, reduced dopamine availability and binding as measured in PET and SPECT imaging studies (Peciña et al., 2017; Sarchiapone et al., 2006), blunted prediction errors (Gradin et al., 2011), and reduced anticipation and response to rewards in ERP and fMRI studies (for a review, see Mackin et al., 2021), all suggest that impaired dopaminergic function is related to anhedonia. Impaired performance on behavioral reinforcement learning tasks also indicate a likely association with anhedonia.

Influence of Early Childhood Adversity and Chronic Life Stress on Dopamine Dysfunction and Reinforcement Learning

A growing body of research has focused on identifying neurodevelopmental mechanisms linking early childhood adversity (ECA) and life stress with risk for psychopathology via reward processing. Children exposed to early adversity (e.g., abuse, neglect, poverty, and institutional

rearing) frequently demonstrate alterations in reward processing (McLaughlin, DeCross, Jovanovic, & Tottenham, 2019). For example, ECA is associated with a lower likelihood of modifying behavior in response to increasing values of reward (Sheridan et al., 2018), indicating reduced approach motivation. Additionally, ECA has been associated with blunted response to anticipation and receipt of reward in the dorsal and ventral striatum (Dillon et al., 2009; Goff et al., 2013; Hanson, Hariri, & Williamson, 2015; Mehta et al., 2010), and retrospective reports of ECA were associated with lower accuracy and blunted electrophysiological differentiation between correct and incorrect responses (Pechtel & Pizzagalli, 2013). Research has also demonstrated that the speed of associative learning following positive reinforcement is reduced in children (Wismer Fries & Pollak, 2017) and adolescents (Harms, Shannon Bowen, Hanson, & Pollak, 2018) with a history of ECA. Although these studies did not utilize computational modeling to estimate learning rates, these findings indicate that ECA is associated with poor reward contingency acquisition, which is suggestive of maladaptive learning rates. Studies that have employed computational modeling to investigate the association between ECA and reinforcement learning report that ECA is associated with lower efficiency in updating behavior based on experience (Hanson et al., 2017), and a weaker link between the expected value of cues and striatal activation (Gerin et al., 2017). Despite the number of studies examining the influence of ECA on reinforcement learning, there is a notable dearth of literature on whether these effects persist past middle adolescence. Moreover, while several studies have utilized fMRI to examine the effect of ECA on response to reward, studies have not specifically examined associations between ECA and dopamine dysfunction.

Research has consistently demonstrated that acute life stress also impacts reward processing in subcortical reward regions; specifically, acute stressors result in blunted neural

response to rewards in the striatum (Admon et al., 2012; Auerbach et al., 2014; Casement et al., 2014; Kujawa, 2020; Vidal-Ribas et al., 2019). Additionally, although task-induced stressors inhibit reinforcement learning (Bogdan et al., 2010), the influence of real-world stressful life events on reinforcement learning has never been directly examined. Chronic stressors during childhood and adolescence, in particular, may have a cumulative effect and be especially important for predicting long-term reward processing and reinforcement learning dysfunction. Indeed, cumulative life stress during childhood and adolescence has been shown to contribute to blunted reward-related activity in the ventral striatum (Hanson et al., 2015). Importantly, the blunted BOLD signal in striatal regions in response during fMRI studies is thought to reflect impaired dopaminergic function in response to acute and cumulative life stressors. This is based on evidence that the neural signal in these subcortical reward areas is generated at least partially due to encoding prediction errors via phasic dopamine release. While studies demonstrating effects of chronic life stress on neural responses to reward provide a proxy for how chronic stressful life events may influence dopamine function, no studies have directly examined this in humans. Therefore, the current project is the first to examine the effect of chronic, ongoing life stress on subsequent dopamine function and reinforcement learning dysfunction.

The Current Study

Given this background, the current study has three main aims: to assess associations between reinforcement learning and NM-MRI-assessed dopamine; to examine associations of NM-MRI-assessed dopamine and reinforcement learning with anhedonia; and to determine what effects ECA and chronic life stress have on NM-MRI-assessed dopamine and reinforcement learning performance.

Aim 1. Assess Associations Between Reinforcement Learning and NM-MRI-Assessed

Dopamine

Aim 1 - Hypothesis 1.1. Given that learning rates incorporate information encoded by prediction errors across the course of a task, and that the dopamine release that constitutes a prediction error corresponds to its magnitude, it is hypothesized that NM-MRI-assessed dopamine in the SN-VTA complex will be negatively associated with positive and negative learning rates.

Aim 1 - Hypothesis 1.2. Approach and avoidance learning are linked to striatal dopamine levels (Frank et al., 2004) and reinforcement learning-related brain activity associated with dopamine signals (Frank, Woroch, & Curran, 2005). Q-values corresponding to stimuli that are more frequently rewarded can be conceptualized as representing a subject's affinity for approach learning (i.e., a high subjective value for a frequently rewarded stimulus represents good approach learning). Conversely, infrequently rewarded stimuli should be assigned a low subjective value, which represents successful avoidance learning. Therefore, it is hypothesized that Q-values for the more frequently rewarded stimuli will be positively associated with NM-MRI-assessed dopamine in the SN-VTA complex, whereas the Q-values for the infrequently rewarded stimuli will be negatively related to NM-MRI-assessed dopamine in the SN-VTA complex.

Aim 2. Examine Associations Between NM-MRI-Assessed Dopamine and Reinforcement Learning with Anhedonia.

Aim 2 - Hypothesis 1. Due to evidence suggesting that blunted responses to reward (Auerbach et al., 2017; Chan et al., 2016; Dowd & Barch, 2010; Epstein et al., 2006; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Stringaris et al., 2015; Zhang et al., 2016) and reduced dopamine availability/binding (Peciña et al., 2017; Sarchiapone et al., 2006) are related

to increased anhedonia, it is hypothesized that NM-MRI-assessed dopamine will be negatively related to anhedonia symptoms.

Aim 2 – Hypothesis 2.1. Based on results from previous studies indicating that poor reinforcement learning performance is associated with anhedonia (Chase et al., 2010; Gradin et al., 2011; Greenberg et al., 2015; Vrieze et al., 2013), it is anticipated that decreased learning rates will be associated with greater anhedonia.

Aim 2 – Hypothesis 2.2. Similarly, I anticipate that decreased Q-values for frequently rewarded stimuli (i.e., poor approach learning) and increased Q-values for infrequently rewarded stimuli (i.e., poor avoidance learning) will be associated with greater anhedonia symptoms.

Aim 3. Determine Effects of ECA and Chronic Life Stress on NM-MRI-Assessed Dopamine and Reinforcement Learning Performance.

Aim 3 – Hypothesis 1.1. Based on literature suggesting that ECA influences reward processing encoded by midbrain dopamine neurons (Dillon et al., 2009; Goff et al., 2013; Hanson et al., 2015; McLaughlin et al., 2019; Mehta et al., 2010), I expect ECA will be negatively correlated with NM-MRI-assessed dopamine in the SN-VTA complex.

Aim 3 – Hypothesis 1.2. Similarly, given that ongoing life stress influences reward processing encoded by midbrain dopamine neurons (Dillon et al., 2009; Goff et al., 2013; Hanson et al., 2015; McLaughlin et al., 2019; Mehta et al., 2010), I expect that chronic life stress will be negatively correlated with NM-MRI-assessed dopamine in the SN-VTA complex.

Aim 3 – Hypothesis 2.1. Due to evidence indicating that ECA is associated with impaired reinforcement learning task performance (Harms et al., 2018; Wismer Fries & Pollak, 2017), I expect that ECA will be positively associated with positive and negative learning rates.

Aim 3 – Hypothesis 2.2. Similarly, it is expected that ECA will be negatively associated

with Q-values from more frequently rewarded stimuli and positively associated with Q-values from less frequently rewarded stimuli.

Aim 3 – Hypothesis 2.3. Given that individuals who experience life stressors demonstrate impaired performance on reinforcement learning tasks (Harms et al., 2018; Wismer Fries & Pollak, 2017), it is hypothesized that chronic life stress will be positively associated with positive and negative learning rates.

Aim 3 – Hypothesis 2.4. Relatedly, it is expected that chronic life stress will be negatively associated with Q-values from more frequently rewarded stimuli and positively associated with Q-values from less frequently rewarded stimuli.

Method

Participants

Participants (N=81; 51.9% female) were recruited for a study including NM-MRI imaging, a behavioral reinforcement learning task, and anhedonia questionnaires from the ongoing Stony Brook Temperament Study (SBTS). SBTS participants have been assessed every 3 years since age 3, and NM-MRI, behavioral reinforcement learning, and anhedonia data was collected shortly after their 18th birthday (M_{age} = 18.80, SD_{age} = 0.57).

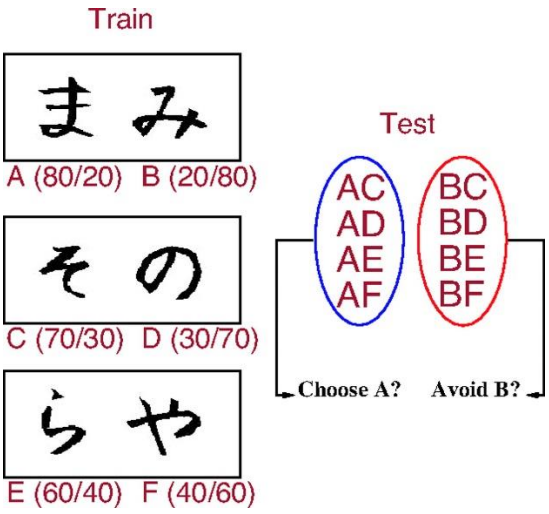
Measures

Reinforcement Learning

Reinforcement learning was assessed using the Probabilistic Selection Task (PST; Frank et al., 2004), a well-established probabilistic reinforcement learning task consisting of training and testing phases. In the training phase, 3 stimulus pairs (AB, CD, and EF) are presented in random order over 4 blocks of 60 trials each (20 of each trial type per block). Participants must choose 1 of the 2 stimuli (see Figure 1).

Figure 1

Probabilistic Selection Task



Note. Example pairs from Probabilistic Selection Task. Three different pairs are presented separately in different trials in a random order. Correct choices are determined probabilistically (percent positive/negative feedback shown in parentheses for each stimulus). A test phase ensues in which stimuli A and B are repaired with all other more neutral stimuli; no feedback is provided in this test phase. Figure adapted from Frank et al. (2007).

Feedback follows each choice to indicate whether it was rewarded ("Reward"; paid 5¢), or not rewarded ("Zero"; not paid). This feedback is probabilistic: in AB trials, a choice of stimulus A leads to reward feedback in 80% of trials (B leads to reward in 20% of trials), in CD trials, C is rewarded in 70% of trials, and on EF trials, E is rewarded in 60% of trials. Participants learn to choose stimuli A, C and E more often than B, D, or F. Because the reward probabilities do not change, a low-moderate learning rate is adaptive (Frank et al., 2007). Because stimuli are presented in fixed pairs during the training phase, successful learners can learn that A, C, and E are the more frequently rewarded, that B, D, and F are less frequently rewarded, or both. During the subsequent testing phase, the same and novel combinations of stimulus pairs are presented without providing feedback. The testing phase can be useful for distinguishing between learning from rewards (i.e., choose A, C, and E stimuli) and learning from penalties (absence of reward in

this context; avoid B, D, and F stimuli) because stimuli are now paired with each of the other stimuli. This data can also be used to ensure that learning occurred (e.g., performance threshold of 50% correct).

Computational Modeling of Reinforcement Learning Data. Individual, trial-level data from the training phase of the PST was used to estimate parameters in a Q-learning model (see Figure 2; Sutton & Barto, 1998). Consistent with previous studies (e.g., Cavanagh, Bismark, Frank, & Allen, 2019; Cox et al., 2015; Frank et al., 2007; Frank et al., 2004), participants' trial-by-trial decisions were used to estimate three free parameters, α_G (positive learning rate), α_L (negative learning rate), and β (stochasticity; Durstewitz, Seamans, & Sejnowski, 2000), which are used to calculate Q-values. Standard optimization techniques were used to find parameter values that maximize the likelihood of each participant's behavioral data. The learning rates reflect that participant's propensity to update their behavior (i.e., stimuli selection) based on prior task-related feedback (i.e., reward or zero) over the course of the task. Positive and negative learning rates provide computational indices of approach and avoidance related learning, respectively. Q-values correspond to the subjective values individual participants assign to each stimulus. It is expected that stimuli that are rewarded more frequently (i.e., have a greater probability of being rewarded) will be assigned a higher Q-value. Testing phase data from the reinforcement learning task was used to ensure validity; participants who did not answer correctly on at least 50% of trials, suggesting that they did not acquire the expected contingencies, were excluded from analyses including reinforcement learning data (N = 10).

Figure 2

Q-Learning Computational Model

After selecting stimulus *i* on trial *t*, Q-values are updated:

$$Q_i(t+1) = Q_i(t) + \alpha[r(t) - Q_i(t)]$$

$$\alpha: = \alpha_G \text{ if } r(t) > Q_i(t)$$

$$\alpha: = \alpha_L \text{ if } r(t) < Q_i(t)$$

- $r(t) = 1$ for positive feedback (win)
- $r(t) = 0$ for negative feedback (zero)
- $Q_i(t)$ = Q-value on current trial
- $Q_i(t+1)$ = Q-value estimate on next trial
- $[r(t) - Q_i(t)]$ = Prediction error term

Choice behavior is modeled by a ''softmax'' logistic function, with inverse gain parameter, β, such that the probability of choosing one stimulus over another (e.g., A over B) was computed:

$$P_A(t) = \frac{e^{\frac{Q_A(t)}{\beta}}}{e^{\frac{Q_A(t)}{\beta}} + e^{\frac{Q_B(t)}{\beta}}}$$

- β is an inverse gain parameter (likelihood to exploit vs. explore)
- A & B replaced by C,D,E,F for other trial types

Note. The computational Q-Learning algorithm used to estimate positive (α_G) and negative (α_L) learning rates, Q-values (predicted value) of each of the six stimuli, and variability in choice behavior/stochasticity (β) parameters at the trial level for each participant. This model has been used previously in papers that employ the Probabilistic Selection Task (e.g., Frank, Seeberger, & O'reilly, 2004; Frank et al., 2004).

Anhedonia

Positive Valence Systems Scale (PVSS; Khazanov, Ruscio, & Forbes, 2019).

Anhedonia symptoms were assessed using the PVSS, a 21-item factor-analytically derived measure of the NIMH RDoC Positive Valence Systems domain. It was designed to capture a variety of anhedonia- and reward-related constructs, including reward expectancy, reward anticipation, reward valuation, initial responsiveness to reward, reward satiation, effort valuation, and action selection. All items from the PVSS are included in Appendix I. Each item was rated based on the extent to which the statement (e.g., I was excited to discover that someone I met

shared my interests) described the participant over the past two weeks on a 9-point Likert-type scale ranging from 1 (extremely untrue of me) to 9 (extremely true of me). To compute a total score, all 21 items are summed. Each of the seven subscales are comprised of 3 items and are computed by summing their respective items. In each case, lower scores reflect greater symptoms of anhedonia. The current study primarily focused on examining the PVSS total score.

The PVSS has good internal consistency, test-retest reliability, and factorial validity, and is closely related to other anhedonia measures (Khazanov et al., 2019). It demonstrates good discriminant validity and is more strongly related to reward than punishment sensitivity, positive than negative affect, and depression than anxiety. In the current sample, internal consistency was substantial (α = .87; Shrout, 1998).

Expanded Version of the Inventory of Depression and Anxiety Symptoms – Well-Being Scale (IDAS-II; **Watson et al., 2012).** The IDAS-II is a self-report inventory that consists of 99 items comprising 18 factor-analytically derived scales (e.g., ill temper, well-being, mania, panic, social anxiety) cutting across internalizing disorders in a manner consistent with the Hierarchical Taxonomy of Psychopathology (Hi-TOP; Kotov et al., 2017). The current study employed the IDAS-II Well-being subscale as a secondary measure of anhedonia. The IDAS-II includes 8 items that are rated on a 5-point Likert-type scale ranging from 1 (not at all) to 5 (extremely) based on the previous two weeks, with lower scores reflecting greater symptoms of anhedonia. All items from the IDAS-II Well-being scale are reported in Appendix II. The IDAS-II demonstrates good internal consistency, test-retest reliability, and factorial validity (Watson et al., 2012). In the current sample, internal consistency of the IDAS-II Well-being scale was substantial (α = .86; Shrout, 1998).

Life Stress

Early Childhood Adversity. A composite variable indexing ECA was created by using data collected from the SBTS at the age 3 and age 6 visits. This scale includes measures of stressful life events, mother- and father-reported hostile parenting (hostility subscale of the Preschool Parenting Measure [PPM; Sessa, Avenevoli, Steinberg, & Morris, 2001]), and mother and father reported authoritarian parenting (verbal hostility, physical coercion, and punitive subscales of the Parenting Styles and Dimensions Questionnaire [PSDQ; Robinson, Mandleco, Olsen, & Hart, 1995]). These measures were selected based on their independent contributions to stressful environments during early childhood, which can be aggregated through the creation of a broad ECA construct. Additionally, the internal consistency for the PPM ($\alpha_{\text{age 3 mother}}$ = .71; $\alpha_{\text{age 3 father}}$ = .68; $\alpha_{\text{age 6 mother}}$ = .65; $\alpha_{\text{age 6 father}}$ = .70) and PSDQ ($\alpha_{\text{age 3 mother}}$ = .75; $\alpha_{\text{age 3 father}}$ = .77; $\alpha_{\text{age 6 mother}}$ = .74; $\alpha_{\text{age 6 father}}$ = .76) were moderate in the current sample (Shrout, 1998). Interrater reliability was not calculated for the measure of stressful life events because it was operationalized as a count of endorsed events.

To create the composite ECA variable, the number of stressful life events was averaged across the age 3 and 6 SBTS visits. This allowed for families who participated at only one of the assessments to be included in the analyses (50 families were added to the study at age 6 to increase diversity of the sample). Similarly, average parenting scores were created separately for mothers and fathers based on their respective scores on the PPM hostile parenting and PSDQ authoritarian parenting scales at the age 3 and 6 SBTS visits. These three variables (age 3 and 6 stressful life events, age 3 and 6 adverse mother parenting behaviors, age 3 and 6 adverse father parenting behaviors) were each z-scored, then averaged together to create a single composite ECA variable reflecting each of these domains. The internal consistency of this measure was only fair (α = .41; Shrout, 1998). This is expected given that the composite measure of ECA

includes information across multiple measures, reporters, and assessments. However, this is inconsequential given that ECA is considered a formative, rather than reflective, variable (Edwards & Bagozzi, 2000).

Chronic Life Stress. Chronic life stress was assessed using the UCLA Life Stress Interview (LSI; Constance Hammen et al., 1987), which was administered at the SBTS age 12, 15, and 18 assessments. The LSI assesses chronic stress in the domains of academics, work, and peer, romantic, and family relationships. A composite score was created by aggregating chronic stress across waves, providing a measure of cumulative stress between the ages of 12 and 18. Specifically, total chronic stress scores were calculated at each wave by averaging across domain scores to create a total chronic stress score at each assessment. Then, the total chronic stress scores from the age 12, 15, and 18 were separately z-scored, then averaged together to reflect the average level of chronic stress from age 12-18. Importantly, the period of the LSI assessment did not overlap with our ECA composite variable.

The average inter-rater reliabilities across all chronic stress domains were moderate at ages 12 (ICC = 0.73), 15 (ICC = .74), and 18 (ICC = .73). Although less relevant given that our chronic life stress variable is a formative variable, the internal consistency was substantial for the aggregate chronic stress variable (α = .91; Shrout, 1998).

Study Procedure

Participants completed the current study shortly after their age 18 SBTS visit. A health and safety screen (e.g., exclusion for pregnancy, urine toxicology) was conducted for each participant prior to imaging to ensure safety. Participants each completed a 26-minute probabilistic reinforcement learning behavioral task (Frank et al., 2004), followed by a 21-item anhedonia questionnaire (Khazanov et al., 2019) on a study laptop computer in a room dedicated

to behavioral data collection. Then, T1w structural images were acquired for anatomical referencing and preprocessing of NM-MRI scans, followed by the NM-MRI scan (Cassidy et al., 2019; Wengler et al., 2020). This protocol required approximately 30 minutes, and the entire visit took approximately 1 hour. IDAS-II Well-being (age 18 visit), ECA (age 3 and 6 visits), and chronic life stress (age 12, 15, and 18 visits) data from prior SBTS visits were also utilized in the current study.

NM-MRI Procedure

Structural magnetic resonance imaging protocol. T1w structural images were acquired for anatomical referencing and preprocessing of NM-MRI scans. The T1w scan was acquired using a 3D-MPRAGE sequence with the following parameters: TR/TE/TI =2400/2.24/1060 ms, FOV=256, voxel size=0.8x.0.8x0.8 mm3, flip angle=8°, slices=208, and GRAPPA parallel imaging factor=2. Consistent with best NM-MRI practices (Cassidy et al., 2019; Wengler et al., 2020), this sequence was acquired twice and averaged to reduce noise.

NM-MRI sequence and imaging protocol. The NM-MRI sequence consisted of 2D gradient echo (GRE) images with magnetization transfer (MT) contrast of the midbrain (2D-GRE-MT, 0.39 mm2 in-plane resolution, 10 slices, FOV=162×200 mm, FA=40°, TR= 260 ms, TE=2.68 ms, MT frequency offset=1200 Hz, AC-PC alignment). This sequence has been compared to alternative NM-MRI sequences (Wengler et al., 2020), and results indicate it offers the highest contrast-to-noise (CNR) and strongest correlations with neuromelanin concentration in post-mortem tissue (Cassidy et al., 2019). To ensure high quality imaging of the NM concentrations in the SN and VTA, the image stack was manually positioned by a trained technician according to anatomical landmarks on the high-resolution T1w scan (Wengler et al., 2020). The top slice of the image stack was positioned immediately inferior to the floor of the

third ventricle at the most superior portion of the midbrain on a sagittal view of the center of the brain (Wengler et al., 2020). The NM-MRI protocol can be acquired in ~13 minutes. NM-MRI scans were evaluated for motion or other artifacts during the MRI session in the scanner console and collected again as needed. Two NM-MRI scans free of visible artifacts were collected to reduce the risk of unusable data.

NM-MRI data processing. A specialized NM-MRI processing pipeline was employed (Wengler et al., 2020). Preprocessing steps involved spatial realignment, averaging, coregistration, spatial-normalization to MNI space using each subject's T1w images using ANTs (Avants, Epstein, Grossman, & Gee, 2008; Avants, Tustison, & Song, 2009), and smoothing. The metric for NM-MRI analysis, contrast-to-noise ratio values (CNR), was generated using an optimized voxel-wise approach using the group averaged normalized image and expressed as the percent signal difference in NM-MRI intensity at a given voxel in the SN-VTA complex relative to the crus cerebri, a nearby white matter tract with minimal neuromelanin content. This method is preferred because conventional ROI approaches can be biased by signal contrast, making it difficult to manually trace the edges of the SN-VTA complex. The thresholds for each subject's SN-VTA complex were calculated using the mean (μ_{ref}) and standard deviation (σ_{ref}) of a reference region manually defined in the cerebral peduncle. Voxels with neuromelanin signal intensity greater than $\mu_{ref} + 3\sigma_{ref}$ were considered part of the SN-VTA complex. The SN-VTA neuromelanin signal (i.e., NM level) was quantified for each subject using CNR defined as: $CNR(x,y,z) = [I(x,y,z) - \mu_{ref}] / \mu_{ref}$, where I(x,y.z) denotes the signal intensity of a voxel located at position (x,y,z). To reduce the risk of type II error, voxels were excluded from the voxel-wise analysis if at least 20% are missing or extreme values. This pipeline and acquisition parameters were shown to exhibit a strong test-retest reliability over 13 days (Wengler et al., 2020).

Multiple comparisons correction. Voxelwise analyses using non-parametric permutation tests with familywise-error-corrected significance were employed, as this method is less prone to false positives than random-field-theory-based and Monte-Carlo-simulation-based corrections (Eklund, Nichols, & Knutsson, 2016). Specifically, the number of voxels with a significant effect of the variable of interest at $p<0.05$ using a robust regression framework (in SPM12 using custom Matlab scripts) was calculated. Then the likelihood of finding such number of significant voxels by chance was determined by reshuffling the variable of interest across individuals in 1,000 permuted datasets and generating a null distribution of number of significant voxels to compare against.

Results

Results reported below are for analyses using non-transformed data. However, the pattern of results was identical when applying several transformations on the learning rate data (e.g., log10 and square root transformations) to obtain a normal distribution. Results using the original data are reported to facilitate interpretation.

Descriptive Statistics

Descriptive statistics for the sample are presented in Table 1.

Table 1

Descriptive statistics

Variable	N	M/N	SD/%
Demographic Characteristics			
Sex (female)	81	42	51.90
Age	81	18.80	0.57
Anhedonia			
PVSS	71	152.81	16.20
IDAS-II Well-being	81	22.41	6.53
Life Stress			
ECA	80	0.00	0.70
Chronic Stress	80	0.05	0.84
Learning Rates			
α_G	71	0.31	0.42
α_L	71	0.11	0.18
Q-values			
A (80%)	71	0.73	0.34
B (20%)	71	0.28	0.33
C (70%)	71	0.70	0.35
D (30%)	71	0.36	0.35
E (60%)	71	0.59	0.36
F (40%)	71	0.48	0.38

Note. N = number. M/N = Mean/number female. SD/% = Standard deviation/% female. αG = gain learning rate. αL = loss learning rate. PVSS = Positive Valence Systems Scale. IDAS-II Wellbeing = Expanded version of the Inventory for Depression and Anxiety Symptoms Well-being scale. ECA = Early childhood adversity. See Method Section for information on scoring of ECA and chronic stress variables.

Aim 1. Assess Associations Between Reinforcement Learning and NM-MRI-Assessed Dopamine

NM-MRI and reinforcement learning data from the training phase of the PST were used to examine Aim 1 hypotheses. Table 2 includes the results from all analyses examining Aim 1.

Aim 1 – Hypothesis 1.1 Data Analysis.

Learning rates (α_G, α_L) were estimated for each participant using the Q-learning model and correlations between each learning rate and the NM-MRI CNR from the SN-VTA complex were calculated to identify significant associations. If associations with both learning rates were statistically significant, partial correlations for each learning rate, controlling for the other learning rate, were computed to isolate specific effects.

Aim 1 – Hypothesis 1.1 Results

Results indicate that associations between both the positive (α_G) and negative (α_L) learning rates and the NM-MRI CNR in the SN-VTA were non-significant.

Aim 1 – Hypothesis 1.2 Data Analysis

Q-values were calculated for each stimulus at the participant level and correlations between each Q-value and the NM-MRI CNR from the SN-VTA complex were estimated.

Aim 1 – Hypothesis 1.2 Results

Results from analyses examining associations between NM-MRI CNR and the A-Q-value from the PST are displayed in Figure 3[1]. All associations between NM-MRI CNR and the Q-values for the more valuable stimulus from each pair (i.e., stimulus with greater probability of being rewarded from each pair; A, C, E) were statistically significant and of moderate magnitude. This suggests that higher NM-MRI CNR in the SN-VTA complex is associated with higher subjective values being assigned to stimuli that are probabilistically advantageous. Conversely, relationships between NM-MRI CNR and the less probabilistically rewarded stimuli were mixed; while correlations for the B (20% reward probability) and F (40% probability) Q-values were non-significant (although trend-level for the B stimulus), the D Q-value was positively and moderately correlated with NM-MRI CNR.

[1] The significant association between the A Q-value and NM-MRI assessed dopamine was selected because there were a greater number of significant voxels than in analyses examining the other Q-values.

Table 2

Bivariate correlations between neuromelanin and reinforcement learning parameters

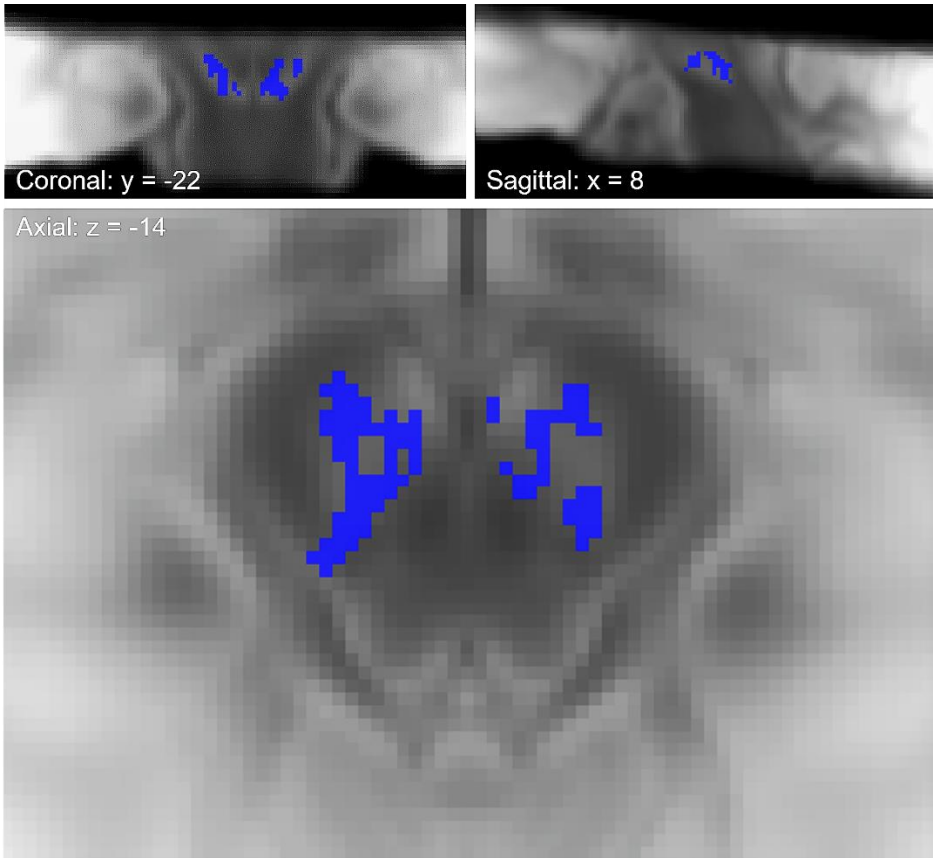
	NM-MRI CNR					
	Positive Correlation			Negative Correlation		
Learning Rates	# Sig + Voxels	+*r*	*p*	# Sig - Voxels	-*r*	*p*
α_G	32	.34	.52	24	-.36	.66
α_L	6	.21	.85	56	-.40	.40

	NM-MRI Signal					
	Positive Correlation			Negative Correlation		
Q-values	# Sig + Voxels	+*r*	*p*	# Sig - Voxels	-*r*	*p*
A (80%)	**625**	**.36**	**.008**	0	--	--
B (20%)	258	.33	.06	0	--	--
C (70%)	**367**	**.35**	**.03**	1	-.22	.98
D (30%)	**480**	**.35**	**.03**	7	-.18	.85
E (60%)	**575**	**.35**	**.008**	0	--	--
F (40%)	207	.32	.11	4	-.28	.93

Note. α_G = positive learning rate. α_L = negative learning rate. NM-MRI CNR = Contrast to noise ratio in the SN-VTA complex according to neuromelanin-sensitive magnetic resonance imaging. # Sig + Voxels = number of voxels in which a significant positive correlation was detected at the p = .05 level. # Sig - Voxels = number of voxels in which a significant negative correlation was detected at the p = .05 level. +r = magnitude of correlation in positive voxels. -r = magnitude of correlation in negative voxels. p = p-value

Figure 3

Associations between NM-MRI-assessed dopamine and reinforcement learning



Note. Map of SN-VTA voxels where NM-MRI contrast to noise ratio (CNR) is positively correlated ($p < 0.05$, voxel level) with the Q-value for the A stimulus from the reinforcement learning task (blue voxels) overlaid on the average NM-MRI CNR image from all subjects.

Aim 2. Examine Associations Between NM-MRI-Assessed Dopamine and Reinforcement Learning with Anhedonia.

NM-MRI, reinforcement learning data from the training phase of the PST, and anhedonia symptoms (PVSS, IDAS-II Well-being) were used to test Aim 2 hypotheses. Table 3 includes the results from all analyses examining Aim 2.

Aim 2 – Hypothesis 1 Data Analysis

NM-MRI CNR from the SN-VTA complex was correlated with anhedonia symptoms (PVSS, IDAS-II Well-being).

Aim 2 – Hypothesis 1 Results

Results indicate that the relationships between the NM-MRI CNR in the SN-VTA complex and anhedonia measured according to both the PVSS, and the IDAS-II Well-being scale are statistically non-significant.

Aim 2 – Hypothesis 2.1 Data Analysis

Correlations between learning rates (α_G, α_L) for each participant and symptoms of anhedonia (PVSS, IDAS-II Well-being) were calculated. If associations with both learning rates were statistically significant, partial correlations for each learning rate, controlling for the other learning rate, were computed to isolate specific effects.

Aim 2 – Hypothesis 2.1 Results

There was a significant positive association of moderate magnitude between α_L (negative learning rate) and anhedonia assessed by the IDAS-II Well-being scale, indicating that as the negative learning rate increases, participants report fewer symptoms of anhedonia. However, associations between α_G (positive learning rate) and both measures of anhedonia, as well as α_L and the PVSS were non-significant.

Aim 2 – Hypothesis 2.2 Data Analysis

Correlations between Q-values for each stimulus at the participant level and symptoms of anhedonia (PVSS, IDAS-II Well-being) were calculated.

Aim 2 – Hypothesis 2.2 Results

All correlations examining the associations between Q-values (expected value of each stimulus) and anhedonia were non-significant.

Table 3

Bivariate correlations between anhedonia and neuromelanin and reinforcement learning parameters

	NM-MRI CNR					
	Positive Correlation			Negative Correlation		
Anhedonia Scale	# Sig + Voxels	+*r*	*p*	# Sig - Voxels	-*r*	*p*
PVSS	26	.20	.58	66	-.43	.41
IDAS-II Well-being	11	.29	.80	158	-.39	.16

	Anhedonia Scale			
	PVSS		IDAS-II Well-being	
Reinforcement Learning	*r*	*p*	*r*	*p*
Learning Rates				
α_G	-.08	.54	-.15	.21
α_L	-.15	.24	**.30**	**.01**
Q-values				
A (80%)	-.10	.43	-.14	.26
B (20%)	.06	.67	-.15	.20
C (70%)	.03	.81	-.14	.34
D (30%)	.14	.30	.02	.87
E (60%)	-.01	.96	-.08	.53
F (40%)	.02	.90	-.18	.14

Note. PVSS = Positive Valence Systems Scale. IDAS-II Well-being = Expanded version of the Inventory for Depression and Anxiety Symptoms Well-being scale. α_G = positive learning rate. α_L = negative learning rate. NM-MRI CNR = Contrast to noise ratio in the SN-VTA complex according to neuromelanin-sensitive magnetic resonance imaging. # Sig + Voxels = number of voxels in which a significant positive correlation was detected at the p = .05 level. # Sig - Voxels = number of voxels in which a significant negative correlation was detected at the p = .05 level. +r = magnitude of correlation in positive voxels. -r = magnitude of correlation in negative voxels. p = p-value

Aim 3. Determine Effects of ECA and Chronic Life Stress on NM-MRI-Assessed Dopamine and Reinforcement Learning Performance.

NM-MRI data, reinforcement learning data from the training phase of the PST, and ECA and chronic life stress scores were used to test Aim 3 hypotheses. Table 4 includes the results from all analyses examining Aim 3.

Aim 3 – Hypothesis 1.1 Data Analysis

A correlation was calculated between ECA and NM-MRI CNR in the SN-VTA complex.

Aim 3 – Hypothesis 1.1 Results

Analyses examining the association between the NM-MRI CNR in the SN-VTA complex and ECA indicate that the relationship is not statistically significant.

Aim 3 – Hypothesis 1.2 Data Analysis

A correlation was calculated between chronic life stress and the NM-MRI CNR in the SN-VTA complex.

Aim 3 – Hypothesis 1.2 Results

Similarly, the association between the NM-MRI CNR in the SN-VTA complex and chronic stress is non-significant.

Aim 3 – Hypothesis 2.1 Data Analysis

Correlations between learning rates ($\alpha_{G,}$ α_{L}) for each participant and ECA were calculated. If associations with both learning rates were statistically significant, partial correlations for each learning rate, controlling for the other learning rate, were computed to isolate specific effects.

Aim 3 – Hypothesis 2.1 Results

Correlations examining the associations between ECA and both α_{L} (negative learning rate) and α_{g} (positive learning rate) were non-significant.

Aim 3 – Hypothesis 2.2 Data Analysis

Correlations between Q-values for each stimulus at the participant level and ECA were calculated.

Aim 3 – Hypothesis 2.2 Results

Similarly, all analyses examining the associations between ECA and Q-values (expected value of each stimulus) were non-significant.

Aim 3 – Hypothesis 2.3 Data Analysis

Correlations between learning rates (α_G, α_L) for each participant and chronic life stress were calculated. If associations with both learning rates were statistically significant, partial correlations for each learning rate, controlling for the other learning rate, were computed to isolate specific effects.

Aim 3 – Hypothesis 2.3 Results

Examination of the association between α_g (positive learning rate) and chronic stress suggested a positive and statistically significant relationship of moderate magnitude. Individuals who reported greater levels of chronic life stress also demonstrated a higher positive learning rate. However, the association between chronic stress and the loss learning rate was non-significant.

Aim 3 – Hypothesis 2.4 Data Analysis

Correlations between Q-values for each stimulus at the participant level and chronic stress were calculated.

Aim 3 – Hypothesis 2.4 Results

All correlations examining the associations between Q-values and chronic life stress were non-significant.

Table 4

Bivariate correlations between life stressors and neuromelanin and reinforcement learning parameters

	NM-MRI CNR					
	Positive Correlation			Negative Correlation		
Life Stress Scale	# Sig + Voxels	+*r*	*p*	# Sig - Voxels	-*r*	*p*
ECA	71	.41	.34	6	-.42	.86
Chronic Stress	65	.29	.38	8	-.23	.83

	Life Stress Measure			
	ECA		Chronic Stress	
Reinforcement Learning	*r*	*p*	*r*	*p*
Learning Rates				
α_G	.003	.98	**.33**	**.004**
α_L	.03	.84	.10	.41
Q-values				
A (80%)	-.01	.92	.07	.58
B (20%)	.03	.80	-.04	.72
C (70%)	.01	.93	.03	.79
D (30%)	.07	.55	-.06	.64
E (60%)	-.08	.53	-.11	.35
F (40%)	.08	.53	.10	.43

Note. ECA = early childhood adversity. α_G = positive learning rate. α_L = negative learning rate. NM-MRI CNR = Contrast to noise ratio in the SN-VTA complex according to neuromelanin-sensitive magnetic resonance imaging. # Sig + Voxels = number of voxels in which a significant positive correlation was detected at the p = .05 level. # Sig - Voxels = number of voxels in which a significant negative correlation was detected at the p = .05 level. +r = magnitude of correlation in positive voxels. -r = magnitude of correlation in negative voxels. p = p-value

Discussion

Prior research indicates that anhedonia is characterized by dopaminergic dysfunction (Der-Avakian & Markou, 2012; Huys et al., 2013; Peciña et al., 2017; Pizzagalli, 2014; Sarchiapone et al., 2006; Treadway & Zald, 2011; Treadway & Zald, 2013), and that reinforcement learning is driven by the dopamine system (Cox & Witten, 2019; O'Doherty et al., 2004). Furthermore, stressful events contribute to anhedonia, possibly via their effect on

dopamine pathways (e.g., reward-related processing) and reinforcement learning (Gerin et al., 2017; Pizzagalli, 2014; Stanton, Holmes, Chang, & Joormann, 2019). Therefore, the current project aimed to establish associations between each of these processes by using a novel imaging technique to assess neuromelanin, a biproduct of dopamine synthesis, in the SN-VTA complex, a well-established reinforcement learning paradigm, longitudinal assessments of ECA and chronic life stress, and anhedonia in a sample of young adults.

Associations Between Reinforcement Learning and NM-MRI-Assessed Dopamine

Results from the current study indicated that associations between NM-MRI-assessed dopamine and the positive and negative learning rates were non-significant. These findings did not support the hypotheses that NM-MRI-assessed dopamine would be positively associated with learning rates in the present study. There are several potential explanations for the absence of significant findings. First, the specific reinforcement learning task employed in the current study may have influenced the results. Because the environment (i.e., rules) does not change in the PST, a low-moderate learning rate is adaptive, allowing for slow and smooth integration of information over the duration of the entire experiment. However, it is also hypothesized that individuals who exhibit low levels of dopamine (i.e., are less responsive to rewards) would also update their responses to not winning money on a behavioral reinforcement learning task less rapidly than individuals who are more sensitive to receiving/not receiving rewards. Therefore, the pattern of behavior expected from individuals who demonstrate lower levels of dopamine (e.g., are less responsive to rewards), despite not being expected to perform as well on reinforcement learning tasks, may be behaviorally identical to the strategy employed by effective learners and (i.e., slow integration of information without rapid responses to feedback) in the current task. Reinforcement learning tasks that employ blocks in which the rules of the task shift

may be more effective in detecting associations between reinforcement learning performance and dopamine. Alternatively, different measures of reinforcement learning (e.g., associations between the magnitude of prediction errors), or non-linear models[2] that may be able to detect an ideal "low-moderate" learning rate, may be more appropriate for examining individual dopaminergic differences. Alternatively, this discrepancy could also be explained by differences in the timeframe that our measures of dopamine function and reinforcement learning assess. While our reinforcement learning task probes current behavioral tendencies, NM-MRI provides a cumulative, life-long assessment of dopaminergic functioning. Therefore, if participants behavior was characterized by different reinforcement schedules at earlier points in their life, or if participants' behavior during the reinforcement learning task varied from their historical behavior for any reason, NM-MRI may not be capable of accounting for the developmental or state-like (e.g., emotional) differences.

However, when examining the relationship between NM-MRI-assessed dopamine and the expected value (Q-value) for each stimulus, associations with the Q-values for the stimuli rewarded more probabilistically (A = 80%, C = 70%, E = 60%) were significant and positive. These findings are supportive of the hypotheses and indicate that greater dopamine production in the SN-VTA complex is associated with assigning higher subjective values to relatively advantageous stimuli. Conversely, when considering the less probabilistically rewarded stimuli from each pair (B = 20%, D = 30%, F = 40%), only the D stimulus was significantly associated with NM-MRI-assessed dopamine. It is unclear why the D Q-value is positively related to SN-VTA complex dopamine production. One explanation is that, when also considering the trend-level effect with the B Q-value, individuals with greater NM-MRI signals in the SN-VTA

[2] Regression analyses examining quadratic learning rate terms were explored but results for both the linear and quadratic effects for gain and loss learning rates were non-significant.

complex broadly assign greater subjective values to all stimuli, regardless of the probability of rewards. Regardless, the A-B and E-F stimuli pairs may be more relevant for establishing relationships with dopamine production than the C-D pair. The A and B stimuli represent the most and least valuable stimuli, respectively, whereas the E-F pair is most difficult to discriminate between; dopamine function may be especially relevant for promoting adaptive learning in either context.

One possible explanation for why NM-MRI-assessed dopamine function may be significantly related to the Q-values from the more frequently rewarded stimuli but not learning rates may have to do with differences in the way that they separate/combine information. The learning rates from the reinforcement learning task distinguish between behavior on trials where outcomes are better than expected (i.e., rewards; positive learning rate) and worse than expected (i.e., zeros; negative learning rates). While both processes are encoded by a dopaminergic response, the response is different; rewards are associated with increased phasic dopamine release, whereas zeros are processed by pauses in tonic dopamine release. Given that NM-MRI-assessed dopamine provides a cumulative measure of dopamine production, it may be capturing dopamine functioning on a broader scale. That is, NM-MRI may not be sensitive to these different underlying processes (i.e., phasic increase vs tonic decrease in dopamine release) and may better capture overall, aggregate dopamine function. The Q-values aggregate information from performance on both gain and loss trials, making them a potentially more congruent measure to examine in combination with NM-MRI-assessed dopamine.

Associations Between NM-MRI-Assessed Dopamine and Reinforcement Learning with Anhedonia

NM-MRI-Assessed Dopamine and Anhedonia

Contrary to our hypotheses, NM-MRI-assessed dopamine was not significantly associated with anhedonia according to either measure. This was surprising given that prior research has established associations between dopamine availability/binding and depression (Peciña et al., 2017; Sarchiapone et al., 2006). Similarly, other processes that are driven at least partially by the dopamine system, notably neural measures of reward anticipation and responsiveness, are associated with depression and anhedonia (Treadway & Zald, 2013; Zald & Treadway, 2017). One potential explanation for the absence of the hypothesized association may be that the level of anhedonia observed in the sample is too low given that it is a community recruited. Prior NM-MRI studies have been successful in identifying associations in disorders characterized by significant dopaminergic disturbance (e.g., Parkinson's disease, schizophrenia) and, therefore, it may be a measure better suited for identifying deficits that are larger in magnitude. For example, NM-MRI may better characterize differences between melancholic depressed patients and healthy controls.

Reinforcement Learning and Anhedonia

Results investigating potential associations between NM-MRI-assessed dopamine and reinforcement learning partially supported our hypotheses. Specifically, a lower negative learning rate was moderately and significantly associated with increased anhedonia on the IDAS-II Well-being scale, but not on the PVSS. This may be due to the PVSS including items related to more specific experiences (e.g., "I looked forward to hearing feedback on my work") compared to the IDAS-II Well-being scale which employs more general items (e.g., "I looked forward to things with enjoyment"; see Appendix I and II). However, our results suggest that participants with greater levels of anhedonia were less likely to update their behavior following loss-related feedback (or the absence of gain-related feedback in the current study). Although

surprising that this finding did not extend to gain-related feedback, the current finding suggests that stress-generation models of depression may be relevant for explaining behavior among people experiencing anhedonia. The stress generation model posits that individuals who are depressed, or are at risk for depression, behave in ways that make their lives more stressful, subsequently increasing risk for depression maintenance or relapse (Hammen, 1991). The current findings indicate that individuals with higher levels of anhedonia may continue to engage in maladaptive behavior despite feedback that their behavior is not beneficial. This is likely to lead to less optimal and more stressful outcomes in daily life, increasing risk for maintenance or exacerbation of anhedonia. Relatedly, prior stress-generation work has suggested that neural processing of loss-related stimuli may be more relevant to stress generation than processing of gain-related stimuli (Mackin et al., 2019).

However, results from models that examined associations between the Q-values of each stimulus and both measures of anhedonia were non-significant. Therefore, the subject values that participants assigned to the stimuli in the reinforcement learning paradigm were not related to anhedonia symptoms.

Effects of ECA and Chronic Life Stress on NM-MRI-Assessed Dopamine and Reinforcement Learning Performance

ECA, NM-MRI-Assessed Dopamine, and Reinforcement Learning

The associations between ECA and NM-MRI-assessed dopamine was non-significant, suggesting that dopamine production in the SN-VTA complex was not influenced by ECA in our sample. Similarly, ECA was not related to reinforcement learning performance across any of the measures. The absence of significant associations was initially surprising given the strong influence of ECA on reward-related neural processing and reinforcement learning performance

in prior studies; however, this may be partially due to the sample. The sample examined in the current study was community-recruited, and levels of ECA were low despite using measure that focuses on assessing less severe aspects of ECA (i.e., parental hostility and authoritarian parenting vs. abuse and neglect). Much of the prior work investigating ECA has examined samples where more severe stressors, such as neglect and abuse, are prevalent (McLaughlin et al., 2019). It is possible that our sample did not experience high enough levels of ECA to detect the effects frequently observed when studying the more severe end of this spectrum. Given that more severe levels of ECA are likely to drive significant effects, this may at least partially explain the absence of any associations with ECA in the current sample, especially given the distal period between the ECA and NM-MRI/reinforcement learning assessments.

Chronic Stress, NM-MRI-Assessed Dopamine, and Reinforcement Learning

The relationship between chronic life stress and NM-MRI-assessed dopamine was also non-significant. This suggests that ongoing, chronic life stressors do not influence the production of dopamine during adolescence. Given the well-documented effect of life stress on neural structure and function, this, in combination with the absence of a significant association between ECA and NM-MRI-assessed dopamine, may be an indicator that cumulative dopamine production as assessed by NM-MRI is too insensitive to capture the effects of specific domains of life-stress.

Similarly, chronic life stress was not significantly related to any of the Q-values from the reinforcement learning task. However, increased chronic life stress from age 12 to 18 was associated with a larger positive, but not negative, learning rate. This indicates that greater levels of life stress were associated with a more rapid, less smooth of behavioral updating in response to feedback on the reinforcement learning task. As noted above, in the context of the current

task, which utilizes a stable, non-changing environment, this is likely to be maladaptive and reflects rapid behavioral switching despite consistent task rules, making it more difficult to adequately learn the task contingencies. Given that the association between NM-MRI-assessed dopamine and learning rates are non-significant, the mechanism by which this relationship occurs is unclear. If stress is influencing the learning process at the neural level, it may be in regions involved in reinforcement learning outside of the SN-VTA complex, such as the nucleus accumbens or dorsal striatum, or in connectivity between the SN-VTA complex and these other regions. Alternatively, this may be a learned approach resulting from ongoing chronic stress making the daily environment less predictable for these individuals.

Strengths and Limitations

The proposed study addresses many gaps in the literature. The primary innovation of this study is the use of NM-MRI as an index of dopamine function, both in establishing a relationship between dopamine and reinforcement learning, and in identifying psychopathological correlates of dopamine dysfunction. Very few studies have used a quantifiable index of dopamine function to specifically examine the association between dopamine and reinforcement learning in humans, and this will be the first to use NM-MRI. Second, despite the use of NM-MRI to study disorders characterized by anhedonia (e.g., Parkinson's disease, schizophrenia) no prior work has directly examined the association between NM-MRI-assessed dopamine dysfunction and anhedonic symptoms despite the role of dopamine in the processing of rewards/pleasure. Similarly, despite prior work suggesting that life stressors have a significant influence on the dopamine system, this is the first study to directly examine the influence of ECA or chronic life stress on any measure of dopamine function. Fourth, computational modeling provides a wealth of information and specificity beyond basic reinforcement learning task performance. This was the first study using

computational modeling of a reinforcement learning task to examine associations with dopamine dysfunction. Finally, NM-MRI is non-invasive and cost-effective. Thus, it is suitable for wide dissemination to complement existing research programs and as the basis for new lines of research. Critically, this project contributes to establishing the construct validity of NM-MRI as an individual difference measure of dopamine function.

However, the current study was not without limitations. First, NM-MRI is a new technique in psychopathology research, so little direct empirical evidence is available. Evidence partially supported our hypotheses, but many of the results were not as anticipated. Second, except for the computational modeling of the reinforcement learning task, the data analytic techniques used are simple. However, little is known about the associations and consequences of dopamine production as assessed by NM-MRI, so beginning with simple, replicable, approaches is an important first step for developing a literature in this area. Third, computational modeling of the PST provides richer and more nuanced characterization of the behavior than simple performance measures (e.g., accuracy). Learning rates and Q-values were selected for analyses because they were most likely to be associated with dopamine dysfunction based on the data collection techniques available. However, given that prior work in this area is limited, it is possible that other parameters (e.g., β parameter [variability in stimuli choice]) are more related to dopamine function or anhedonia (Kunisato et al., 2012).

Future Directions

While all measures used in the current study are well-validated, it is possible that certain measures limited the opportunity to detect certain effects. For example, the stable environment of the selected reinforcement learning task may have reduced the likelihood of detecting significant associations between NM-MRI-assessed dopamine and learning rates. Reinforcement learning

paradigms that involve blocks during which the environment shifts or where the reinforcement probabilities shift throughout may be more effective for detecting associations between reinforcement learning parameters and neural or psychological correlates.

Relatedly, the process captured by reinforcement learning models that may be most closely related to dopamine function may be the trial-level prediction errors. Prediction errors reflect the difference between the expected and actual outcomes, and they are encoded by increases or pauses in dopamine release when receiving feedback that is better or worse than expected, respectively. While learning rates and Q-values incorporate information from the prediction error terms on each trial to provide a person-level aggregate measure, the prediction errors can be examined in trial-by-trial analyses in conjunction with physiological data that reflects that dopaminergic response (e.g., fMRI, ERP). Therefore, future work should build upon the current findings to examine associations between NM-MRI-assessed dopamine and the magnitude of trial-level prediction errors.

While NM-MRI provides the opportunity to answer new questions and expand research programs, it may be too insensitive of a measure to answer some of the questions proposed here. Given that NM-MRI provides a cumulative measure of dopamine function, it may not be sensitive enough to use when examining associations with current behavior or symptoms, especially if the measures are prone to changes over time or state-effects. Relatedly, NM-MRI may be likely to be associated with pervasive trait-like characteristics or impairments present across time given its cumulative nature. Future investigations should keep this in mind when employing NM-MRI as an imaging technique.

Finally, a community sample, especially a cohort that has been repeatedly assessed since childhood, is extremely useful for identifying potential predictors and correlates between a novel

neuroimaging technique and psychological processes. However, prior research that has detected significant associations between NM-MRI-assessed dopamine and psychopathology has been conducted in patient populations characterized by severe dysfunction in the dopamine system (i.e., Parkinson's disease, schizophrenia). Therefore, relationships between NM-MRI-assessed dopamine and anhedonia may be better detected in more severe patient samples, such as individuals currently experiencing a melancholic depressive episode. Similarly, the severity of ECA is limited in the current community sample, and stronger effects may be observable in samples that have experienced greater levels of adversity. Future work should investigate patient populations where significant anhedonia is more likely to be present and populations that have been exposed to ECA characterized by greater severity, such as abuse and neglect.

Conclusions

Results from the current investigation indicate that NM-MRI-assessed dopamine was significantly associated with certain measures of reinforcement learning, but not others. Additionally, other measures of impaired reinforcement learning were related to increased concurrent anhedonic symptoms. Finally, higher levels of chronic life stress were also associated with impairments in reinforcement learning performance. Taken together, there are links between dopaminergic function, reinforcement learning, life stress, and anhedonia, but these associations vary across measures. Future work should continue to elucidate potentially important etiological processes in the development of reinforcement learning and anhedonia.

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Appendices

Appendix I

Positive Valence Systems Scale 21 Items (PVSS-21; Khazanov et al., 2019)
Please indicate to what extent these statements describe your **responses over the last two weeks, including today.**

Did you NOT have this experience? No problem. Please indicate how you would have responded if you had experienced the situation over the last two weeks.

Please consider only the aspect of the situation that is described, paying particular attention to the underlined text. For example, if the statement says, "I wanted to meet new people," rate how much you wanted or would have wanted to meet new people over the last two weeks, assuming that the opportunity presented itself. Do not consider what the situation would have required of you or whether it would have been possible for you to meet people.

1	2	3	4	5	6	7	8	9
Extremely untrue of me	Very untrue of me	Moderately untrue of me	Slightly untrue of me	Neutral	Slightly true of me	Moderately true of me	Very true of me	Extremely true of me

1. I savored my first bite of food after feeling hungry
2. I put energy into activities I enjoy
3. I was delighted to catch a breath of fresh air outdoors
4. I wanted to spend time with people I know
5. A fun activity during the weekend sustained my good mood throughout the new week
6. It felt good to have physical contact with someone I felt close to
7. I expected to enjoy a brief moment outdoors
8. I looked forward to hearing feedback on my work
9. I expected to enjoy my meals
10. Receiving praise about my work made me feel pleased for the rest of the day
11. I looked forward to spending time with others
12. I wanted to accomplish goals I set for myself
13. I expected to enjoy being hugged by someone I love
14. I wanted to participate in a fun activity with friends
15. I worked hard to earn positive feedback on my projects
16. I looked forward to an upcoming meal
17. I felt pleased when I reached a goal I set for myself
18. Getting a hug from someone close to me made me happy even after we parted
19. I expected to master the tasks I undertook
20. I actively pursued activities I thought would be fun
21. I went out of my way to admire the beauty around me

Appendix II

IDAS-II Well-Being Scale (Watson et al., 2012)

Below is a list of feelings, sensations, problems, and experiences that people sometimes have. Read each item to determine how well it describes your recent feelings and experiences. Then, circle the choice that best describes how much you have felt or experienced things this way during the past two weeks, including today. Use this scale when answering:

1	2	3	4	5
not at all	a little bit	moderately	quite a bit	extremely

1. I felt optimistic
2. I was proud of myself
3. I felt that I had accomplished a lot
4. I looked forward to things with enjoyment
5. I felt hopeful about the future
6. I felt that I had a lot to look forward to
7. I felt like I had a lot of interesting things to do
8. I felt like I had a lot of energy