AVERY, BRADLEY M., PhD. Effects of Recent Chronic and Episodic Life Stress on Ventral Striatal Activation During Reward Anticipation (2020)
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Dysregulated reward processes are a transdiagnostic feature of several psychiatric disorders, and reward-related deficits predict a relatively poor prognosis in individuals with depression. Research utilizing animal models and limited human research suggests that the experience of stress is associated with disrupted reward processes, an effect that is likely mediated by the deleterious effects of stress on dopaminergic signaling. However, neurobiological mechanisms contributing to reward deficits are poorly understood, and no studies to date have examined the association of naturalistic life stress and functional neural correlates of reward processes in humans. As such, it is unclear whether either the main effects of stress or stress acting together with certain individual differences might predict disrupted neural reward functioning. Thus, the present study sought to examine this association, initially hypothesizing that greater interpersonal, but not non-interpersonal life stress assessed using the UCLA Life Stress Interview would be associated with blunted blood oxygen level-dependent (BOLD) reactivity in the ventral striatum in response to reward anticipation during the Monetary Incentive Delay task.

Contrary to hypotheses, there was no main effect of naturalistic life stress in any domain (chronic, episodic, interpersonal, non-interpersonal) on ventral striatal reactivity to reward anticipation. Secondary exploratory analyses instead revealed a moderating effect of the personality trait Grit, defined as perseverance towards long-term goals, such that higher levels of Grit predicted significantly less negative effects of chronic interpersonal stress on bilateral ventral striatal reactivity during reward anticipation.

Results implicate robust reward-related ventral striatal reactivity in the context of life stress as a critical underpinning of goal-pursuit in the context of life stress, and support a wider literature indicating a role of reward and positive emotion in general coping.

EFFECTS OF RECENT CHRONIC AND EPISODIC LIFE STRESS ON VENTRAL STRIATAL ACTIVATION DURING REWARD ANTICIPATION

by

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CHAPTER I

INTRODUCTION

Deficits in reward-related processes are a core feature of depression (American Psychiatric Association, 2013), and represent a transdiagnostic domain of impairment observed across several forms of psychopathology (Buckholtz & Meyer-Lindenberg, 2012; Sharma et al., 2017). Although etiological factors contributing to reward deficits have not been clearly elucidated, emerging evidence suggests that life stress (i.e., objective exposure to environmental threat) may play an important role. Decades of research in humans suggests that chronic (extended stressful life circumstances) and episodic (acute stressful life events) life stress are associated with an increased risk of depression onset broadly (e.g., G. Brown & Harris, 1978; Kendler, Karkowski, & Prescott, 1998, 1999; Vrshek-Schallhorn et al., 2015). Moreover, experimental research in animals (e.g., Papp, Willner, & Muscat, 1991; Willner, Towell, Sampson, Sophokleous, & Muscat, 1987) and limited research in humans (e.g., Bogdan & Pizzagalli, 2006) has found that several forms of stress cause alterations in a variety of reward processes. Animal research suggests that stress effects on reward processes are likely mediated by alterations in dopaminergic signaling (e.g., Abercrombie, Keefe, DiFrischia, & Zigmond, 1989). However, to date, little research has examined the relationship between life stress and neurobiological processes related to reward in humans, and the few studies that have been performed used questionnaire-based

assessments of early life adversity, a methodology that has been noted to have critical limitations (Monroe, 2008). Moreover, *recent* life stress is more strongly implicated in adult depression than is early life stress (Kendler & Gardner, 2017; Vrshek-Schallhorn et al., 2015). Thus, here I examined the association between recent life stress, assessed using an objective life stress interview, and neural reactivity (assessed using functional magnetic resonance imaging) during reward anticipation in the ventral striatum, a region known to be the primary target of mesolimbic dopaminergic neurons that is critical to encoding reward anticipation in humans (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Fong, Adams, Varner, & Hommer, 2001; O'Doherty et al., 2004; Schultz, Apicella, Scarnati, & Ljungberg, 1992). Furthermore, the purpose of this study was to examine the effects of different types of recent life stress on ventral striatal reactivity to reward. I hypothesized that greater recent chronic and episodic life stress would be associated with blunted ventral striatal reactivity to reward for interpersonal, but not non-interpersonal stress.

Reward Deficits and Depression

Reward deficits have long been studied in depression (e.g., Feighner et al., 1972), and include deficits in several processes involved in approach motivation and reward learning (for reviews, see Pizzagalli, 2014; Treadway & Zald, 2011). Individuals with Major Depressive Disorder exhibit a range of reward deficits, including diminished anticipation of reward (McFarland & Klein, 2009), diminished expenditure of effort during reward seeking (Treadway, Bossaller, Shelton, & Zald, 2012), dissociation of reward "liking" from motivation to obtain a reward (Sherdell, Waugh, & Gotlib, 2012),

and altered neural activity during reward anticipation in brain regions known to be involved in reward processing (e.g., Forbes et al., 2006; Pizzagalli et al., 2009; Smoski, Rittenberg, & Dichter, 2011; Zhang, Chang, Guo, Zhang, & Wang, 2013).

Of note, there has been some debate as to whether depression is characterized by deficits in consummatory aspects of reward (e.g., derived pleasure); studies examining positive affective ratings in individuals with depression have shown mixed results, and one hypothesis posits that observed consummatory differences in individuals with depression may be due to a general "affective flattening" rather than specific deficits in reward processes per se (for a review, see Treadway & Zald, 2011). For example, studies in which participants are asked to rate the pleasantness of tasting sweet solutions show no differences between individuals with depression and controls (Amsterdam, Settle, Doty, Abelman, & Winokur, 1987; Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010). In contrast, studies examining neural processing of rewards show that the ventral striatum exhibits blunted reactivity during both anticipation and consumption of rewards in depressed individuals (for a meta-analysis, see Zhang et al., 2013). Thus, although the precise nature of reward deficits in depression is not fully clear, there is much evidence that reward processes are disrupted, especially processes related to anticipation of reward.

Reward deficits are a critical feature of depression: Self-reported anhedonia, a reward deficit operationalized as a subjective loss of interest or pleasure in typically-rewarding activities, predicts poor responsiveness to antidepressant medications (Uher et al., 2012) and a more chronic course of the disorder (Moos & Cronkite, 1999). Furthermore, accumulating evidence supports the hypothesis that reward deficits may

occur prior to the onset of major depression, and are associated with a host of risk factors for depression (for a review, see Whitton, Treadway, & Pizzagalli, 2015). For example, never-depressed adolescents whose mothers had a history of recurrent depression exhibited blunted ventral striatal reactivity to reward relative to controls (Gotlib et al., 2010), and this finding was conceptually replicated in a sample of males and females (Olino et al., 2014). In turn, reduced ventral striatal reactivity to reward was associated with greater increases in depression symptoms over the course of two years in adolescents with no history of depression (Morgan, Olino, McMakin, Ryan, & Forbes, 2013). Last, lower levels of reward-seeking were associated with higher rates of depression onset and more depressive symptoms at a one-year follow-up in a non-depressed sample (Rawal, Collishaw, Thapar, & Rice, 2012). Indeed, reward processes have been thought to play a key role in depression risk since the 1970's, when a popular theory of depression etiology suggested that depression is caused by infrequent response-contingent reinforcement (Lewinsohn, 1974). Together, these findings indicate that understanding the etiology of reward deficits is critical to understanding the etiological mechanisms for depression more broadly. However, factors that contribute to reward deficits in humans are poorly understood.

Objective Life Stress

Life stress is critical to the etiology of depression and thus very likely also to reward deficits. Indeed, behavioral genetic studies indicate that non-shared, individual-specific environmental factors such as life stress account for approximately 63% of variance in occurrence of major depression (Sullivan, Neale, & Kendler, 2000). In

previous work, the term “stress” has been used to refer to not only the objective experience of adverse stimuli such an environmental threat (e.g., Hammen et al., 1987) but also an organism’s psychological or physiological response to a stressor (Selye, 1936). Notably, these concepts are not synonymous: An organism’s response to a stressor is influenced by numerous factors, including both the nature of the stressor and biological and psychological individual differences in the organism such as genetics and previous exposure to stress, and is potentially confounded with risk for negative outcomes. Thus, when examining whether stress predicts outcomes such as depression, it has been argued that utilizing an organism’s response to stress or their perception of stress as the predictor is inappropriate (Harkness & Monroe, 2016). Therefore, throughout this paper, the terms “life stress,” “objective stress,” and “stressor” are intended to denote objective exposure to an environmental challenge or threat. The terms “stress response,” “response to stress,” “stress reactivity,” “subjective stress,” and “perceived stress” are used to denote the organism’s physiological, affective, cognitive, or behavioral response to a stressor.

Research examining the effects of stress in humans has typically either naturalistically assessed life stress or induced controlled doses of stress in a laboratory (“lab-induced stress”); while naturalistic life stress has been a focus of etiological depression research, lab-induced stress protocols have been used to examine the impact of reward processes in humans.

Naturalistic life stress. Naturalistic life stress can be further categorized as daily hassles, defined as relatively minor day-to-day events or inconveniences (e.g., getting stuck in a long traffic jam), more infrequent stressful life events, defined as acute events

that are aversive or unpleasant (Muscatell, Slavich, Monroe, & Gotlib, 2009), chronic stress, defined as ongoing aversive conditions that are typically present for at least several months to years (G. Brown & Harris, 1978), and early life adversity, defined as stressful experiences and circumstances during childhood and adolescence (e.g., experience of maltreatment; Kessler, Davis, & Kendler, 1997). Daily hassles are typically assessed using ecological momentary assessment or daily diary methodologies. Early life adversity may be assessed using a variety of methods, including retrospective self-report questionnaires and interviews, prospective parent questionnaires and interviews, and records from departments of social services.

Recent stressful life events and chronic stress are typically assessed using questionnaires, checklists, or semi-structured interviews. Although checklists and questionnaires tend to be faster and less personnel-intensive to administer and score than interviews, they have several well-documented drawbacks. The primary drawback is that self-rated severity of events and determination of whether an event is reported may be influenced by whether an individual has depression (or risk factors for depression, such as high levels of neuroticism), resulting in potentially spurious associations between self-reported life stress and subsequent depression (G. Brown & Harris, 1978). Additionally, comparisons of checklists with responses on semi-structured interviews suggest that less than 50% of stressors reported by participants on checklist measures are consistent with the timing (e.g., past 6 months) and type of stressor (e.g., acute event as opposed to chronic stressor) requested by the researcher (McQuaid et al., 1992). As a result, it has been argued that participants typically do not interpret instructions for stress checklists in

the manner that is intended by researchers, resulting in a misclassification of stressors (Harkness & Monroe, 2016). Thus, semi-structured interviews have been recommended as a best practice in stress assessment, despite the increased time and effort they require to complete (Harkness & Monroe, 2016). These interviews have several advantages relative to checklists: They allow researchers to ask follow-up questions to ensure that the researcher's conceptualization of the stressor is consistent with the event or circumstance that the participant is reporting, they can collect greater amounts of information and allow researchers to make more objective ratings about a stressor's severity blind to the participant's characteristics and event-response, and they offer greater flexibility that allows the participant to report rarely-encountered stressors that may not be included on a checklist.

Lab-induced stress. Because stressful life events are relatively infrequent and their effects can be difficult to examine in a research study, lab-induced stressors are frequently utilized as a "scaled-down" model for stressful events. Although not the focus of the proposed research, lab-induced stress is relevant to understanding the broader literature that informs the proposed questions. Lab-induced stress protocols typically utilize social evaluative threat (e.g., the Trier Social Stress Test; Kirschbaum, Pirke, & Hellhammer, 1993), physical pain/discomfort (e.g., the cold pressor task), or threatened pain/discomfort (e.g., threat of shock; Bogdan & Pizzagalli, 2006) to induce immediate and brief changes in neuroendocrine functioning, cognitive processes, or affect. For obvious ethical reasons, these stressors tend to be relatively brief, and are thought to have no lasting effects on participants; thus, chronic stress is not experimentally induced in

humans. However, animal models allow for experimental induction of both acute and chronic stressors. Thus, the animal literature is particularly valuable in understanding the effects of chronic stressors on psychological processes underlying reward and motivation.

Stress and Depression

Both chronic and episodic stress have been linked to the onset of major depression (e.g., Hammen, 2005; Kendler et al., 1999; Kessler et al., 1997; Monroe, Harkness, Simons, & Thase, 2001; Vrshek-Schallhorn et al., 2015), although the etiological mechanisms linking these forms of stress to depression are not particularly well-elucidated. In emerging adults, evidence is strongest for the direct effects of recent adversity (episodic and chronic stress) on depression onset, and suggests that early adversity may both moderate the effect of recent adversity by potentiating greater stress sensitization, or by contributing to stress generation in more recent experiences (e.g., McLaughlin, Conron, Koenen, & Gilman, 2010). Thus, due to clearer evidence for recent stress as contributing to depression etiology, the present study adopts a focus on recent chronic and episodic stress, acknowledging that early adversity is likely to be highly impactful via its indirect effects. The following section briefly reviews evidence that recent episodic and chronic stress are associated with depression.

Episodic stress. A large body of research has demonstrated that recent episodic stress, also referred to as stressful life events, predict the onset of major depressive episodes (e.g., G. Brown & Harris, 1978; Kessler, 1997). Additionally, studies establishing temporal precedence (i.e., evidence that the stressor indeed preceded depressive episode onset) have found that stressful life events likely have causal effects

on depression onset (Kendler et al., 1999). In examining the effects of stressful life events on depression, four primary qualities of the stressor are typically examined: Severity (typically conceptualized as level of "contextual threat" or the level of threat the average person would experience given the same context), interpersonal nature (i.e., whether an event primarily affects the quantity or quality of an individual's interpersonal relationships), dependence (i.e., whether the individual's own behaviors, abilities, or characteristics caused the stressor), and timing.

Severity is a key characteristic of a stressful life event that determines whether it predicts the onset of a major depressive episode. Stressful life events with moderate or severe contextual threat, deemed "major stressful life events," predict depression onset much more robustly than stressful life events with lower levels of contextual threat ("minor stressful life events;" G. Brown & Harris, 1978; Kendler et al., 2010; Vrshek-Schallhorn et al., 2015). Although the most parsimonious explanation for this finding is that more severe life stressors have more severe and lasting emotional consequences, minor stressful life events may also be less reliably recalled by participants during retrospective assessments (Brewin, Andrews, & Gotlib, 1993; Monroe, 2008), which may mask associations between minor stressful life events and depression onset. However, despite the precise reason, evidence overwhelmingly indicates that endorsement of major stressful life events more robustly confer risk for depression than minor stressful life events.

The interpersonal nature of a stressor also plays a key role in determining the effects of stressful life events on depression onset. In two samples of emerging adults,

major interpersonal stressful life events uniquely predicted depression onset over and above other forms of life stress, including major non-interpersonal stressful life events (Vrshek-Schallhorn et al., 2015). Additionally, major interpersonal stressful life events, but not major non-interpersonal stressful life events, interacted with a certain genetic variable to predict risk for a major depressive episode (Vrshek-Schallhorn et al., 2014). These findings are consistent with theory indicating that social factors are particularly important for coping (Coyne & Downey, 1991), and suggest that interpersonal stressful life events likely confer greater risk for depression.

The role of the dependence of a stressor (whether the stressor depends upon on an individual's own behavior, abilities, or characteristics) has also been investigated as a feature that influences the effects of stressful life events on depression onset. Independent events are considered to be events that are "fateful" and occur regardless of the behavior of the individual (e.g., an individual's house being destroyed in a flood, or the death of a loved one). In contrast, dependent events are somewhat or entirely dependent on the behavior of the individual (e.g., being fired for poor job performance or an argument with a friend). Evidence for the effect of dependence is mixed, however: Some studies have found that independent stressful life events more strongly predict depression (Monroe et al., 2006; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011), while other findings indicate that dependent stressful life events may be more strongly linked to depression occurrence (Hammen, Mayol, DeMayo, & Marks, 1986; Kendler et al., 1999). Still other studies have found no difference between effects of dependent and independent stressful life events on depression onset (e.g., Vrshek-Schallhorn et al., 2015). Thus, although

stressor dependence has been thought to play an important role in determining the effects of stress on depression, there is not currently strong evidence for this notion.

Last, the timing of stressful life events is particularly important for predicting its effects on depression onset. One of the first studies to examine the duration of stressful life event depressogenic effects estimated that effects last for approximately 9 weeks (G. Brown & Harris, 1978). A more recent study utilizing a sophisticated decay model found that stressful life events significantly predicted depression onset for no more than 13 weeks following the event (Surtees & Wainwright, 1999). Last, a third study found that the strongest effects of stressful life events on depression onset typically occur in the month following the event, with increased risk lasting no more than three months following the event (Kendler et al., 1998). Thus, available evidence indicates that stressful life events have a relatively short window of three months or less in which they contribute to depression onset, with little evidence for long-term depressogenic effects.

Chronic Stress. The experience of chronic stress, or extended stressful circumstances over time, has also been linked to depression onset (Hammen, 2005; Vrshek-Schallhorn et al., 2015). Notably, chronic stress is typically not conceptualized according to dependence (most chronic stressors are due to both controllable and uncontrollable factors) or timing. Furthermore, chronic stressor severity is typically only examined continuously rather than being divided dichotomously into "major" or "minor" stressors. However, chronic stress is typically assessed across life domains (e.g., family relationships, social relationships, finances; Hammen et al., 1987), and these domains may be categorized as either interpersonal or non-interpersonal in nature (e.g., Vrshek-

Schallhorn et al., 2015). Similar to stressful life events, interpersonal, but not non-interpersonal, chronic stress was uniquely associated with depression onset over and above other forms of stress (Vrshek-Schallhorn et al., 2015), and interpersonal (but not non-interpersonal) chronic stress was associated with depression recurrence in emerging adults (Sheets & Craighead, 2014). Together, these findings suggest that interpersonal chronic stress may be more impactful in conferring depression risk than non-interpersonal chronic stress.

Life Stress and Reward Deficits

One potential contributing mechanism in the pathway between life stress and depression is deficient reward functioning. In both humans and animal models, various forms of experimentally-induced stress have been shown to alter reward processes. Animal studies especially have provided strong evidence for a causal link between chronic stress and anhedonic behavior (for a review, see Willner, 2005). For instance, rats exposed to chronic mild stress display reduced consumption of sucrose solutions (Bekris, Antoniou, Daskas, & Papadopoulou-Daifoti, 2005; Elizalde et al., 2008) and reduced preference for spaces where rewards have been administered (Papp et al., 1991). In human studies, acute laboratory-induced stress has been shown to induce deficits in reward learning (Bogdan & Pizzagalli, 2006), especially in individuals with greater cortisol reactivity to stress (Avery, Ironside, Whitton, Pizzagalli, & Vrshek-Schallhorn, in preparation). Supporting the generalizability of the impact of stress on positive valence systems, naturalistic life stress has been associated with behavioral symptoms of anhedonia (Lumley & Harkness, 2007), as well as neural abnormalities in reward

processing (Dillon et al., 2009). The following sections will briefly review evidence that stress elicits deficits in reward processes in animals and humans.

Stress Effects on Behavioral Reward Processes in Animals

Chronic Stress. Research utilizing animal models of depression overwhelmingly indicates that chronic stress causes behavioral reward deficits. This effect was first shown in a seminal study by Katz, Roth, and Carroll (1981), who found that rats exposed to 95 dB of white noise for one hour (interpreted as an acute stressor) exhibited greater levels of behavioral activity than control mice, while rats that were chronically exposed to unpredictable and various forms of stress over the course of 21 days showed reduced behavioral activity. A follow-up study then found that a similar chronic stress procedure caused rats to reduce their consumption of sweet solutions (sucrose and saccharine), an effect that was reversed by administration of tricyclic antidepressants (Katz, 1982).

Much evidence that chronic stress causes disruptions in reward processes in animals has been derived from studies utilizing the Chronic Mild Stress (CMS) paradigm, an adaptation of the chronic stress protocol used by Katz et al. (1981). In this paradigm, rodents are exposed at unpredictable time intervals to a variety of mild stressors over the course of several weeks, and then examined for signs of behavioral reward deficits (e.g., reduced sucrose consumption; Willner, Muscat, & Papp, 1992; Willner et al., 1987). Although this procedure has at times produced inconsistent or even opposite effects, including the original research team reporting difficulty replicating effects after moving to a new facility (Willner, 1997) and others finding that it resulted in greater sucrose consumption (Murison & Hansen, 2001), the vast majority of studies utilizing the CMS

paradigm have found that it causes deficits in behavioral reward processes (for reviews, see Willner, 2005, 2017a, 2017b).

The CMS paradigm has been used to show that a variety of reward-related behaviors are impaired under chronic stress. The most common behavioral outcome used in this paradigm is the consumption of sweet solutions (most commonly sucrose and saccharine); several studies have found that CMS reduces that amounts of sweet solutions consumed by rodents (Bekris et al., 2005; Muscat, Towell, & Willner, 1988; Papp & Moryl, 1994; Willner et al., 1987), with one study observing reduced sucrose consumption one month after the discontinuation of CMS (Elizalde et al., 2008). However, CMS has been shown to induce deficits in a number of other reward-related behaviors as well, including preference for sites of food (Muscat, Papp, & Willner, 1992) and drug (Papp et al., 1991) administration, and frequency of sexual behaviors in male rodents (Brotto, Gorzalka, & LaMarre, 2001; D'Aquila, Brain, & Willner, 1994).

Additional chronic stress paradigms have also been shown to cause blunted reward-related behaviors in animal models. Two additional common paradigms are restraint stress, in which rats are placed in a small tube for several hours a day for several weeks, and social subordination, in which subjects are placed in the cage of a dominant rat and attacked, and then placed in a separate compartment within the dominant rat's cage. Restraint stress for 6-hours per day for 28 days induced multiple forms of reward learning deficits in rats (Xu et al., 2017). Specifically, rats exposed to restraint stress showed deficits in operant conditioning as operationalized by performing fewer lever presses to receive sucrose pellets, as well as deficits in modulating their behavior to

receive rewards following increases in a fixed-ratio reinforcement schedule. Rats exposed to social subordination exhibited a reduced preference for sucrose and saccharine solutions, as well as decreased locomotion (Rygula et al., 2005). Similarly, prairie voles subjected to social isolation for four weeks also exhibited reduced consumption of sucrose solutions (Grippo et al., 2007). Taken together, this evidence indicates that, across multiple paradigms, chronic stress causes deficits in a variety of reward processes in rodents.

Acute stress. Animal evidence for the effects of acute stressors on reward-seeking behaviors is less consistent. Several studies have found that acute stressors induce deficits in reward processes. For example, rats that were exposed to one hour of restraint stress did not show a preference for saccharin solution over water observed in control rats for a 24-48 hour after the stressor (Płaźnik, Stefański, & Kostowski, 1989). In contrast, rats exposed to brief stressors such a single session of intermittent foot shock or two hours of restraint exhibited increases in place-preference for sites of administration of addictive drugs, including morphine (Dai, Kang, Wang, & Ma, 2006), nicotine (Brielmaier, McDonald, & Smith, 2012), and D-amphetamine (Capriles & Cancela, 1999). Differences in effects likely depend on a complex interaction of factors such as individual differences in genetics of the animal, characteristics of the reward, and characteristics of the stressor. For example, one study found that a single session of inescapable footshock elicited blunted intracranial self-stimulation of the nucleus accumbens (a putatively pleasurable behavior) in one strain of mice, no effects in another strain of mice, and increased nucleus accumbens intracranial self-stimulation in a third

strain of mice (Zacharko, Lalonde, Kasian, & Anisman, 1987). Differences in the effects of stress on reward-seeking behaviors may be partially explained by differences in dopaminergic signaling following the stressor in the three strains (Zacharko, Gilmore, MacNeil, Kasian, & Anisman, 1990).

A characteristic of the stressor thought to influence its effects on reward-seeking behavior is its controllability, a construct that is related to (although not synonymous with) stress dependence in the human stress literature. In a seminal study, mice that were allowed to escape shock by moving into a separate chamber (controllable condition) were yoked to partners that could not escape the foot shock (uncontrollable condition) to control for timing and duration of shocks delivered across conditions. Notably, mice in the uncontrollable condition exhibited decreased rates of nucleus accumbens intracranial self-stimulation relative to mice in the controllable condition and a third non-shocked group, which did not exhibit changes in rates of self-stimulation (Zacharko, Bowers, Kokkinidis, & Anisman, 1983). Additionally, stressor chronicity may play an important role in determining behavioral effects of acute stressors: Rats exposed to continuous social subordination for 5 weeks exhibited decreased intravenous cocaine self-administration, decreased preference for sucrose solutions, and decreased motor activity while rats exposed to four episodes of social defeat within a 10-day span exhibited increased intravenous cocaine self-administration and no changes in sucrose preference or motor activity (Miczek, Nikulina, Shimamoto, & Covington, 2011). It has been hypothesized that reward processes may become more active in the context of acute or controllable stressors to facilitate coping, and may become blunted during prolonged or

uncontrollable stress to conserve resources in the face of insurmountable challenges (Cabib & Puglisi-Allegra, 2012). Thus, similar to the stress-depression literature in humans, characteristics of the acute stressor play a significant role in influencing its effects on reward-seeking behaviors in animals.

Stress Effects on Behavioral Reward Processes in Humans

In contrast to animal research, which is characterized by highly controlled experimental studies of chronic and acute stress effects, there are relatively few well-controlled studies in humans. Additionally, due to difficulties in assessing chronic stress (and the inability to experimentally induce chronic stress in humans), most studies utilizing human participants rely on brief lab-induced stressors. Indeed, despite extensive research establishing a link between chronic stress and depression broadly, as well as animal research showing a robust association between chronic stress and reward deficits, no study to date has examined the effects of recent chronic stress on reward processes specifically in humans.

Acute stress effects on reward learning. No studies to date have specifically examined the effects of acute naturalistic life stress on behavioral reward processes in humans. Thus, almost all evidence for acute stress effects on reward processes in humans are derived from studies utilizing lab-induced stressors. The most well-studied reward process in the context of acute lab-based stress is reward learning. Several studies examining the effects of stress on reward learning have used a threat-of-shock paradigm in which participants are asked to categorize ambiguous stimuli while attached to an electrode that will ostensibly shock them at an unpredictable interval (no shock is

actually administered). Categories for the stimuli are differentially reinforced using monetary rewards, leading to a bias towards placing ambiguous stimuli in that category in control samples. Three separate studies utilizing this paradigm have found that participants threatened with shock develop less bias (e.g., display lower rates of reward learning) relative to control participants (Bogdan, Perlis, Fagerness, & Pizzagalli, 2010; Bogdan & Pizzagalli, 2006; Bogdan, Santesso, Fagerness, Perlis, & Pizzagalli, 2011). In all three studies, participants in the stress condition did not display deficits in accuracy, suggesting that results were specific to reward learning and not due to more general cognitive processes (e.g., differences in attentional capacity).

Notably, however, several other studies utilizing lab-induced stress have failed to replicate this effect. One study utilizing a threat-of-shock paradigm found no group differences in reward learning between conditions (Berghorst, Bogdan, Frank, & Pizzagalli, 2013), and one study in which participants completed a reward learning paradigm following a cold pressor task found that the stress induction resulted in enhanced reward learning relative to controls (Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013). Additionally, two studies using a common public speaking stress manipulation, the Trier Social Stress Test (Kirschbaum et al., 1993), failed to find a main effect of stress on reward learning (Avery et al., in preparation; Petzold, Plessow, Goschke, & Kirschbaum, 2010), and a third study in which social evaluative threat was induced by giving participants negative feedback while completing a probabilistic classification test also failed to find a main effect of stress on reward learning (Cavanagh, Frank, & Allen, 2010).

Despite these mixed findings, one consistent result has emerged: Individuals with physiological markers for heightened or dysregulated neuroendocrine reactivity to stress—that is, those who have clearly been impacted by experimental manipulations—have exhibited blunted reward learning under stress. For example, two studies found that participants with genetic polymorphisms associated with dysregulated hypothalamic-pituitary-adrenal reactivity to stress exhibited blunted reward learning under stress (Bogdan et al., 2010; Bogdan et al., 2011). Two additional studies found that heightened cortisol reactivity to stress significantly (Berghorst et al., 2013) or marginally (Avery et al., in preparation) predicted blunted reward learning under stress, although a third study did not observe a significant association between cortisol reactivity to stress and reward learning (Petzold et al., 2010). This pattern of findings is consistent with a diathesis-stress viewpoint in which individuals differ in their vulnerability to stress, and those who demonstrate vulnerability also experience outcomes consistent with greater risk for depression.

Acute stress and other reward processes. There is also mixed evidence in humans for the association of acute stress and risk-taking, a behavior that is influenced by a combination of motivational reward and inhibitory control processes (for a review, see Mather & Lighthall, 2012; Steinberg, 2008). For example, males asked to complete the Balloon Analogue Risk Task in which both potential monetary rewards and risk of receiving no money (i.e., the balloon "popping") are increased with each "pump" tend to exhibit more risk-taking behaviors following stress relative to controls, while the opposite effect is observed in females (Lighthall, Mather, & Gorlick, 2009). These gender

differences are also observed in Iowa Gambling Task performance, with males selecting more "high-risk/high-reward" cards following stress, and females selecting fewer high-risk cards following stress (Preston, Buchanan, Stansfield, & Bechara, 2007). Last, greater levels of self-reported daily hassles are associated with greater levels of risk-taking in both male and female adolescents (Galván & McGlennen, 2012). Importantly, it is unclear whether results indicating increased risk-taking are due to enhanced reward processes or impaired inhibitory control processes under stress.

Last, one study found that participants who completed a cold-pressor task in which they were ostensibly evaluated by judges were willing to squeeze a hand grip more times to smell a pleasant odor than control participants, although conditions did not differ in their reported "liking" of the odor (Pool, Brosch, Delplanque, & Sander, 2015). This finding suggests that individuals may display an increased willingness to expend effort to receive rewards following mild acute stressors. Interestingly, this finding mirrors a finding that reward learning was enhanced following a cold pressor task (Lighthall et al., 2013). These findings may be framed in the context of a reactivity threshold model, such that milder stressors (e.g., cold pressor tasks) may enhance motivational components of reward, while more severe stressors (e.g., threat of shock) elicit blunted motivational reward processes. Although there are not objective data suggesting that one task is generally perceived as "more stressful" than the other, stressors that are uncertain in nature (e.g., threat of shock) tend to elicit more intense and prolonged emotional responses than stressors that are certain (e.g., a cold pressor task that has ended; for a review, see Wilson & Gilbert, 2008). Thus, these findings offer further evidence that the

characteristics of a stressor are important in determining their effects on reward processes.

Mesolimbic Dopaminergic Signaling and Neural Instantiation of Reward Processes

The neurotransmitter dopamine plays a critical role in the etiology of reward deficits (Wise, 1982), and individual differences in dopaminergic functioning might predict the onset of reward deficits in response to stress (for a review, see Pizzagalli, 2014). Originating in the ventral tegmental area and projecting to the nucleus accumbens and olfactory tubercle, which together form the ventral striatum, as well as the amygdala and hippocampus (Fallon & Moore, 1978), mesolimbic dopaminergic neurons exhibit two firing modes: a low-frequency "tonic" firing mode, and a higher frequency "phasic" (or "burst") firing mode (Floresco, West, Ash, Moore, & Grace, 2003), the latter of which is associated with encoding reward (Grace, Floresco, Goto, & Lodge, 2007). Mesolimbic dopaminergic pathways were once thought to encode hedonic properties of reward—such as liking or enjoying (e.g., Wise, 1980). However, this theory has been discounted by evidence that lesions to dopaminergic pathways do not influence "liking-type" behaviors in animal models (Berridge & Robinson, 1998; Berridge, Venier, & Robinson, 1989) as well as evidence that hedonic feelings are likely modulated by endogenous opioids (for a review, see Berridge, Robinson, & Aldridge, 2009). More recent evidence has resulted in two leading views on the role of dopamine in reward processes; these views suggest that dopamine is critical to encoding reward learning (Flagel et al., 2011; Schultz, 1998; Schultz, Dayan, & Montague, 1997), and the encoding of incentive salience (i.e., the experience of "wanting" that is closely tied to reward seeking; for a review, see Berridge,

2007) respectively. However, despite debate about its precise role in the neural instantiation of the reward system, there is strong evidence to suggest that dopamine plays a critical role in anticipatory or motivational, but not consummatory, aspects of reward.

A large body of research has implicated the ventral striatum, a primary target of mesolimbic dopaminergic neurons, as an important region for the encoding of motivational reward processes. In addition to projections from the ventral tegmental area, the ventral striatum receives afferent projections from a number of regions known to play a key role in motivational aspects of reward, such as the amygdala (McDonald, 1991), hippocampus (McGeorge & Faull, 1989), anterior cingulate cortex (Kunishio & Haber, 1994; Müller-Preuss & Jürgens, 1976) and orbitofrontal cortex (Zald & Kim, 1996a, 1996b), among other regions. In monkeys, microelectrode single-neuron recordings indicated that increased ventral striatum signaling was elicited by the presentation of conditioned stimuli that were associated with reward (Schultz et al., 1992).

Assessing ventral striatal activation using blood oxygen-level dependent response. In humans, the ventral striatum reliably shows a robust blood oxygen-level dependent (BOLD) response during reward anticipation, but not consumption of rewards (Knutson, Adams, et al., 2001; Knutson, Fong, et al., 2001; Knutson, Westdorp, Kaiser, & Hommer, 2000). Simply stated, the BOLD response is a measure of the hemodynamic change in blood flow thought to be caused by an increased demand of a given brain region for oxygen associated with an increase in neural activity in that region (Logothetis, 2002; Ogawa, Lee, Kay, & Tank, 1990). Indeed, there is an abundance of evidence that

ventral striatal BOLD reactivity is substantially correlated with increased dopaminergic signaling within the ventral striatum (for a review, see Knutson & Gibbs, 2007). For example, simultaneous microdialysis and fMRI indicated that extracellular dopamine in the nucleus accumbens follows a similar dynamic profile as the BOLD response following amphetamine administration (Chen et al., 1997). Similarly, a biologically-informed multilocus profile putatively associated with greater dopaminergic signaling was associated with an enhanced BOLD response in the ventral striatum during reward (Nikolova, Ferrell, Manuck, & Hariri, 2011). Further supporting the role of the ventral striatum in reward processing, one study using positron-emission tomography to assess dopaminergic signaling found that reward anticipation but not receipt was associated with dopaminergic signaling in the ventral striatum (de la Fuente-Fernández et al., 2002). Thus, measurement of the BOLD response is widely accepted as a valid indicator of neural activity in a given brain region, and there is strong evidence that the BOLD response in the ventral striatum specifically is indicative of dopaminergic signaling in that region.

Stress effects on dopaminergic signaling

The experience of both chronic and acute stress influences dopaminergic signaling in humans and non-human animals (for reviews, see Cabib & Puglisi-Allegra, 2012; Hollon, Burgeno, & Phillips, 2015; Pani, Porcella, & Gessa, 2000; Pizzagalli, 2014). Interestingly, however, stress appears to differentially affect mesolimbic dopaminergic signaling depending on qualities of the stressor (e.g., severity, chronicity, controllability), although the precise mechanisms by which it does so are also unclear

(Hollon et al., 2015; Pizzagalli, 2014). For example, rodent models suggest that exposure to novel stressors (restraint) temporarily induces increased dopaminergic signaling (Imperato, Cabib, & Puglisi-Allegra, 1993) that may facilitate coping behavior (for a review, see Cabib & Puglisi-Allegra, 2012). However, following repeated severe or uncontrollable stressors, rodents exhibit blunted mesolimbic dopaminergic signaling in response to restraint (Imperato et al., 1993), which may be associated with helplessness (Cabib & Puglisi-Allegra, 2012). The following section reviews the effects of stress on dopaminergic signaling and ventral striatal functioning in humans and animals.

Stress effects on dopaminergic signaling in non-human animals. A number of studies utilizing rodent models have established that acute stressors cause greater dopaminergic signaling, and chronic stressors typically elicit blunted dopaminergic signaling (for a review, see Cabib & Puglisi-Allegra, 2012). For example, in rats, intermittent tail shocks elicited a 25-39% increase in free dopamine in the ventral striatum relative to controls (Abercrombie et al., 1989), and two hours of acute restraint stress also elicited increased dopaminergic signaling in the ventral striatum (Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991). Similarly, one episode of social defeat elicited greater ventral tegmental area phasic dopaminergic signaling (Anstrom, Miczek, & Budygin, 2009), an effect that was observed three weeks following the stressor in an independent replication (Razzoli, Andreoli, Michielin, Quarta, & Sokal, 2011).

However, as stressors are repeated, increases in dopaminergic signaling become progressively smaller in magnitude until the stressor eventually elicits blunted dopaminergic signaling. For example, daily restraint stress lasting 60 minutes initially

elicited increases in nucleus accumbens extracellular dopamine, but this effect decreased each day and was not observed at all by the fourth day of testing (Imperato, Angelucci, Casolini, Zocchi, & Puglisi-Allegra, 1992). Additionally, rats exposed to 240 minutes of restraint stress showed a biphasic response—nucleus accumbens extracellular dopamine initially increased, but gradually decreased until dopamine levels were significantly lower than levels in unstressed rats (Puglisi-Allegra, Imperato, Angelucci, & Cabib, 1991). Last, rats exposed to daily restraint stress for 6 days did not exhibit increased extracellular dopamine on the sixth day, and exhibited blunted extracellular dopamine in the nucleus accumbens following 80 minutes of restraint stress (Imperato et al., 1993), further supporting that more prolonged stress results in blunted dopaminergic signaling.

Similarly, stressor controllability is also an important variable in determining dopaminergic activity following stress, with controllable stress typically eliciting increased phasic dopaminergic signaling, and uncontrollable stress typically eliciting blunted dopaminergic signaling. For example, in a study mirroring that by Zacharko et al. (1983), mice exposed to controllable shock that could be escaped by entering a different chamber of their enclosure exhibited increases in extracellular nucleus accumbens dopamine, while yoked mice (i.e., mice receiving the same amount of shock at identical intervals) that could not control the shock exhibited blunted extracellular dopamine in the nucleus accumbens (Cabib & Puglisi-Allegra, 1994). Other research probes the role of individual differences in mouse temperament as it relates to dopamine and stress responding. Interestingly, mice that displayed social avoidance behaviors (deemed "susceptible mice"), exhibited *increased* firing of ventral tegmental area dopaminergic

neurons when faced with chronic (10 days) social defeat (Cao et al., 2010). These "susceptible mice" also displayed a lack of preference for sucrose under stress. Although it is unclear why differential effects are seen in these mice and findings related to temperament have not been replicated, these findings collectively suggest that differences in both the stressor and individual differences in the organism can influence the effects of stress on dopaminergic signaling.

Stress effects on neurobiological substrates of reward in humans. Few studies have examined the effects of stress on neurobiological substrates of reward in humans. In fact, a thorough literature review found one study examining the effects of lab-induced stress, three studies examining the effects early life stress, and no studies examining the effects of recent chronic or episodic life stress on neural reactivity to reward in humans.

One study examining the effects of lab-induced stress found that participants who were exposed to a cold pressor task for two minutes before a card-guessing task that elicits reward reactivity did not show robust ventral striatal reactivity observed in control participants (Porcelli, Lewis, & Delgado, 2012). However, although participants did not differ in their reaction times to the card guessing task, it is unclear whether this difference in neural reactivity is due to specific deficits in reward reactivity, or due to general disengagement with the task due to pain-related distraction.

Several studies have examined the relationship between early life adversity and ventral striatal reactivity to reward. One study assessed the cumulative number of events endorsed by parents on a stressful life events checklist covering kindergarten through the twelfth grade and found that cumulative life stress for childhood through adolescence was

associated with lower levels of ventral striatal reactivity to monetary rewards at age 26 (Hanson et al., 2015). A second study examining the effects of childhood maltreatment found that self-reported maltreatment prior to age 14 was associated with blunted left globus pallidus (a region closely linked with the ventral striatum) reactivity during reward anticipation in early adulthood. Third, a study examining the effects of social stress on 11-12 year-old girls found that low parental warmth, but not self-reported peer victimization (both assessed via questionnaires), was associated with blunted ventral striatal, medial prefrontal cortex, and amygdala reactivity to reward at age 16 (Casement et al., 2014).

Notably, although all three studies consistently support that naturalistic life stress is associated with blunted ventral striatal reactivity to reward, several critical gaps in the literature remain. First, all three studies utilized questionnaires or self-report checklists, and none used gold-standard semi-structured stress interviews. Thus, it is likely that the effect sizes in these studies underestimate the true effect of life stress on ventral striatal reactivity to reward due to measurement error, or may even be spurious all together due to recall bias for negative events in individuals prone to depression. Second, there are currently no studies examining the effects of recent chronic or episodic life stress on neural reactivity to reward, which is a critical gap in the literature in light of evidence suggesting that stressful life events typically do not increase the risk for depression onset after 3 months (Kendler et al., 1998) and other evidence that recent forms of stress account for a majority of the environmental contribution to depression (Kendler & Gardner, 2017). Third, no studies to date have examined the ways that key characteristics

of a stressor (e.g., severity, interpersonal nature, and dependence) exhibit differential effects on neural instantiation of reward processes. This is also a crucial gap in the literature given the extensive evidence in the human literature that these factors influence the association between stress and depression (Vrshek-Schallhorn et al., 2015), and evidence from animal models that these factors moderate the effects of stress on reward processes (Cabib & Puglisi-Allegra, 2012).

Diathesis-Stress Models

Although the animal literature suggests that it will be possible to detect main effects of stress at the level of neural functioning in humans, significant evidence also suggests that stress interacts with individual vulnerability or resilience factors to predict deficits (Monroe & Simons, 1991). For example, trait neuroticism, an individual difference linked to poor emotion regulation (Bono & Vey, 2007) and dysregulated physiological response to stress (Oswald et al., 2006; Phillips, Carroll, Burns, & Drayson, 2005), moderates the relationship between life stress and depression such that individuals with greater trait neuroticism show increased levels of depression in the context of life stress (T. A. Brown & Rosellini, 2011). Thus, it is unclear whether main effects of stress will be associated with neural functioning or whether those effects might be identifiable only in a vulnerable subgroup of the population.

One individual difference that may be particularly salient in predicting risk or resilience of reward-related dysfunction in response to stress is Grit. Simply stated, Grit is defined as passion and perseverance in the pursuit of long-term goals (Duckworth, Peterson, Matthews, & Kelly, 2007), and is closely linked to the Big 5 personality trait of

conscientiousness (Credé, Tynan, & Harms, 2017; Rimfeld, Kovas, Dale, & Plomin, 2016). Notably, Grit has been shown to predict perseverance and success in a number of stressful contexts, including surgical residency (Salles et al., 2017), military special forces training (Eskreis-Winkler, Duckworth, Shulman, & Beal, 2014), and academics (Duckworth et al., 2007). Thus, Grit may be characterized as the result of top-down self-regulatory processes that allow an individual to continue pursuing long-term goals in spite of stress and adversity.

Grit has also been linked specifically to reward-related processes: Individuals with higher levels of Grit also tend to have higher levels of positive affect (Hill, Burrow, & Bronk, 2016). Furthermore, individuals with higher levels of Grit exhibit larger grey matter volume in the putamen (Wang et al., 2018), a structure of the dorsal striatum that is linked to reward-related processes (for a review, see Balleine, Delgado, & Hikosaka, 2007). Finally. Grit has also been positively correlated with resting-state connectivity within ventral striatal networks, particularly between the ventral striatum medial prefrontal and rostral anterior cingulate cortices (Myers, Wang, Black, Bugescu, & Hoeft, 2016), two regions strongly implicated in top-down emotion regulation (for a review, see Etkin, Egner, & Kalisch, 2011). Thus, Grit is a possible risk/resilience factor for stress-related reward system dysfunction.

Despite the possibility of diathesis-stress interactions predicting reward functioning, the present study was primarily designed to test a main effects model rather than a diathesis-stress model because of a) the clear main effects of stress in animal research, b) the potential for moderating personality traits to act downstream of basic

neural functioning rather than contributing to neural functioning, c) the scant previous literature examining risk/vulnerability factors specific to reward, and d) presumably greater power to identify main effects of stress.

The Present Study

The present study sought to fill critical gaps in understanding stress and reward functioning. Here, I examined the associations between recent chronic and episodic life stress, assessed via a semi-structured life stress interview, and ventral striatal reactivity to reward, assessed using the blood oxygen-level dependent (BOLD) response during a functional magnetic resonance imaging (fMRI) scan. Additionally, consistent with work in the broader depression literature, I examined how life stress within interpersonal and non-interpersonal domains independently predict ventral striatal reactivity to reward. I hypothesized that 1) ventral striatal BOLD reactivity during reward anticipation is negatively associated with combined recent chronic and episodic stress severity for interpersonal ("Overall Interpersonal Stress"), but not recent non-interpersonal life stress ("Overall Non-Interpersonal Stress"). Additionally, I hypothesized that 2) this effect would be observed for both chronic and episodic interpersonal stress individually, but not chronic or episodic non-interpersonal stress. Last, I hypothesized that 3) episodic life stress severity would be negatively associated with ventral striatal reactivity to reward for major, but not minor, stressful life events. Given mixed results in the literature on depression etiology, I did not make hypotheses for whether dependent or independent stressful life event severity would be uniquely associated with ventral striatal reactivity to reward; however, I planned to examine the differential effects of stressor dependence in

an exploratory analysis. Additionally, although the primary goal of this study was to examine a main effects model of stress, I conducted an exploratory analysis examining the possible moderating effects of Grit on the relationship between stress and ventral striatal reactivity to reward.

CHAPTER II

METHODS

Participants

Participants consisted of 53 right-handed individuals aged 18-26. This age range was selected due to evidence that "emerging adulthood" is one of several critical developmental stages for first onset of depression (Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013). Individuals with a history of neurological disorder or head trauma (including concussions), implanted electronic devices (e.g., pacemaker, neurostimulator), cerebral aneurysm clips, or metallic shrapnel, as well as individuals currently using psychoactive medications, were excluded from the study. Women who were pregnant were also excluded from the study, as there is insufficient data to determine whether magnetic resonance imaging has deleterious effects in this population. Despite screening participants twice prior to the MRI scan, two participants disclosed during the interview portion of the study that they were taking psychotropic medications and were excluded from analyses. An additional 5 participants exhibited excessive motion (> 1.5 mm) during the Monetary Incentive Delay task and were excluded from all analyses. Thus, the final sample included in our analyses consisted of 46 participants (38 female, 8 male; 18 White, 13 African American, 9 Hispanic, 4 Asian, 2 multi-racial; age M = 19.52 (18-26) years). Within this final sample, one participant did not complete the Grit scale, and was

therefore excluded from analyses including the variable Grit but was included in all other analyses.

Participants were recruited using fliers posted around the UNCG campus and via an Introductory Psychology Subject Pool. Fliers indicated that "Participants are paid $75 in cash, have the opportunity to earn bonus money during computer tasks, and will get to keep a picture of their brain." The "bonus money" was used as an incentive to increase participant engagement during fMRI tasks. All community participants (i.e., individuals who were recruited via fliers) were paid $80 total (i.e., $75 plus $5 bonus) regardless of their performance on the MRI tasks. Introductory Psychology Subject Pool participants earned class credit and were told they could win "bonus money" during their participation, and all were paid a $5 bonus. Participants received a standard screening for magnetic resonance safety (e.g., to screen for ferromagnetic bodily implants) over the phone. Eligible individuals completed an initial questionnaire battery and 7 daily diaries as part of a larger study prior to participating in the MRI portion of the study. Participants were screened for current or past manic episodes using the SCID-I/NP due to evidence that reward processes are substantially altered in individuals with Bipolar Disorder (Dutra, Cunningham, Kober, & Gruber, 2015; Nusslock et al., 2012); however, no participants in this sample screened positive for a history of manic episodes.

Materials

Functional Magnetic Resonance Imaging Acquisition: All images were acquired on a Siemens 3.0 Tesla MR Scanner. First, to obtain structural images for normalization and registration of functional images, participants completed a three-

dimension magnetization-prepared rapid gradient echo (MP-RAGE) sequence, a relatively high-resolution T1-weighted whole-brain structural imaging sequence (Mugler & Brookeman, 1990). Blood-oxygen-level dependent (BOLD) functional images were acquired during functional scans using a gradient echo planar imaging sequence (repetition time [TR] = 2000 ms, echo time [TE] = 25 ms, field of view [FOV] = 20 cm. Field maps were acquired to facilitate echo planar imaging distortion correction during analyses. Total scan time was approximately 40 minutes.

Monetary Incentive Delay Task. During the fMRI scan, participants completed a frequently employed reward task, the Monetary Incentive Delay task (MID; Knutson et al., 2000). This task was programmed in E-PRIME Standard 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) and consisted of 90 6-second trials during which participants attempted to win a monetary reward. Participants interacted with the task using an MR-compatible serial response (SR) box. In each trial, participants viewed a cue shape (2000 milliseconds), followed by a fixation cross (variable anticipation period; 2000-2500 milliseconds), and then attempted to press a button using their index finger during the presentation of a target of variable duration. Target durations was determined by participant reaction times recorded during a 90-trial practice session and were calibrated so that participants would succeed on approximately 66% of all trials. Following the target presentation, participants viewed feedback (1920 milliseconds) displaying whether they gained or lost money on the trial, and their total earnings for the task. Participants completed three basic task conditions: 1) a reward condition, in which participants won money if they pressed the button during the target display; 2) a punishment condition, in

which participants lost money if they were not able to press the button during the target display; and 3) a control condition, in which participants did not gain or lose money regardless of their performance. Cue shapes indicated the condition at the beginning of each trial: A circle indicated the reward condition, a square indicated the punishment condition, and a triangle indicated the control condition. There were also four levels within each of the reward and punishment conditions, such that the amount they would gain or lose was indicated to the participant by the number of lines inside the cue shape. Shapes with zero lines were worth $0.00 (control conditions), shapes with one line were worth $0.20, shapes with two lines were worth $1.00, and shapes with three lines were worth $5.00. Only "reward" trials (circles with 0, 1, 2, or 3 lines) were included in analyses. Participants were told that the money they receive would be proportional to the monetary value displayed on the screen.

UCLA Life Stress Interview. Following the MRI scan, participants completed the UCLA Life Stress Interview (LSI; Hammen et al., 1987). This interview was used to assess chronic life stress occurring in the previous 6 months within 4 interpersonal (best friend, social circle, romantic relationships, family relationship) and 5 non-interpersonal (academics, occupational work, finances, own health, family's health) domains. The LSI also assesses episodic life events both in the context of each life domain and via a series of miscellaneous events (e.g., moving, being the victim of a crime, auto accidents) probed at the interview's conclusion. The interviewer assigned a chronic stress score for each domain on a scale ranging from 1 (least stressful circumstances) to 5 (most stressful circumstances). All interviews were conducted by a trained graduate student (BMA) who

has demonstrated competence in administering and rating the LSI by conducting a "mock interview" with the lab principle investigator, an expert in life stress assessment (SVS), and by matching a set of internal "gold standard" ratings (within 0.5 points) for chronic stress on pre-recorded interviews. Each episodic stressful life event was then presented by the interviewer to a team of two or more raters trained in the LSI who were blind to the participant's response to the event and any psychiatric diagnoses the participants may have. Blind raters scored each event on severity (from 1-5 in increments of 0.5), independence (1-5 in increments of 1, with 1 being fateful and 5 being dependent on the participant), and interpersonal status (whether the event primarily impacted the quality or quantity of the participant's relationships, coded 0 or 1), and assigned a code indicating event type (e.g., romantic breakup). In the event of initial rating discrepancies, raters discussed the event ratings until a consensus was reached. Events with a severity rating of 1 were considered "non-events," and were excluded from analyses. Episodic stressors with a severity rating of 2.5 or greater were classified as "major stressful life events," while stressors with a severity rating of 1.5 or 2.0 were considered "minor stressful life events" (Vrshek-Schallhorn et al., 2014). Additionally, events with dependence scores of 1-2 were classified as "independent," while events with dependence scores of 3-5 were classified as "dependent."

Mini-Mood and Anxiety Symptom Questionnaire (MMASQ). Participants completed the MMASQ, a 26-item measure assessing symptoms of depression and anxiety (Casillas & Clark, 2000). The MMASQ is composed of 3 sub-scales: General Distress, Anhedonic Depression, and Anxious Arousal. The 8-item General Distress

subscale (present sample, $\alpha = 0.92$), a measure of non-specific depression and anxiety, was used as a covariate in regression analyses described below. The General Distress subscale was utilized as a covariate to rule out the possibility that any observed reward-related differences in neural reactivity was due to the general relationship between stress and depression. The Anhedonic Depression subscale was not utilized for this purpose due to its specific measurement of reward-related constructs rather than general depression.

Grit-S Scale. For secondary analyses, participants completed the short form of the Grit Scale (Duckworth & Quinn, 2009), an 8-item measure assessing "Grit," a construct closely related to the Big-5 trait of conscientiousness, with an additional component of perseverance in the face of adversity (Credé et al., 2017). The Grit-S Scale has good internal consistency ($\alpha = 0.77$) and is composed of two factors: Consistency of interests and Perseverance of effort (Duckworth et al., 2007). Although each factor has good internal consistency, most prior work has utilized the entire scale score as an overall measure of "Grit," and the overall scale score was utilized in analyses in the present study.

Procedures

All procedures were approved by the IRB of the University of North Carolina at Greensboro. All interested individuals received an initial screening for study eligibility over the phone. Eligible participants then completed an initial survey of several questionnaires including the MMASQ and Grit Scale, and 7 daily diary entries as part of a larger study prior to being scheduled for the MRI scan. Prior to the MRI scan, participants received a second standard magnetic resonance safety screening and

informed consent. Following provision of informed consent and completion of a standard MR safety screening, participants completed 1) a brief questionnaire about their current affect (not included in this study) and 2) practice runs of three tasks they completed in the MRI scanner (the MID task and two tasks not included in this study). Prior to entering the scanner, participants received a brief explanation of MRI safety protocols, and were instructed on the use of an emergency ball and stimulus response box. Participants then completed the MRI scan.

Following completion of the MRI scan, participants completed a follow-up session no more than two weeks after the scan during which participants completed the UCLA Life Stress Interview (LSI; Hammen et al., 1987) and the Mood Disorders module of the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2001; not examined in this proposal). Following the interview, participants were compensated with money or class credit, plus a $5 bonus.

Statistical Analyses

LSI Data Reduction. To examine "overall" effects of stress, an omnibus test strategy for examining the effects of chronic and episodic stress with a composite index was utilized. Chronic stress ratings for each interpersonal and non-interpersonal domain were averaged to create Chronic Interpersonal and Non-Interpersonal Stress scores. These scores were then mean-centered and standardized across all participants as z-scores. Because stressful life events retain statistically significant impact for no more than three months (Kendler et al., 1998; Surtees & Wainwright, 1999), I computed the sum of severity scores for interpersonal and non-interpersonal stressful life events

occurring in the 3-months prior to the scan. Events occurring between MRI and LSI administration were excluded from analyses. These scores were summed for interpersonal and non-interpersonal events for each participant, and then mean-centered and standardized as z-scores across all participant. Last, I averaged each participant's standardized chronic and episodic severity scores within the interpersonal and non-interpersonal domains to create Overall Interpersonal and Non-Interpersonal Stress severity composite scores to minimize multiple testing.

For secondary analyses examining differential effects of major versus minor stressful life events, I calculated Major and Minor Stressful Life Event Severity Scores by summing all stressful life events with a severity rating of 2.5 or greater (for major events) and 2.0 or less (for minor events) respectively. I then standardized these scores by calculating z-scores based on summed severity ratings across participants within each domain (major interpersonal, major non-interpersonal, minor interpersonal, minor non-interpersonal).

For exploratory analyses examining whether stressor dependence plays a role in influencing its effects on reward, I separately summed the severity scores for all dependent and independent stressful life events to create Dependent and Independent Stressful Life Event severity scores.

fMRI Pre-processing. Structural images were brain-extracted (i.e., non-brain material such as skull and eyes was removed from head images) using Advanced Normalization Tools Brain Extraction Tool (Avants, Tustison, & Song, 2009); data were visually examined for each participant to ensure adequate removal of all non-brain tissue

and inclusion of all brain tissue, and no significant problems were identified. The remainder of pre-processing was conducted using programs from the FMRIB Software Library (FSL), described below. Data were spatially smoothed using a 6 mm full-width at half-maximum Gaussian filter, slice-timing corrected using Fourier-space time-series phase-shifting based on interleaved slice acquisition, motion corrected using FSL MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), and subjected to highpass temporal filtering. Functional images were registered to high resolution structural images using FSL FLIRT linear registration with a "Full Search BBR" algorithm (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Registration to standard stereotactic space was then completed using FNIRT nonlinear registration using a 12 degree-of-freedom search (Andersson, Jenkinson, & Smith, 2007). To mitigate signal loss in anterior-ventral regions that are prone to distortion due to the presence of sinus cavities, distortion correction was applied using fieldmaps constructed for each participant from phase and magnitude images acquired during scanning (Jenkinson, 2003). Data were visually inspected to ensure these processes achieved adequate registration of functional to structural images for each participant, and no significant issues were identified.

fMRI Data Analyses. Functional MRI data analyses were completed using fMRI Expert Analysis Tool Version 6.0 (Version 6.0; Woolrich, Ripley, Brady, & Smith, 2001). Canonical hemodynamic response functions were estimated during the anticipation phase of each reward trial using gamma functions with width fixed to the moment the MID cue first appeared to the moment that the MID target appeared (i.e., the period of the trial during which the participant was anticipating the possibility of

receiving a reward). FSL FILM pre-whitening with local auto-correlation correction was applied to time-series during the estimation of these statistics (Woolrich et al., 2001). I then constructed first-level (person-level) linear contrasts assessing differential BOLD responses to cumulative reward versus control conditions, coding neutral, small, medium, and large reward trials as -3, 1, 1, 1 respectively. These analyses generated "contrast of parameter estimate" values for each voxel, which cumulatively formed contrast of parameter estimate maps for each participant (i.e., a map of the brain with a contrast value computed for each voxel).

First-level contrast estimates were then subjected to FSL MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Probabilistic Independent Components Analysis Version 3.14 (Beckmann & Smith, 2004), consistent with best-practices to reduce functional signal artifacts cause by motion or biological features (e.g., white matter tracts). Individual components for each participant were visually examined to identify well-established motion-related (e.g., rings of activation on distal surface of the brain) and physiological (e.g., high-intensity signals closely following white-matter tracts) artifacts that may result in "false-positive" signals. Although the visual identification of such artifacts is inherently subjective, I maintained a conservative approach, identifying components as artifacts only if they closely resembled well-established artifact patterns that are not associated with known brain networks. To further maintain a conservative approach, components containing activation within the region of interest were not selected, even if aspects of the component resembled a possible artifact. Components identified as artifacts were then regressed out of individual

contrast of parameter estimate maps prior to applying these maps to higher-level analyses.

Region-of-Interest Analysis: A binary mask of the ventral striatum was created using the Oxford-Imanova Striatal Structural Atlas in FSLView (Lancaster et al., 2000; Mazziotta et al., 2001). This mask was applied to second-level analyses to limit parametric tests to the ventral striatum. I then constructed second-level random effects models examining the sample averages for first-level contrast of parameter estimate values using one-sample t-tests with a $p<0.001$ cluster threshold, corrected to control the family-wise error rate. Stated plainly, this analysis examined the average intensity of activation in response to reward anticipation across our sample to determine voxel clusters within the ventral striatum that were significantly responsive to reward anticipation.

Binary masks were then created from significant clusters within the ventral striatum identified in the second-level analysis. These masks were then applied to first-level (individual-level) data and the maximum contrast of parameter estimates, calculated as a z-score, within these clusters was extracted for each participant. These z-scores were entered into OLS regression models during hypothesis testing and are referred to throughout the remainder of this document as Ventral Striatal Reactivity to reward anticipation.

Hypothesis testing. Person-level contrast values from clusters in the ventral striatum showing a main effect of reward anticipation ("Ventral Striatal Reactivity") were entered into regression models in IBM SPSS Version 25. To address Hypothesis 1

(Overall Interpersonal Stress, but not Overall Non-Interpersonal Stress, would be negatively associated with Ventral Striatal Reactivity), I regressed left and right Ventral Striatal Reactivity onto Overall Interpersonal and Non-Interpersonal Stress in separate models (4 models total). To address Hypothesis 2 (Chronic and Episodic Interpersonal Stress would independently be negatively associated with Ventral Striatal Reactivity), in separate models, I regressed left and right Ventral Striatal Reactivity onto Chronic Interpersonal and Non-Interpersonal Stress and Episodic Interpersonal and Non-Interpersonal Stress. To control the family-wise Type-1 error rate, I chose to only test effects of major vs. minor stressful life events and stressor dependence if results for Hypothesis 2 showed an overall effect of episodic stress on Ventral Striatal Reactivity. To test Hypothesis 3 (Episodic Interpersonal Stress severity would be negatively associated with Ventral Striatal reactivity for major, but not minor, stressful life events), I planned to regress Ventral Striatal Reactivity onto Episodic Stress Severity Scores for Major Interpersonal, Major Non-Interpersonal, Minor Interpersonal, and Minor Non-Interpersonal stressors in separate models. Last, to examine whether independent or dependent stressors exhibit differential effects, I planned to regress Ventral Striatal Reactivity on Independent and Dependent Event Severity Scores in separate models.

Consistent with prior work (Nikolova et al., 2011), biological sex was entered as a covariate in all regression models due to evidence of sex-related differences in reward-related neural reactivity (Spreckelmeyer et al., 2009). Additionally, to control for stress-related effects on Ventral Striatal Reactivity that may be accounted for by the general effect of stress on depressive symptoms, all regression models were constructed with and

without MMASQ General Distress as a covariate. Statistics reported below are derived from models including MMASQ General Distress as a covariate, unless otherwise noted.

Power Analysis. Estimating the precise effect size for the association of recent life stress and ventral striatal reactivity to reward from pre-existing studies is not appropriate, as no studies to date have examined these variables together. Although previous studies have examined the effects of recent life stress on depression, the effect sizes from these studies would likely underestimate the effects of recent stress on ventral striatal reactivity to reward: Neural functioning is considered an intermediate phenotype that is likely more sensitive to stress effects than whether someone meets criteria for a clinical diagnosis (Meyer-Lindenberg & Weinberger, 2006). Similarly, studies examining the effects of early life stress on ventral striatal reactivity to reward likely underestimate the effect sizes of hypothesized analyses in this study, as there is evidence that more recent stress has a much more robust effect on current diagnostic classification than early adversity (Kendler & Gardner, 2017). However, because studies examining the effects of genetic variability in the dopaminergic system on ventral striatal reactivity to reward estimated an effect size of $R^2 = 0.10$ (Nikolova et al., 2011), and genetics are thought to have a much smaller effect on depression than environmental differences (Sullivan et al., 2000), I anticipated the hypothesized effects in the present study to have at least moderate effect sizes.

Thus, required samples sizes for moderate and large effect sizes were calculated using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007), estimating the R^2 change with 3 predictors. Assuming a moderate effect size of $R^2 = 0.15$, a sample of 55 participants

would be required to achieve power of 0.80. Assuming a large effect size of $R^2 = 0.35$, a sample of 25 participants would be required to achieve power of 0.80. Given the obtained sample size included in analyses ($N = 46$), I conducted a sensitivity analysis that estimated power to be approximately 0.73 for a moderate effect size and 0.97 for a large effect size.

CHAPTER III

RESULTS

LSI Summary Statistics

Examination of summary statistics for LSI data indicated that both Interpersonal and Non-Interpersonal Episodic Stress exhibited a restricted range and were positively skewed, with the modal score for both variables being "1" (see Table 1). Thus, although I proceeded with planned analyses for Overall and Episodic Stress, it should be noted that parametric tests using these variables violated the assumption of data normality and should therefore be interpreted with caution. To partially address this issue, analyses below were repeated after log-transforming Episodic Stress to reduce skew. Chronic Interpersonal and Non-Interpersonal Stress variables were within acceptable limits for skewness and kurtosis and were therefore normally distributed. The range for Chronic Interpersonal Stress was within acceptable limits; however, the range of Non-Interpersonal Chronic Stress was restricted to approximately 30% of the scale, suggesting that participants were relatively similar to each other on this construct.

fMRI Group Analysis

Group-level analyses revealed a significant main effect of reward anticipation in one cluster within the right ventral striatum (coordinates: $x = 8$, $y = 10$, $z = 0$; $Z = 6.45$; cluster size = 126 voxels) and one cluster within the left ventral striatum (coordinates: $x = -6$, $y = 8$, $z = 0$, $Z = 5.06$, cluster size = 63 voxels; see Figure 1). Activation within both

clusters was normally distributed across participants (left VS M= 143.79, *SD* = 171.83, *skewness* = -0.03, *kurtosis* = -0.63; right VS *M* = 130.24, *SD* = 150.07, *skewness* = -0.32, *kurtosis* = -0.22). These findings support that the Monetary Incentive Delay task and image acquisition and processing yielded a valid measure of Ventral Striatal Reactivity to reward anticipation.

Interpersonal Stress and Ventral Striatal Reactivity to Reward

Inconsistent with hypotheses, no interpersonal stress variables—Overall Interpersonal Stress, Chronic Interpersonal Stress, or Episodic Interpersonal Stress—were significantly associated with either right (all $t \leq 0.807$, all $p \geq 0.424$; Table 2) or left (all $t \leq 0.203$, all $p \geq 0.840$; Table 3) Ventral Striatal Reactivity to reward anticipation in main effect. Results did not differ for any of the above analyses when excluding Sex or MMASQ General Distress from models as a covariate. Effects of Episodic Interpersonal Stress did not differ after log-transformation. Because the tests of general Episodic Interpersonal Stress effects on Ventral Striatal Reactivity were not significant, and because there was limited variability in Episodic Interpersonal Stress within the sample, I did not conduct tests examining the effects of major versus minor stressful life events or stressor Independence on Ventral Striatal Reactivity.

Non-Interpersonal Stress and Ventral Striatal Reactivity to Reward

Similarly, consistent with expectations, no non-interpersonal stress variables—Overall Non-Interpersonal Stress, Chronic Non-Interpersonal Stress, or Episodic Non-Interpersonal Stress—were significantly associated with right (all $t \leq 0.374$, all $p \geq 0.710$; Table 2) or left (all $t \leq 01.022$, all $p \geq 0.312$; Table 3) Ventral Striatal Reactivity to

reward in main effect. Results did not differ when excluding Sex or MMASQ General Distress as a model covariate. Effects of Episodic Non-Interpersonal Stress did not differ after log transformation.

Exploratory Analyses

Depression and VS Reactivity to Reward: To determine whether data in the present sample were consistent with prior findings that depression is associated with blunted ventral striatal reactivity to reward anticipation (Pizzagalli et al., 2009), I regressed Ventral Striatal Reactivity onto MMASQ General Distress, entering biological sex as a covariate, consistent with the preceding analyses. Partially supporting previous findings, MMASQ General Distress was negatively associated with right (b = -7.806, $SE(b)$ = 3.378, $t(43)$ = -2.311, p = 0.026), but not left (b = -0.913, $SE(b)$ = 4.005, $t(43)$ = -0.079, p = 0.937) Ventral Striatal Reactivity to reward anticipation.

Stress and Depression: To determine whether data in the present sample were consistent with prior findings that interpersonal, but not non-interpersonal stress is associated with depression, I conducted an exploratory OLS regression analysis regressing MMASQ General Distress onto Overall Interpersonal Stress and Overall Non-Interpersonal Stress in separate models. Consistent with prior findings, Overall Interpersonal Stress (b = 2.602, $SE(b)$ = 1.221, $t(43)$ = 2.131, p = 0.039), but not Overall Non-Interpersonal Stress (b = 0.356, $SE(b)$ = 1.368, $t(43)$ = 0.260, p = 0.796), was significantly and positively associated with MMASQ General Distress. These findings appeared to be driven by the effects of chronic stress: Chronic Interpersonal Stress (b = 5.382, $SE(b)$ = 1.822, $t(43)$ = 2.954, p = 0.005), but not Episodic Interpersonal Stress (b =

0.456, *SE(b)* = 1.247, *t*(43) = 0.366, *p* = 0.716), was significantly associated with MMASQ General Distress.

Moderating Effects of Grit: In an exploratory analysis, I examined the potential moderating effect of "Grit," an individual difference associated with resilience, conscientiousness, and perseverance towards goals in the face of adversity, on the relationship between Chronic Interpersonal Stress and Ventral Striatal Reactivity to reward. As in the previous analyses, models included biological sex as a covariate, and were examined with and without MMASQ General Distress as a covariate. Although hypotheses were not established prior to data collection, I expected that individuals with higher levels of Grit would exhibit a less negative association between chronic interpersonal stress and ventral striatal reactivity to reward than individuals with lower levels of Grit. Consistent with these expectations, there was a significant Grit × Chronic Interpersonal Stress interaction predicting both right (*b* = 248.282, *SE(b)* = 105.158, *t*(39) = 2.361, *p* = 0.023) and left (*b* = 328.621, *SE(b)* = 116.924, *t*(39) = 2.811, *p* = 0.008) Ventral Striatal Reactivity. Results did not differ when MMASQ General Distress was not included as a covariate. There was not a significant Grit × Chronic Non-Interpersonal Stress interaction predicting right (*b* = 123.563, *SE(b)* = 127.768, *t*(39) = 0.967, *p* = 0.339) or left (*b* = 184.579, *SE(b)* = 143.464, *t*(39) = 1.287, *p* = 0.206) Ventral Striatal Reactivity.

To decompose these interactions, results were probed using the Johnson-Neyman technique implemented in the MODPROBE macro for SPSS (Hayes & Matthes, 2009). This analysis revealed a full crossover interaction for the left ventral striatum, such that

Chronic Interpersonal Stress and left Ventral Striatal Reactivity exhibited a significant negative association for individuals with low Grit scores ($z \leq -0.820$), and a significant positive association for individuals with high Grit scores of ($z \geq 0.717$; see Figure 2). Similar findings were observed for the right ventral striatum, where Chronic Interpersonal Stress and right Ventral Striatal Reactivity exhibited a significant negative association for individuals with low Grit scores ($z \leq -0.543$), and a positive association that was approaching significance ($p = 0.053$) for the upper end of the range of Grit scores observed in our sample ($z = 2.246$; see Figure 3).

To further decompose these interactions, the two factors of Grit ("Consistency of Interests" and "Perseverance of Effort") were individually examined in interaction with life stress. Consistent with findings for overall Grit, there was a significant Perseverance of Effort × Chronic Interpersonal Stress interaction predicting right Ventral Striatal Reactivity ($b = 205.293$, $SE(b) = 84.407$, $t(39) = 2.432$, $p = 0.020$). Similarly, there was a marginal Perseverance of Effort × Chronic Interpersonal Stress interaction predicting left Ventral Striatal Reactivity ($b = 199.758$, $SE(b) = 99.899$, $t(39) = 2$, $p = 0.053$. There was not a significant Consistency of Interest × Chronic Interpersonal Stress interaction predicting right ($b = 48.362$, $SE(b) = 71.541$, $t(39) = 0.676$, $p = 0.503$) or left ($b = 141.410$, $SE(b) = 78.214$, $t(39) = 1.808$, $p = 0.078$) Ventral Striatal Reactivity.

CHAPTER IV

DISCUSSION

In the present study, I examined the hypothesis that interpersonal, but not non-interpersonal, life stress is associated with blunted ventral striatal reactivity to reward anticipation. Despite an expansive literature supporting that the experience of stress is associated with altered reward-seeking behavior and disrupted mesolimbic dopaminergic signaling in animal models, results of the present study do not support a main effect association between recent life stress and ventral striatal reactivity during reward anticipation in humans. These non-significant findings held for both interpersonal and non-interpersonal, as well as chronic and episodic life stress, and were robust to the inclusion/exclusion of a continuous measure of depression as a model covariate. In contrast, exploratory findings did support a diathesis-stress interaction such that Chronic Interpersonal Stress and bilateral Ventral Striatal Reactivity showed a *positive* association for individuals with high levels of the personality trait Grit, and a *negative* relationship for individuals with low Grit. Thus, results support a role for Grit as a significant resilience factor in the preservation of reward function in the context of life stress. Examination of individual factors in the Grit-S Scale suggest that these findings are primarily driven by the perseverance of effort factor.

Lack of Significant Main Effects of Stress on Ventral Striatal Reactivity

Several factors may have contributed to the non-significant findings described above. First, this study may have been under-powered: Although power analyses suggested the study likely had sufficient power to detect a moderate effect size based on the planned sample, the final sample size was relatively modest. Second, there was limited variability in participants' reported episodic life stress, which likely influenced the ability to detect effects of overall interpersonal and non-interpersonal stress, and which likely precluded the possibility of finding significant effects of episodic stress. Third, during fMRI data pre-processing, removal of ICA "noise" components was purposefully conservative, which may have resulted in the inclusion of signal artifacts (i.e., error variance) that occluded significant effects.

Alternatively, it may be the case that there is no main effect, or only a small main effect, of stress on ventral striatal reactivity in humans. However, given the overwhelming evidence that stress disrupts dopaminergic signaling and reward-seeking behavior in animals, it is somewhat implausible that stress and ventral striatal reactivity to reward are entirely unrelated in humans. More plausibly, it may be the case that deleterious effects of stress on ventral striatal reactivity to reward are moderated by factors not included in the primary analyses, such as top-down self-regulatory processes that play an important role in emotion regulation and resilience. For example, it is possible that individuals with better self-regulatory abilities exhibited less deleterious effects of stress on ventral striatal reactivity to reward than individuals with poorer regulatory abilities. Indeed, individuals with a high degree of neuroticism, who tend to

have relatively poor emotion regulation abilities (e.g., Bono & Vey, 2007), exhibit more dysregulated responses to (e.g., Oswald et al., 2006; Phillips et al., 2005) and more severe deleterious effects of stress, including greater levels of depression (T. A. Brown & Rosellini, 2011; Kendler, Kuhn, & Prescott, 2004).

Grit, Chronic Interpersonal Stress, and Ventral Striatal Reactivity

Although exploratory in nature, analyses showed that Grit significantly moderated the relationship between Chronic Interpersonal Stress and bilateral Ventral Striatal Reactivity to reward anticipation, such that individuals with low Grit exhibited a negative relationship between life stress and bilateral Ventral Striatal Reactivity to reward, and individuals with high levels of Grit showed a positive relationship between the same variables. Importantly, the full-crossover nature of this interaction suggests that effects of stress on reward processing would not be detectable without accounting for Grit (or a construct with similar interactive effects) in the model. Thus, despite the substantial evidence in animal models that stress exerts effects on reward processes via main effect, the present data suggest that a main effect model of stress exposure on reward processes in insufficient, and that a diathesis-stress model more accurately characterizes the relationship between stress and reward processes in the brain.

There are several possible explanations for these findings. First, individual differences in Grit may be reflective of differences in top-down regulatory processes that either 1) confer general resilience to stress by enhancing emotion regulation generally, or 2) specifically confer resilience of reward-related processes to stress. Prior research has indicated that Grit is associated with enhanced emotion regulation (Ivcevic & Brackett,

2014) and generally associated with self-regulatory processes (Muenks, Wigfield, Yang, & O'Neal, 2017). However, research in this area is in early stages, and it is unclear whether these factors are driven specifically by the regulation of reward-related processes, or by more general emotion regulatory processes. Regardless of the specific mechanism, data in the current study suggest that individuals with high levels of Grit may upregulate reward processes in the context of life stress.

Second, the significant interaction may indicate that individuals with higher levels of Grit are able to pursue goals in spite of adversity *because* reward functioning of these individuals is enhanced in the context of stress (and conversely, individuals with lower levels of Grit do not persist in goal pursuit because reward functioning is negatively affected by stress). Although causality cannot be inferred from the present study, this possibility is consistent with prior research suggesting that striatal dopaminergic signaling is associated with willingness to expend effort to obtain rewards (Treadway, Buckholtz, et al., 2012).

Third, it may also be the case that these two processes act in a reciprocal manner, such that individuals with enhanced self-regulatory processes associated with more Grit exhibit ventral striatal reactivity to reward that is relatively unaffected by stress, which in-turn enables continued pursuit of rewards, which facilitates further self-regulation, and so on. Although the present study does not have sufficient data to evaluate this possibility, such a hypothesis is consistent with a robust literature examining the effects of positive valence functioning on stress and resilience, which is briefly discussed below.

The present results also support previous findings suggesting that interpersonal stress uniquely predicts onset of depressive symptoms in interaction with pre-existing vulnerability factors (Sheets & Craighead, 2014; Starr, Vrshek-Schallhorn, & Stroud, 2019), although it should be noted that Chronic Non-Interpersonal Stress was more restricted in range within the present sample than Chronic Interpersonal Stress, which may have accounted for the differential observed effects. Notably, the interpersonal nature of stress has been largely disregarded in animal models of stress-induced reward dysfunction, which constitute the vast majority of studies investigating the effects of stress on reward pathways. Thus, the present findings suggest that future research investigating the effects of stress on reward processes ought to specifically focus on the study of interpersonal stressors. Additionally, the present findings add to a growing body of literature supporting that interpersonal stress uniquely predicts depression-related outcomes.

Reward Processes and Resilience

The present findings that individuals with higher levels of Grit have a positive relationship between Ventral Striatal Reactivity and recent Chronic Interpersonal Stress are correlational in nature, indicating several possible directional interpretations. It could be that higher Grit and its associated behaviors (goal pursuit under stress) causally contribute to Ventral Striatal Reactivity in the context of increased stress. In contrast, it may be that greater Ventral Striatal Reactivity or its correlates including positive emotion causally contribute to higher goal pursuit under stress, and therefore higher Grit. Last, it could be that both of these directional effects occur in a reciprocal manner. Of these

interpretations, the second possibility is particularly intriguing, and suggests that reward processes generally, and ventral striatal reward reactivity specifically, may be involved in facilitating the ongoing pursuit of goals in the context of life stress. These findings are consistent with a large body of work implicating positive emotions, reward-related processes, and their neurobiological substrates (e.g., dopamine) as critical elements of effective coping.

For example, in a series of experiments, rats that were given sweet solutions, a putatively rewarding stimulus, exhibited reduced adrenocorticotropic hormone and corticosterone secretion, as well as less tachycardia in response to restraint stress, and increased exploratory behavior when caged with an unfamiliar rat (putatively a behavioral indicator of lower anxiety) than control rats, with some beneficial effects lasting up to 14 days after the last administration of reward (Ulrich-Lai et al., 2010). Similar effects were observed in male rats who were allowed to engage sexual behavior, and positive effects were not observed in rats given sweet solutions in a way that bypassed gustation (via gastric gavage), suggesting that beneficial effects on stress coping were likely the result of reward system activation more generally, and not specific to macronutrient absorption (Ulrich-Lai et al., 2010).

In humans, a growing body of research supports that positive emotions are critical to successful coping and goal attainment in the context of stress. For example, Behavioral Activation, an evidence-based treatment for depression, is thought to facilitate depression recovery by encouraging individuals to engage in activities that increase experiences of mastery (e.g., goal achievement) and pleasure (Mazzucchelli, Kane, &

Rees, 2009; Sturmey, 2009). Similarly, the Broaden and Build Theory of Positive Emotions posits that positive emotions facilitate coping by "broadening" the scope of thoughts and actions, which promotes the gathering of physical and social resources that enhance coping (Fredrickson, 1998). This process is thought to continue forth in a reciprocal interaction that positively influences well-being.

In support of the "Broaden and Build" theory, several studies have found that positive mood induction by watching emotionally-salient videos facilitates one indicator of positive coping, cardiovascular return to baseline, following fear and social evaluative threat inductions (Fredrickson & Levenson, 1998; Fredrickson, Mancuso, Branigan, & Tugade, 2000). Trait positive emotionality has also been associated with greater respiratory sinus arrhythmia (Oveis et al., 2009), which is associated with another indicator of better coping, lower levels of negative emotional reactivity to daily stressors (Fabes & Eisenberg, 1997). In another study, participants viewed cartoons prior to undergoing a lab-induced stressor; participants who were told that they could view more cartoons following the stressor exhibited greater increases in positive affect and contemporaneously greater decreases in negative affect immediately following the stressor (Monfort, Stroup, & Waugh, 2015).

Finally, D2-receptor agonist administration (which would putatively acutely augment reward functioning) was associated with greater set-shifting abilities in individuals with a genetic vulnerability known to confer lower levels of dopaminergic signaling as compared to those without the vulnerability (a variable tandem repeat polymorphism in *DAT1/SLC6A3;* van Holstein et al., 2011). Conversely, D2-receptor

antagonist administration was associated with impaired set-shifting in another sample (Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004). These findings specifically implicate dopaminergic signaling as an important underpinning of cognitive flexibility, and potentially adaptive problem-solving, which may facilitate goal pursuit when faced with adversity.

Future Directions

Findings that Grit moderates the effects of Chronic Interpersonal Stress on Ventral Striatal Reactivity to reward suggest three possible mechanisms: 1) Top-down cognitive self-regulatory processes associated with the personality trait Grit, such as emotion-regulation abilities, facilitate the preservation or enhancement of reward processes in the face of stress (i.e., Grit causes preserved or enhanced reward functioning under stress), 2) Reduced effects of stress on Ventral Striatal Reactivity may facilitate continued goal pursuit in spite of adversity (i.e., preserved or enhanced reward functioning under stress gives rise to Grit), or 3) A combination of both. Thus, results suggest that reward functioning under stress may play an important role in facilitating coping, and future studies should examine the extent to which reward processing generally, and ventral striatal reactivity to reward anticipation specifically, plays a role in facilitating coping with stress. Such research may lead to identification of reward-related neural activity in the ventral striatum as a useful biomarker for prospectively predicting depression.

Additionally, because Grit is associated with long-term goal pursuit, it is likely associated with pre-frontal cortical functioning. Thus, the moderating effect of Grit on the

association of stress and reward processing in the ventral striatum suggests that frontal-striatal connectivity may be an important predictor of resilient reward processing under stress. Additionally, as high levels of chronic stress are associated with structural changes in the prefrontal cortex, an avenue for future study is examining the extent to which life stress alters frontal-striatal connectivity, and how this is in-turn associated with the behavioral pursuit of goals and rewards.

Limitations

Despite several strengths, including measurement of an objective biomarker of reward responsivity and utilization of investigator-rated contextual threat interviews, the present study had several limitations. As discussed above, the study had a relatively modest sample size, and several of the findings were exploratory in nature. Furthermore, given the ethical and practical implications of randomly assigning and manipulating life stress or neural functioning in humans, and the logistic challenge of collecting repeated MRI assessments, the present study was necessarily correlational in nature, and therefore not suitable for drawing causal conclusions in isolation. Although findings might have supported prior animal research establishing a causal effect of stress on reward processes in the brain if the primary hypotheses had been supported, causal effects cannot be inferred for correlational analyses implicating ventral striatal reactivity to reward anticipation as a possible resilience factor to stress.

Related, given that the primary aim of this study was to investigate the relationship between life stress and ventral striatal reactivity to stress, the study was not optimally designed to examine questions of whether ventral striatal reactivity facilitates

resilience to adverse mental health outcomes in the face of stress. Indeed, the design of the present study allowed for the establishment of temporal precedence such that life stress *preceded* neuroimaging. Studies primarily seeking to examine possible risk or resilience conferred by reward processes ought to use a prospective approach, such that neuroimaging precedes the window of stress and mood assessment.

Last, it should be noted that the pre-study screening did not assess or screen for a number of factors that might contribute to error variance, including recent use of illicit psychoactive substances. However, it should be noted that any significant findings were likely uncovered *in spite* of such factors, although failure to account for such factors may partially explain the lack of significant effects of life stress on ventral striatal reactivity to reward in the present study.

Conclusions

In this paper, I present data suggesting that, despite extensive evidence that stress disrupts neurobiological reward pathways in animal models, there is either not a main effect of recent chronic life stress predicting ventral striatal reactivity during reward anticipation in humans, or such an effect is small. These negative findings held irrespective of stress characteristics (interpersonal/non-interpersonal). No conclusions about the effects of episodic stress can be drawn given the relatively low prevalence of recent stressful life events in this sample. Exploratory analyses support a possible role of ventral striatal reactivity in facilitating goal pursuit in the context of life stress. Specifically, the association of chronic interpersonal stress and bilateral ventral striatal reactivity to reward is moderated by "Grit," suggesting that preserved ventral striatal

reactivity in the face of chronic stress may be associated with continued perseverance towards the pursuit of goals. Exploratory analyses also partially supported the previous literature suggesting that depression is associated with blunted ventral striatal reactivity to reward (Pizzagalli et al., 2009), as well as evidence that chronic interpersonal stress is uniquely associated with depression over and above non-interpersonal stress (Vrshek-Schallhorn et al., 2015). Future research should further examine the possible role of ventral striatal reactivity specifically, and reward systems in general, in conferring resilience to deleterious effects of life stress.

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APPENDIX A. TABLES

Table 1. ***UCLA Life Stress Interview Descriptive Statistics***

Stress Type	Mean	SD	Skew	Kurtosis	Range
Interpersonal Episodic	1.587	0.777	1.221	0.508	1 – 3.5
Non-Interpersonal Episodic	1.217	0.344	1.742	3.327	1 – 2.5
Interpersonal Chronic	2.478	0.485	0.465	1.220	1.5 – 4
Non-Interpersonal Chronic	2.359	0.277	-0.265	-0.344	1.7 – 2.9
Interpersonal Overall	0	0.756	0.557	-0.261	-1.3 – 1.8
Non-Interpersonal Overall	0	0.708	0.413	0.429	-1.5 – 1.9

Note: Interpersonal Overall and Non-Interpersonal Overall Stress were computed by averaging Z-scores of Episodic and Chronic Stress.

Table 2. ***Regression Results for Effects of Stress on Right Ventral Striatal Reactivity to Reward***

Effect	*b*	*SE(b)*	*df*	*t*	*p*
Overall Interpersonal Stress	-18.455	30.123	42	-0.613	0.543
Overall Non-Interpersonal Stress	-14.295	30.622	42	-0.467	0.643
Chronic Interpersonal Stress	-39.359	48.751	42	-0.807	0.424
Chronic Non-Interpersonal Stress	-29.273	78.245	42	-0.374	0.710
Episodic Interpersonal Stress	-4.070	28.020	42	-0.145	0.885
Episodic Non-Interpersonal Stress	-18.040	63.149	42	-0.286	0.777

Note: Each variable listed above was entered in a separate model. Sex and MMASQ General Distress were included as covariates in every model.

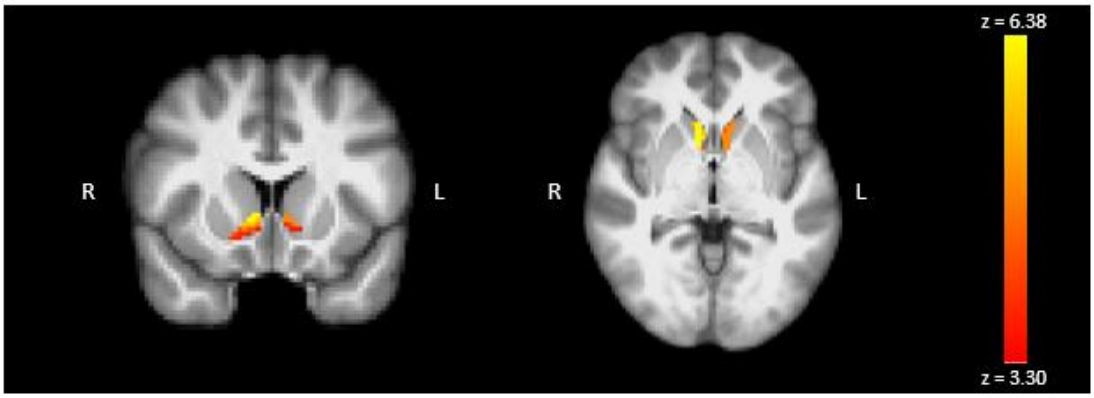
Table 3. R*egression Results for Effects of Stress on Left Ventral Striatal Reactivity to Reward*

Effect	*b*	*SE(b)*	*df*	*t*	*p*
Overall Interpersonal Stress	2.844	35.868	42	0.079	0.937
Overall Non-Interpersonal Stress	-31.616	36.068	42	-0.877	0.386
Chronic Interpersonal Stress	11.803	58.212	42	0.203	0.840
Chronic Non-Interpersonal Stress	-20.455	92.860	42	-0.220	0.827
Episodic Interpersonal Stress	-2.366	33.224	42	-0.071	0.944
Episodic Non-Interpersonal Stress	-75.685	74.020	42	-1.022	0.312

Note: Each variable listed above was entered in a separate model. Sex and MMASQ General Distress were included as covariates in every model.

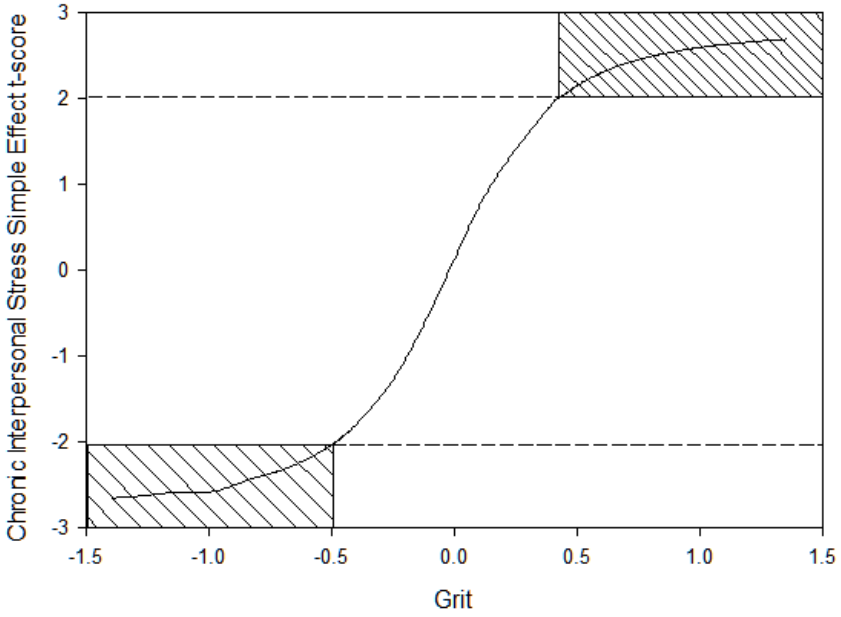
APPEXNDIX B. FIGURES

Figure 1. ***Significant Clusters in the Bilateral Ventral Striatum***



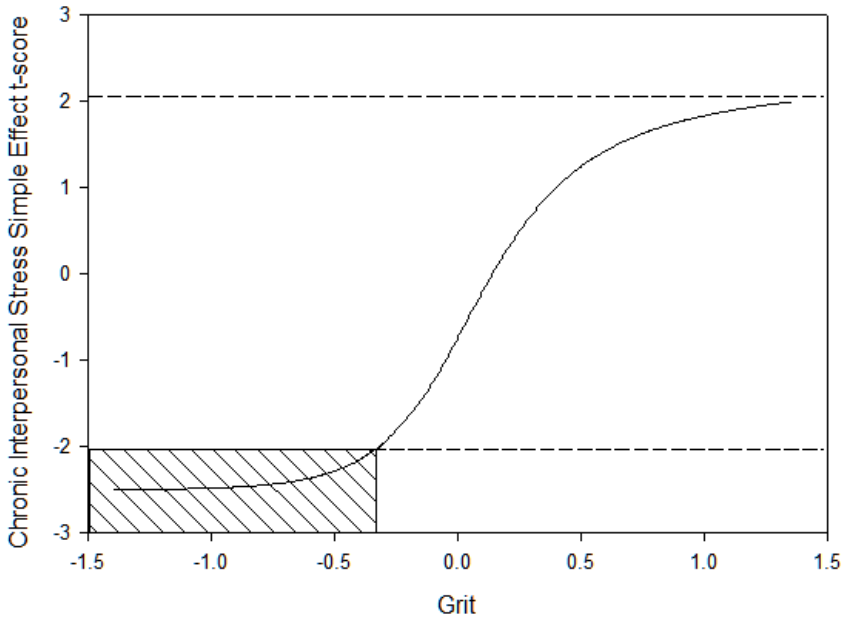
Note:. Images are displayed in a standard radiographic view (coronal slice is displayed as if the viewer is observing the brain from the front, and the horizontal slice is displayed as if the viewer is observing the brain from the bottom). Clusters in the above images are thresholded at a minimum of z = 3.30

Figure 2. Left Ventral Striatum ROS Curve



Note: Shaded regions represent regions of significance, or values of Grit (mean-centered) at which the simple effect of Chronic Interpersonal Stress on left Ventral Striatal Reactivity is significant. Negative t-scores represent a negative regression coefficient (i.e., an inverse relationship), while positive t-scores represent a positive regression coefficient (i.e., a positive relationship).

Figure 3. Right Ventral Striatum ROS Curve



Note: Shaded regions represent regions of significance, or values of Grit (mean-centered) at which the simple effect of Chronic Interpersonal Stress on right Ventral Striatal Reactivity is significant. Negative t-scores represent a negative regression coefficient (i.e., an inverse relationship), while positive t-scores represent a positive regression coefficient (i.e., a positive relationship).