ABSTRACT

Title of Document: HPA AXIS REACTIVITY TO PSYCHOLOGICAL STRESS AMONG COCAINE DEPENDENT INDIVIDUALS

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Due to the high prevalence of illicit drug use and subsequent costs to society, researchers have focused on potential mechanisms underlying continued substance use and dependence. One mechanism of interest is the hypothalamic-pituitary-adrenal (HPA) axis and its primary hormone, cortisol. Chronic substance use is associated with elevated basal cortisol concentrations and a blunted cortisol response to stress which has been shown to predict substance use outcomes. However, little is known about the specific conditions under which drug users display a dysregulated cortisol response to stress. Therefore, the current study compared HPA axis response to two different psychological stressors among a sample of cocaine dependent individuals. Results indicated no significant differences in cortisol response across the three conditions. Future researchers should conduct larger scale studies with carefully matched healthy non-drug using participants to determine whether the absence of a significant stress effect on cortisol functioning is specific to chronic cocaine use.

HPA AXIS REACTIVITY TO PSYCHOLOGICAL STRESS AMONG COCAINE DEPENDENT INDIVIDUALS

By

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Chapter 1: Introduction

1.1 Stress and Addiction

Illicit substance use is a pervasive and costly problem in the United States. According to the 2006 National Survey on Drug Use and Health, 22.6 million people aged 12 and older met criteria for substance dependence or abuse in the past year (SAMHSA, 2007). Of those, 7.0 million people were dependent on or abused illicit substances, with 1.7 million meeting criteria for dependence or abuse of cocaine in particular (SAMHSA, 2007), making cocaine the second most prevalent illicit drug used in the United States (SAMHSA, 2008). Besides being highly prevalent, illicit substance use disorders, and cocaine use disorders in particular, come with dire public health and economic consequences including increases in unemployment (Luck, Elifson, & Sterk, 2004), homelessness (e.g. Nyamathi, Wenzel, Keenan., 1999), crime (e.g. Friedman, Glassman, & Terras, 2001), and transmission of sexually transmitted diseases (STDs) including HIV (e.g., Avants, Marcotte, Arnold, & Margolin, 2003; Ensminger, Anthony, & McCord, 1997; Miller & Neaigus, 2002).

Due to the high prevalence of illicit drug use and subsequent costs to society, it is imperative to gain a comprehensive understanding of the mechanisms involved in the initiation, maintenance, and relapse to drug addiction. A majority of theories of addiction have emphasized the role of acute and chronic stress in substance use and relapse (Conger, 1956; Khantzian, 1985; Koob & LeMoal, 1997, 2001, 2008; Levanthal & Cleary, 1980; Marlatt & Gordan, 1985; Russel & Mehrabian, 1975; Sher & Levenson, 1982; Shiffman, 1982; Solomon, 1977; Tomkins, 1966; Wikler, 1948; Wills & Shiffman, 1985; for review see Sinha, 2001, 2008). For example, Marlatt & Gordon's (1985)

relapse prevention model suggests that in addition to bio-psychosocial risk factors such as parental substance use, peer pressure, and positive expectancies regarding the benefits of substance use, poor coping resources in the face of stress serve to increase one's vulnerability to addiction. Further, the stress-coping model of addiction suggests that addictive substances function not only to increase positive affect but to decrease negative affect as well, thereby serving as an effective, yet maladaptive coping strategy (Shiffman, 1982; Wills & Shiffman, 1985). In fact, a number of models addressing the underlying mechanisms responsible for addiction and relapse to drug use have centered around negative reinforcement processes (Baker et al., 2004; Khantzian, 1985; Solomon, 1977; Wikler, 1948), which collectively emphasized that the motivational basis of addictive drug use is the reduction or avoidance of aversive internal states, including stress.

A number of studies have provided evidence for the role of psychological stress and affective distress in substance use initiation, progression to addiction, and relapse. For example, exposure to early adversity such as emotional, physical, and sexual abuse in childhood is associated with increased risk for addiction and with early initiation of substance use (Bensley et al., 1999; Dembo et al., 1988; Harrison et al., 1997; Widom et al., 1999). Similarly, frequency of trauma history is significantly greater among drug-dependent individuals (especially in women) than among non-drug users (Najavits et al., 1998). Additionally, high levels of social and environmental stress have been associated with a rapid progression in tobacco, marijuana, and alcohol use (Kaplan and Johnson, 1992; Wills et al., 1996). Further, direct exposure to an acute stressor has been shown to increase desire to smoke and the subsequent number and duration of puffs in smokers (Payne et al., 1991), as well as drug craving in cocaine users (Sinha, Catapano, &

O'Malley, 1999). Finally, self-reported stress-induced cocaine craving has been shown to predict cocaine relapse following release from inpatient treatment (Sinha et al., 2006).

Specific to relapse, not only do external stressors pose a risk to individuals in the early stages of abstinence, but the withdrawal symptoms themselves can serve as significant stressors. Studies show that negative affect often arises in addicted individuals as a result of withdrawal syndromes that cause feelings of irritability, anxiety, stress, and depression (Baker, Japuntich, Hogle, McCarthy, Curtin, 2006), and the severity of these withdrawal symptoms predict treatment outcome and relapse among smokers, cocaine addicts, heroin dependent individuals, and alcoholics (Carroll, Power, Bryant, & Rounsaville,1993; Doherty, Kinnunen, Militello, & Garvey, 1995; McLellan, Luborsky, Woody, O'Brien, & Druley, 1983; Mulvaney, Alterman, Boardman, & Kampman, 1999; Tennant, Shannon, Nork, Sagherian, & Berman, 1991). For example, findings from Miller, Westerberg, Harris, & Tonigan (1996) indicate that affective distress, specifically depression and anxiety, is a significant predictor of 6-month, post-treatment substance use outcomes. Second, recent prospective studies have shown that affective distress at the beginning of treatment and after quitting predicts poor outcome (El-Geili & Bashir, 2005; Hser, Huang, & Teruya, 2003; McMahon, 2001). Third, a number of studies have consistently reported that relapse to drug use often occurs in situations involving negative moods such as anxiety, anger, and depression (Brandon, Tiffany, Obremski, & Baker, 1990; El-Geili & Bashir, 2005; Litman, Stapleton, Oppenheim, & Peleg, 1983; Marlatt & Gordon, 1985; Tate, Brown, & Unrod, 2004).

The above research supports existing theories of addiction that emphasize the role of stress and negative reinforcement in the addictive process and relapse to drug use.

However, the above mentioned studies rely on self-report methodology, which is limited by the ability of participants to recall events and emotions that may have occurred weeks or months ago, as well as the quality of participant insight into their own emotions and behavior. Moreover, not every individual relapses to drug use in response to affective distress. Therefore, researchers have turned to biopsychological mechanisms underlying the stress response in order to further their understanding of the relationship between stress and deleterious substance use treatment outcomes. One such biopsychological mechanism of interest is the hypothalamic-pituitary-adrenal (HPA) axis.

1.2 Hypothalamic-Pituitary-Adrenal (HPA) Axis: An Overview

The HPA axis, which controls the secretion of hormones from the pituitary gland and adrenal cortex, plays a central role in mediating the body's response to stress and is extremely sensitive to inputs from the limbic system and prefrontal cortex, two brain areas that are important in modulating reinforcement and motivational processes (Li & Sinha, 2008). The anatomical structures of the HPA axis are localized in the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal cortex (Smith & Vale, 2006). In response to stress, the HPA axis is activated when corticotrophin-releasing factor (CRF), the principle regulator of HPA axis functioning, is released by neurons in the PVN (Smith & Vale, 2006). CRF then binds to receptors in the anterior pituitary where it stimulates the secretion of adrenocorticotropin hormone (ACTH) (Charmandari, Tsigos, & Chrousos, 2005; Smith & Vale, 2006). ACTH then targets the adrenal cortex where it stimulates the synthesis and release of glucocorticoids (i.e. cortisol in humans and corticosterone in rats) from the zona

fasciculate (Smith & Vale, 2006). Glucocorticoids are the final effectors in the HPA axis, regulating physiological changes in response to stress through ubiquitiously distributed intracellular receptors throughout the body (Bamberger, Schulte, & Chrousos, 1996; Kino & Chrousos, 2001; Munck, Guyre, & Holbrook, 1984). Glucocorticoids also play an important role in the termination of the stress response by providing negative feedback to inhibit the further secretion of CRF and ACTH, thereby limiting the duration of total exposure of the organism to the catabolic, lipogenic, antireproductive, and immunosuppressive effects of these glucocorticoids (Charmandari, Tsigos, & Chrousos, 2005). In the absence of any provocation, glucocorticoid secretion tends to follow a circadian rhythm, with concentrations peaking in the morning 20-45 minutes after waking and subsequently declining throughout the course of the day (Clow et al., 2004).

1.3 The HPA Axis and Addiction: Evidence from Animal Models

Findings from animal models of addiction provide substantial evidence for the role of HPA axis functioning in addiction processes. In terms of acquisition of drug self-administration, rats who respond to stressful stimuli with prolonged secretion of corticosterone have shown a higher tendency to self-administer psychostimulants, and among rats that previously did not self-administer, injections of exogenous corticosterone have been shown to facilitate the acquisition of psychostimulant self-administration (Piazza et al., 1991). Additionally, stress-induced increases in corticosterone have been shown to positively correlate with increased self-administration of low doses of cocaine following a stressor, suggesting that rats become more sensitive to the reinforcing effects of low doses of cocaine when corticosterone is elevated in response to stress (Goeders &

Guerin, 1996a). Further, increased self-administration of low doses of cocaine can be induced by pretreatment with exogenous corticosteroid injections (Mantsch et al., 1998), while adrenalectomy (which significantly reduces plasma corticosterone concentrations) prevents the acquisition of cocaine self-administration at any dose (Goeders & Guerin, 1996b). As such, animal models of cocaine initiation suggest that corticosterone both increases the reinforcing effects of psychostimulants, and is necessary for the acquisition of self-administration to occur.

As animals progress from acute to chronic administration of drugs of abuse, progressive changes in HPA axis functioning have been observed. Specifically, acute administration of drugs is associated with increased activation in HPA axis functioning during the acquisition phase (e.g., Goeders et al., 1997), while HPA activation becomes blunted with repeated drug administration (e.g., Goeders, 2002). Dysregulation is also observed following cessation from chronic drug administration, as HPA hormones including CRF, adrenocorticotropic hormone, and corticosterone are elevated in rats following acute withdrawal across drug classes (see Koob & LeMoal, 2008b). Further, CRF antagonists (which reduce HPA activation) have been shown to reverse the anxiety-like behaviors and increased drug self-administration that are observed in rats during acute cocaine withdrawal (Specio et al., 2008), and to prevent stress-induced reinstatement of drug seeking among cocaine dependent rats following extinction procedures (Erb, Shaham, & Stewart, 1998). Thus, findings from animal models of dependence and withdrawal suggest that the HPA axis becomes dysregulated over the course of addiction, and that CRF (the primary activator of the HPA axis) plays a critical role in cocaine withdrawal and stress-induced relapse. Taken together, animal models of

addiction have provided compelling evidence for the role of HPA axis functioning in addictive behavior, and have formed the basis of current neurobiological models of addiction.

1.4 The Neurobiology of Addiction: The Role of HPA Dysregulation

Neurobiological models of drug addiction, largely stemming from animal findings, hypothesize that dysregulated HPA axis functioning contributes to a state of chronic deviation of the regulatory system from its normal operating level, resulting in the establishment of a "negative affect" or psychologically distressed state during abstinence in addicts which increases the reinforcing effects of drugs and thus vulnerability to relapse (Koob, 2009; Koob & Le Moal, 2001, 2008). Specifically, when reward pathways (i.e. the mesocorticolimbic dopamine system) are activated by drug administration, opposing antireward systems (i.e. brain stress circuits involved in CRF secretion) are recruited to limit reward function and maintain homeostasis. Over the course of chronic drug administration, neuroadaptive changes occur in response to the excessive utilization of brain reward systems, including decreased activation of brain reward systems and increased activation in opposing brain stress circuits. This combination of depressed reward circuits and elevated antireward circuits is hypothesized to be the driving force motivating continued drug seeking behavior (Koob & Le Moal, 2008). Further, elevated activation of brain stress systems is hypothesized to reduce an individual's ability to adapt or cope with additional stressors during abstinence, thereby contributing to the increased risk of relapse that is observed in response to stress.

In addition to dysregulation in basal reward and antireward system functioning, the sequence of events associated with HPA reactivity to stress is also believed to be a key mechanism mediating the relationship between stress and increased drug use (Sinha, 2001, 2008). Specifically, CRF activation and subsequent release of ACTH and glucocorticoids in response to stress is associated with increases in dopaminergic neurotransmission in mesolimbic regions (Dunn, 1988; Kalivas & Duffy, 1989; Oswald et al., 2005; Piazza & Le Moal, 1996; Prasad, Sorg, Ulibarri, & Kalivas, 1995; Thierry, Tassin, Blanc, & Glowinski, 1976). Dopaminergic functioning in these regions is believed to be a key component of the brain reward systems, critical for the reinforcing properties of drugs of abuse (Di Chiara & Imperato, 1988; Koob & Le Moal, 1997; Roberts, Koob, Klonoff, & Fibiger, 1980; Taylor & Robbins, 1984). Thus, in chronic substance users who are already suffering from altered reward and antireward system functioning, dopaminergic activation in times of stress may serve to further enhance the motivational salience of illicit drug use, thereby providing the neural substrate by which stress may enhance the reinforcing effects of drugs and increase self-administration (Sinha, 2001, 2008).

Taken together, neurobiological models suggest that chronic drug use is associated with neuroadaptive changes, including decreased reward system activation and increased antireward system functioning, which may contribute to the affective distress experienced by addicts during abstinence, and that these changes may further limit one's ability to adapt or cope in the face of additional stressors during early abstinence. Additionally, research shows that HPA axis reactivity to stress is associated with increased dopaminergic activation in reward pathways, thus increasing the reinforcing

effects of drugs in times of stress and increasing the risk of stress-induced relapse to substance use. Therefore, a deeper understanding of HPA axis stress reactivity during abstinence from chronic drug use, including a more thorough characterization of the specific types of psychological stressors that are associated with a dysregulated HPA axis response to stress, is critical given that individuals in early recovery are likely to face a wide variety of psychosocial stressors that could trigger a dysregulated HPA axis response and potentially increase the risk of relapse, including reconnecting with family and friends, looking for employment, and finding housing. As such, determining whether specific stressors lead to different HPA axis responses could be useful for clarifying the specific conditions that may contribute to stress-induced relapse.

1.5 Studying HPA Reactivity to Stress in the Laboratory

Given the convergent evidence from animal models for the role of HPA axis dysfunction in drug use acquisition and stress induced relapse, researchers have placed a strong emphasis on the need to develop valid and reliable laboratory paradigms that can be used to examine these mechanisms among humans and in the clinical context (e.g., Sinha, 2009). There are a number of factors that one must consider when modeling and studying stress in the laboratory, particularly among chronic drug users. Sinha (2009) argues that "ecological relevance of the provocation method is among the more important of these factors" (p. 86). Early stress researchers argued that the biological stress response, including HPA axis activation, is nonspecific in the sense that all stressors, regardless of type, were believed to elicit the same physiological reaction (Selye, 1956). Subsequent researchers, however, have used animal models to provide substantial support

for stressor-specific pathways to cortisol activation, identifying differential neurological correlates and downstream physiological effects leading to activation of an HPA axis response depending on the stressor type (Dickerson & Kemeny, 2004; Sawchenko & Ericsson, 2000). Less is known, however, about the specific impact of different types of stressors on physiological response, including HPA axis activation, among humans. Therefore, if researchers hope to draw inferences about real-world stress responses based on their laboratory findings, such as making predictions about stress-induced relapse to drug use, it is important to utilize stressors that are ecologically relevant to real-world experiences.

Another factor to consider is the available evidence suggesting widespread individual differences in what is considered "stressful" (Cohen, Kessler, & Gordon, 1995; Lazarus, 1999). Psychological stressors influence physiological processes by activating components of the central nervous system, including the prefrontal cortex and the limbic system, that are associated with cognitive appraisals and affective responses (Dickerson & Kemeny, 2004). The extensive connections between the prefrontal cortex, limbic structures, and the hypothalamus serve as the primary pathway for activating and regulating the HPA axis (see Dickerson & Kemeny, 2004; Feldman, Conforti, & Weidenfeld, 1995; Lovallo, 1997 for reviews). These same neural pathways have been implicated in substance use vulnerability, drug craving, and stress- and drug cue-induced relapse (Li & Sinha, 2008). Thus, individual differences in neural functioning in response to stress in these regions, and subsequent variation in cognitive and affective appraisal processes, can contribute to substantial variation in the magnitude of HPA axis response to a scenario (Dickerson & Kemeny, 2004), and to variation in vulnerability to stress-

induced relapse (Li & Sinha, 2008). These individual differences become even more important to consider when attempting to differentiate HPA responses among a clinical sample, such as chronic substance users, from the "normal" responses among healthy non-drug users (Sinha, 2009). That is, between-group differences in HPA axis response to a task may be driven by differential perceptions of the "stressfulness" of the paradigm, rather than by the between-group variable of interest (i.e., chronic drug use). Therefore, use of personalized stressors that are developed on an individualized basis may be useful to insure that the stressor will induce a reliable and robust HPA axis response in the laboratory. Additionally, it is important to further account for individual differences in perceived stressfulness by including sensitive measures of affect to assess the effectiveness of the paradigm to induce a psychologically distressed state across participants.

Despite individual differences in the appraisal and perception of stressful scenarios, two specific components have been identified as being important for reliably inducing the largest HPA axis responses, as well as the longest recovery periods following stress exposure. Specifically, a meta-analysis of 208 laboratory studies of HPA axis reactivity to acute laboratory stressors revealed that cortisol responses were most reliably induced when the stress paradigm included an element of uncontrollability or social-evaluative threat (i.e., a risk of being negatively judged by others) (Dickerson & Kemeny, 2004). Laboratory stressors that included elements of both uncontrollability and social-evaluative threat elicited the largest cortisol responses of all. Although the meta-analysis excluded studies of HPA axis functioning among clinical samples, the robust findings regarding the role of controllability and social-evaluative threat suggest that

studies examining HPA axis reactivity among pathological samples, such as chronic substance users, should include laboratory stressors with these two characteristics in order to maximize the likelihood that the stressor will be perceived as "stressful" and will induce an HPA axis response that deviates from normal basal functioning.

Finally, when examining HPA axis response to stress in the laboratory, it is important to include a stable baseline measure of HPA axis functioning prior to stress exposure, as well as an adequate within-group control condition that includes no stress at all (Sinha, 2009). This final point is particularly important when attempting to draw conclusions about the extent to which a laboratory paradigm effectively induces an HPA axis response that is significantly different from what would have occurred in the absence of the stressor. Including a non-stressed control condition ensures sensitive measurement of basal HPA axis functioning and the ability to relate it to the experimental stress response.

With the above considerations in mind, the following sections will provide descriptions of some of the specific laboratory stress paradigms that have been used to assess HPA axis reactivity to stress among chronic drug users, and provide a brief review of the extant literature on HPA axis reactivity to psychological stress among chronic substance users. Because it is beyond the scope of the current study to examine differences in HPA axis reactivity across drug classes, the following literature review will focus specifically on HPA axis dysregulation in crack/cocaine dependent individuals, as will be the focus of the current proposed study.

1.6 Overview of Existing Laboratory Stress Paradigms

There are many laboratory paradigms that have been developed to study HPA axis reactivity to stress. The most well-established among them is the Trier Social Stress Task (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) which is a standardized social stress test that involves the combination of a public speaking test and a challenging math task. The entire paradigm generally lasts between 10-15 minutes depending on the specific variation that is used, and this long exposure duration may partially underlie its ability to consistently produce a robust cortisol response (Sinha, 2009). Intense physical stressors have also been utilized to induce a physiological stress response, including a 90 second cold-presser task and hyperthermia tasks; however, the effects of these paradigms on HPA axis response in particular is generally low (Dickerson & Kemeny, 2004). Further, physiological stressors have rarely been utilized in the study of HPA axis response to stress among chronic cocaine users. As such, the following review will focus on two laboratory stress paradigms that have been specifically evaluated among chronic illicit substance users.

Regarding the study of stress in the context of cocaine use, the most commonly used stressor is the personalized stress imagery procedure developed by Sinha and colleagues (unpublished manuscript) (see Section 2.4.2 for more details). Prior to experimental testing, participants complete a script development session in which are asked to describe a recent situation involving an interaction with another person, during which they were "mad, sad, or upset, and in which at that moment you felt as though you could not do much to change it". A trained researcher then develops an auditory personalized imagery script that is played back to the participant through headphones

during the experimental testing session. The participant is instructed to "Imagine the situation as if it were happening right now. Allow your body to become completely involved in the situation, doing what you would do in the real situation". Sinha and colleague's stress imagery paradigm has a number of strengths, including the personalization of the stress script to fit individual perceptions of what is considered "stressful", thus increasing the reliability of the paradigm for inducing an HPA axis response across individuals, as well as an element of "uncontrollability" given that participants are encouraged to choose a scenario in which "you felt as if you could not do much to change it". Further, stress imagery scripts have proven to be a valuable tool in the field of cocaine addiction research as both subjective and physiological responses to this stress paradigm have been shown to predict substance use outcomes (Sinha et al., 2006). However, there are some limitations in using the stress imagery paradigm. Specifically, the script development procedures are time consuming and can be resource intensive given that script development and training sessions must be conducted with all participants individually, separate scripts must be written for each individual condition, and Sinha and colleagues specifically recommend that only graduate or post-graduate level individuals conduct the script development sessions and generate the imagery scripts (Sinha, 2009; Sinha et al., unpublished manual).

Alternatively, the computerized Paced Auditory Serial Addition Task (PASAT-C; Lejuez, Kahler, & Brown, 2003) has been used in fewer studies of HPA axis functioning, but has shown considerable strengths as a stress induction strategy as well (see Section 2.4.1 for more details). The PASAT-C is a challenging mathematical processing task that is purposely set to a difficulty level that is impossible to complete successfully.

Moreover, while completing the task, participants are bombarded with constant forced failure and aversive auditory feedback. The PASAT-C clearly incorporates the crucial element of "uncontrollability" in the paradigm, given that the task is specifically designed to function at a level of difficulty that is impossible to complete successfully. It could also be argued to have a social evaluative component to the extent that participants complete the task (and invariably fail to complete it well) in front of the research assistant that administers the task. Additionally, behavioral responding to the PASAT (i.e., quitting the task; Daughters et al., 2005) and HPA axis response to the task (Daughters et al., 2009) have both been shown to predict premature dropout from residential substance use treatment. Despite these strengths, the task lacks the personalization that is inherent in the stress imagery paradigm used by Sinha and colleagues, thus leaving it open to vast individual differences in the extent to which the task is perceived as being "stressful", and potentially reducing the reliability and robustness with which it may activate the HPA axis stress response across individuals.

1.7 HPA Axis and Addiction: Evidence from Human Research

A number of studies have used the acute laboratory stress paradigms described above to examine the relationship between stress, HPA axis functioning, and relapse among drug-dependent individuals. For example, a series of studies by Sinha and colleagues utilized the personalized stress imagery script paradigm to examine the relationship between stress, drug craving, HPA axis functioning, and treatment outcome in a sample of treatment-seeking cocaine dependent individuals. As a first step, Sinha, Catapano, & O'Malley (1999) examined the effects of personalized stress imagery scripts

on cocaine craving and salivary cortisol concentrations. Ten cocaine dependent participants recently admitted to substance use treatment were recruited to participate. In each laboratory session, beginning at 3:00pm, participants were exposed to a 5-minute baseline period, two 5-minute imagery scripts (one neutral and one stressful) counterbalanced across participants, a 3-minute recovery period following each script, and a 10-minute break following the first script. Cortisol samples were collected following each baseline, imagery, and recovery period. Researchers found significant increases in cocaine craving, subjective anxiety, and heart rate, following the stressful imagery script compared to the neutral script. Researchers also reported a significant increase in salivary cortisol concentrations following the stressful imagery script; however, the reported increase was small (less than 0.1 μg/dl) compared to increases in cortisol of 0.2-0.3 μg/dl that have been reported in non-drug using participants following psychological laboratory stressors in other studies (e.g. Kirschbaum, 1993, 1995). Further, while subjective anxiety and heart rate decreased during the recovery period, cortisol concentrations continued to rise. However, both of these findings (i.e. the relatively small increase in cortisol following the stressor and the continued increase during the recovery period) may be explained by the 3-minute recovery period that was used to assess HPA functioning following the imagery scripts, which may not have allowed for a complete assessment of HPA response to the stressors. It has been found that cortisol secretion peaks 12 minutes after a stressor (Chatterton et al., 1997; Kirschbaum et al., 1993), and makes the transit from circulation to saliva in another 5 minutes (Tunn et al., 1992). Therefore, a longer post-stressor assessment duration is desirable in order to capture the entire pattern of HPA response to stress. Despite this

limitation, this study provided the first documented evidence of a relationship between stress and drug craving in cocaine dependent individuals, and suggested that the method of stress that was utilized (i.e. stress imagery) is sensitive enough to bring about neurobiological changes in the form of increased salivary cortisol concentrations in response to stress.

Building from this study, Sinha, Fuse, Aubin, & O'Malley (2000) extended their research by examining the effects of a stress imagery script and a drug imagery script on cocaine and alcohol craving, subjective ratings of anxiety, heart rate, and salivary cortisol concentrations within a sample of twenty treatment-seeking cocaine dependent participants. Laboratory procedures were very similar to the 1999 study, except participants were exposed to 3 imagery scripts in a single laboratory session (stress imagery, drug imagery, and neutral), and participants reported both cocaine and alcohol craving at each assessment throughout the session. Similar to the 1999 study, researchers reported increases in cocaine and alcohol cravings, subjective anxiety ratings, heart rate, and salivary cortisol concentrations following the stress and drug-cue imagery compared to neutral imagery. Although this study also faces the limitation of short recovery periods following stressors, findings suggested that psychological distress-induced and drug-cue-induced cravings are both associated with similar patterns of HPA axis activation.

A third study by Sinha et al (2003) utilized a longer recovery period as they again employed both stress- and drug-cue imagery scripts to examine HPA and sympatho-adrenal-medullary responses to stress via blood samples for 75 minutes following exposure to the stressors. Fifty-four cocaine dependent individuals seeking treatment were recruited to participate in three laboratory sessions over the course of three days,

beginning in the second week of their treatment stay. Each laboratory session began at 7:45am at which time participants were allowed a final smoke break. By 8:15am a nurse brought the participants into the testing room and inserted a catheter into the participant's arm in order to obtain blood samples throughout the testing session. Participants were then given a 1-hour adaptation period during which they were instructed to relax. Beginning at 9:30am, participants were exposed to a 5-minute imagery script, during which their pulse was continuously measured and their blood pressure was measured four times. Cocaine craving, anxiety, pulse, blood pressure, and blood draws were made immediately following the imagery script, and every 15 minutes thereafter for a total of 75 minutes.

Similar to the 1999 and 2000 studies, Sinha and colleagues (2003) found significant increases in cocaine craving, anxiety, pulse, and blood pressure following the stress and drug imagery scripts compared to the neutral script. Plasma cortisol levels decreased following all three conditions; however, cortisol concentrations decreased significantly less following the stress and drug imagery scripts compared to the neutral scripts, suggesting a significant activation of the HPA axis in response to both the stress and drug-cue imagery conditions compared to the neutral condition. Although cortisol concentrations following both of the experimental conditions were significantly higher than concentrations following the neutral condition, the overall pattern of HPA reactivity to the stress and drug-cue imagery scripts (i.e., the decrease in cortisol following script exposure) was unexpected, and may provide additional support for the role of HPA axis dysfunction in chronic cocaine users during early abstinence.

A similar dysfunctional pattern of HPA axis reactivity to a laboratory stressor was shown by Harris and colleagues (2005) in a sample of cocaine and methamphetamine dependent individuals. Specifically, in the only study to our knowledge to examine HPA reactivity to two different psychological stress paradigms within the same sample of cocaine/stimulant users, Harris and colleagues (2005) recruited 24 cocaine- or methamphetamine-dependent participants with a median of 18 days since last drug use to examine the effects of repeated laboratory stressors on psychological, physiological, and hormonal measures. In laboratory sessions beginning at 1:30PM, researchers administered a stress-imagery task using the same protocol as Sinha et al. (1999), and the TSST two times each over the course of 4 sessions spaced apart by at least one day each. Researchers found no significant changes in cortisol concentrations following either TSST administration, and significant decreases in cortisol concentrations following both stress imagery scripts; however, no control condition (i.e. no stressor) was utilized to which these findings may be compared. Therefore, it is unclear what the pattern of cortisol concentrations would have looked like in the absence of stress. Additionally, the primary aim of this study was to assess the effect of repeated stress exposure on HPA axis response to the tasks; therefore, analyses were only conducted to compare HPA axis response to the first stress imagery administration versus the second stress imagery administration, and the first TSST administration versus the second TSST administration. No analyses were conducted to test for differences in HPA axis response to the two different tasks, leaving unanswered questions about whether the two tasks differed significantly from one another in their ability to induce an HPA axis response.

Lovallo and colleagues (2000) reported similar findings to Harris and colleauges (2005) using a stressor similar to the TSST in a sample of control, alcohol dependent, and alcohol + stimulant (cocaine and/or amphetamines) dependent participants who were abstinent for between 3-4 weeks. Participants were exposed to a 20 minute public speaking task and a neutral resting condition counterbalanced across two separate testing sessions, both running from 7:00am to 9:30am. Researchers found the expected increase in salivary cortisol concentrations following the stressor in control participants, but no significant change in cortisol concentrations among the alcohol dependent and alcohol + stimulant dependent participants.

Finally, Daughters and colleagues also found evidence of a dysregulated pattern of HPA axis stress reactivity in a sample of illicit substance users (47.1% crack/cocaine dependent) in residential substance use treatment following exposure to computerized psychological stressors (Daughters, Richards, Gorka, & Sinha, 2009). Daughters and colleagues used the PASAT-C and one other computerized psychological stress task (the Mirror Tracing Persistence Task; MTPT-C) to examine the effects of emotional distress on HPA axis reactivity in illicit substance users in their second week of residential substance use treatment. Researchers reported a decrease in salivary cortisol levels following the stressors; however, similar to Harris and colleagues (2005), no neutral condition was employed in order to examine how HPA reactivity to stress compares to normal, non-distressed functioning, making these findings difficult to interpret. That said, these findings appear to provide yet another example of HPA axis dysregulation in illicit substance users during the early stages of abstinence.

1.8 Summary and Significance

Due to the prevalence and public health cost of drug addiction, it is imperative that researchers gain a deeper understanding of the mechanisms underlying substance use and relapse. One mechanism of interest is the role of dysregulated HPA axis functioning in response to psychological stress. Neurobiological theories, largely based on animal models of addiction and relapse, suggest that HPA axis dysfunction is a consequence of neuroadaptive changes resulting from chronic substance use, and that these changes in HPA functioning limit one's ability to cope with additional psychological stress during an abstinence attempt and may increase the reinforcing effects of drug administration during periods of elevated distress, thereby increasing the risk of stress-induced relapse. In order to test these theories in human illicit drug users, laboratory stress paradigms have been developed to model stress in order to elucidate potential mechanisms underlying the relationship between stress and addiction, and translate these findings into novel treatment interventions for human drug users. A variety of stress paradigms have been used to examine HPA axis response to stress among illicit drug users, with findings largely corroborating animal models of addiction such that chronic drug use is associated with a blunted cortisol response to psychological stress (Daughters et al., 2009; Harris et al., 2005; Lovallo et al., 2000; Sinha et al., 1999; 2000; 2003), and a larger HPA axis response to stress is associated with poorer substance use outcomes (Daughters et al., 2009; Sinha et al., 2006).

Despite the advances that have been made in our knowledge of the physiological underpinnings of the relationship between stress and illicit substance use, unanswered questions remain. As one example, to our knowledge, no study to date has directly

compared HPA axis response to different types of psychological stressors among chronic drug users. Given the relationship between HPA axis dysfunction and substance use outcomes, an important aspect of modeling stress among drug users in the laboratory is to understand the extent to which HPA axis dysregulation is stressor-specific, or generalized across different types of stressful scenarios. Clearly, a direct comparison of HPA axis reactivity to different types of laboratory psychological stressors among a sample of chronic substance users who are characterized by stress dysregulation would be a critical advancement in the field of addiction neurobiology, with important clinical implications.

In a first step to address this specific gap in the literature on HPA axis functioning among substance users, the current study seeks to examine the pattern of HPA axis response to two different previously validated psychological stressors, compared to a neutral no-stress condition, among cocaine-dependent individuals in residential substance use treatment. Examining HPA axis response to different types of psychological stress among chronic drug users represents a first step toward identifying the specific conditions under which individuals may be at the greatest risk of stress-induced relapse. Additionally, this line of research could be extended in the future to examine the links between the cognitive and affective responses associated with specific stressful circumstances, the neural substrates of these responses, and the activation of the HPA axis. Both of these long-term research efforts have the potential to substantially inform the development of novel behavioral and pharmacological treatments designed to target the processes that may serve to increase the risk of stress-induced relapse under specific conditions.

1.9 Current Study

The current study aims to directly compare HPA axis reactivity among cocaine dependent individuals to three different conditions: a personalized stress imagery script, a personalized neutral "no stress" imagery script, and a non-personalized computerized stress task. We will use three different approaches for analyzing the cortisol data collected during each experimental condition in order to fully characterize the specific pattern, magnitude, duration, and intensity of the cortisol response across the three conditions. Moreover, including multiple analytic approaches to examining the cortisol data will provide information about the reliability and the robustness of the differential effects of the three experimental conditions on HPA reactivity. In doing so, we hypothesize that the personalized stress imagery script will induce a greater salivary cortisol response than the personalized neutral imagery script, the computerized psychological stress task (i.e., the PASAT-C) will induce a greater salivary cortisol response than the personalized neutral imagery script, and the personalized stress imagery script will induce a greater salivary cortisol response than the PASAT-C. These relationships between the three conditions will be manifested in the following ways:

Hypothesis 1: Linear mixed effects (LME) analyses predicting salivary cortisol concentrations across time following exposure to the experimental conditions will reveal:

Hypothesis 1a: Significantly greater cortisol concentrations across time points during the stress imagery condition as compared to neutral imagery.

Hypothesis 1b: Significantly greater cortisol concentrations across time points during the PASAT condition as compared to neutral imagery.

Hypothesis 1c: Significantly greater cortisol concentrations across time points during the stress imagery condition as compared to the PASAT.

Hypothesis 2: LME analyses predicting peak cortisol response to the three conditions will reveal:

Hypothesis 2a: Significantly greater peak cortisol response to the stress imagery condition as compared to neutral imagery.

Hypothesis 2b: Significantly greater peak cortisol response to the PASAT condition as compared to neutral imagery.

Hypothesis 2c: Significantly greater peak cortisol response to the stress imagery condition as compared to the PASAT.

Hypothesis 3: LME analyses predicting area under the curve (AUC) values across the three conditions will reveal:

Hypothesis 3a: Significantly greater AUC values in response to the stress imagery condition as compared to neutral imagery.

Hypothesis 3b: Significantly greater AUC values in response to the PASAT condition as compared to neutral imagery.

Hypothesis 3c: Significantly greater AUC values in response to the stress imagery condition as compared to the PASAT.

1.10 Methodological Considerations in HPA Axis Research

When conducting and evaluating HPA axis research, there are a number of methodological and individual difference factors that may systematically influence salivary cortisol concentrations. Methodologically, it is important to consider the effects

of diurnal variation on salivary cortisol sampling. Specifically, cortisol secretion tends to follow a distinct circadian rhythm with cortisol levels peaking in the morning within 20-45 minutes of awakening (Stone et al., 2001). The subsequent decline is sharpest during the morning hours, and becomes less steep over the course of the day (Lovallo, 2006). This steep morning decline in cortisol concentrations may explain the extremely dysregulated stress response that was reported by Sinha and colleagues (2003; 2006). Due to this wide range of diurnal variation, it is crucial that researchers carefully control and document the time of sampling across participants, and choose a time in the diurnal cortisol curve in which steep changes are not the norm, in order to avoid the confounding influence of normal diurnal variation on cortisol reactivity to stress. As such, the current study collected all cortisol samples in the evening when cortisol concentrations have reached their circadian nadir.

Within individuals, factors such as age and gender may exert systematic variability on cortisol findings. Older individuals (>70 years old) have shown higher basal levels of salivary cortisol and reduced cortisol reactivity to stress compared to younger individuals (Nicolson et al., 1997). Gender differences have also been found, with researchers reporting a smaller salivary cortisol response to psychological stress in both healthy women (Kirschbaum, et al., 1999) and cocaine dependent women (Fox, Garcia et al., 2006) than in men. Further, menstrual cycle phase and use of oral contraceptives have also been found to systematically influence salivary cortisol response to psychological stress, with women in the luteal phase showing greater cortisol reactivity than women in the follicular phase, and women currently taking oral contraceptives showing a smaller salivary cortisol response to psychological stress compared to women

who are not (Kirschbaum, et al., 1999). Therefore, the current study controlled for these factors by limiting the age range to 18-55, and excluding females from participating.

Additional factors such as psychopathology, medications, and nicotine use may also influence findings. A number of psychological disorders have been associated with alterations in HPA axis functioning, including hypocortisolism in adults with PTSD (see Yehuda, 2002 for review) and hypercortisolism in depressed individuals (e.g. Galard et al., 1991; see Carroll & Mendells, 1976 for an early review). Further, medications prescribed to treat psychopathology may alter HPA axis functioning, with individuals taking benzodiazepines showing an attenuated HPA axis response to psychological stress (Fries, Hellhammer, & Hellhammer, 2006). Finally, increased basal salivary cortisol concentrations and reduced cortisol reactivity have been documented in habitual smokers (al' Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Steptoe & Ussher, 2006; Tersman, Collings, & Eneroth, 1991). As such, the current study addressed these issues by excluding individuals with Axis I psychopathology, as well as individuals who were prescribed psychotropic medications. Given the high frequency of nicotine use in the residential treatment center, it was not feasible to exclude habitual cigarette smokers. Therefore, steps were taken to assess smoking status through both self-report and biological methods to test for a significant effect of nicotine use on HPA axis functioning.

Finally, there are many mathematical and statistical approaches that can be used to examine time-series cortisol data, including assessing the general pattern of cortisol secretion across time points using the general linear model, calculating the peak cortisol response to stress for each condition in order to test for differences in the magnitude of

change from baseline, and calculating area under the curve (AUC) for each condition in order to measure the total cortisol output over time (see section 2.6 for more details). Because each of these approaches captures slightly different information pertaining to the HPA axis response to stress, it may be useful to use more than one approach to examine cortisol data in order to gain a better understanding of the reliability and robustness of any significant effects on cortisol functioning. As such, the current study will test for differences across conditions by using all three approaches.

Chapter 2: Research Design and Method

2.1 Overall Design

A within subjects 3x5 repeated measures design was used with condition (3; PASAT, Stress Imagery Script, and Neutral Imagery Script) and time-point (5; post-stress exposure cortisol assessment time points) as the repeated measures factors. The PASAT, stress imagery, and neutral imagery conditions were presented on separate testing days with only one stimulus presentation per day. Every attempt was made to conduct the three laboratory sessions on consecutive days for each participant, unless there was a scheduling conflict with the research staff or the participant (mean number of days to complete all three laboratory sessions: 4.0; *SD*= 1.7). The order of PASAT, stress imagery, and neutral imagery conditions was assigned randomly. Testing sessions commenced an average of 16.63 days (SD=7.15) after admission to the residential treatment center to allow for normalization of neurobiological changes associated with acute cocaine abstinence. Participants remained blind to the order of the testing condition until their arrival in the testing room each day.

2.2 Recruitment

Participants (*n*=22) recruited for this within subjects study were inner-city substance users living in a residential substance use treatment facility located in Washington DC. Treatment at this center involves a mix of strategies adopted from Alcoholics and Narcotics Anonymous as well as group sessions focused on relapse prevention and functional analysis. When needed, detoxification from an outside source is required prior to entry into the center. Typical treatment lasts between 30 and 180 days

and aside from scheduled activities (e.g., group retreats, physician visits), residents are not permitted to leave the center grounds during treatment. Complete abstinence from drugs and alcohol is required upon entry into the center and throughout the duration of the program, with the exception of nicotine. Regular drug testing is provided and any drug or alcohol use results in immediate dismissal from the center; therefore, acute drug effects likely did not influence the current findings.

Within the first week of admission to the treatment center, all individuals entering the center had a screening assessment session in which they were given the SCID-IV-NP (First et al., 2002) and a standard drug use history interview (DUH; e.g., Babor & Del Boca, 1992; Grant, Contoreggi, & London, 2000; Daughters, Lejuez, Bornovalova, et al., 2005). Individuals who conducted the intake assessments were trained interviewers predominantly independent of the current study. Recruitment for the study was based on the initial assessment. Inclusion criteria consisted of the following: 1) age 18-55 years of age; 2) male; and 3) DSM-IV diagnosis of current cocaine dependence as measured by the SCID-IV-NP (First et al., 2002). Clients were excluded from the study if 1) they met DSM-IV criteria for opiate abuse or dependence (as measured by the SCID-IV-NP, First et al., 2002); 2) met DSM-IV diagnostic criteria for any current Axis I disorder or psychotic symptoms (as measured by the SCID-IV-NP, First et al., 2002); 3) reported current use of psychotropics or corticosteroids; and 4) reported any current major medical conditions, including but not limited to neurological illness, diabetes, HIV/AIDS, autoimmune disorders, and cardiovascular disease.

Residents at the treatment center who met initial eligibility requirements based on the SCID-IV and their drug use history were approached by a research assistant on the

following Friday afternoon (no center implemented treatment groups are scheduled for these times). The research assistant asked the resident if they would like to participate in a study that focuses on the relationship between mood and substance use. They were told that they would complete a screening assessment that day that would last up to 1.5 hours in order to confirm their eligibility. Study staff informed participants that upon confirmation of study eligibility and completion of the baseline session, they would be scheduled for a one hour training session to learn the study procedures, and three 1.5-hour testing sessions, all to be completed in the following week. Participants were informed that not all individuals who participate in the screening would be chosen to complete the remainder of the study. Participants were also informed that payment in the form of grocery store gift cards would be provided for all research assessments ($15 for each study session, plus a $20 bonus for completing all research assessments). Individuals who agreed to participate in the study provided informed consent and were assigned subject numbers that were listed on all data forms. Given issues of reading comprehension, efforts were made to ensure that participants understood all facets of the consent form and the study itself. All testing sessions were held in private rooms at the residential treatment facility during designated “free time” periods at the center.

After obtaining informed consent, the baseline session commenced, beginning with a thorough Health Screening Questionnaire (HSQ) and a Medication Questionnaire. Once participants were determined to meet all eligibility criteria on the basis of their self-reported health status and list of current medications, the session continued with a packet of questionnaires and an imagery script development interview (outlined below). If participants declined participation (which occurred twice during recruitment), or failed to

meet eligibility criteria based on the results of their HSQ and Medication Questionnaire (which happened three times during recruitment) they were able to return to unsupervised free time activities to prevent any knowledge by treatment center staff as to whether or not they had chosen to participate, thereby limiting any appearance of coercion to participate. Individuals who were dismissed from the study due to ineligibility were compensated $10 in grocery store gift cards before returning to center activities.

2.3 Testing Procedures

2.3.1 Session 1 (Consent, Imagery Script Development, and Questionnaires)

Once consent was provided, participants began the screening assessment (Session 1) in a private room. Session 1 began with the HSQ and Medication Questionnaire (as outlined above) in order to confirm their eligibility, as well as a packet of baseline self-report measures which included the demographics questionnaire. A member of the research staff was available at all times to provide instruction and answer questions. As a part of a larger study, participants were also administered the PASAT and given the option to quit the task in the final round in order to assess distress tolerance. Distress tolerance data collected at baseline was not analyzed for the current study.

Following completion of the baseline measures, eligible participants were asked to recount a recent stressful event which was tape recorded and used for the stress imagery script development (See section 2.4.2). They also reviewed a list of standard neutral scripts and selected one to be used for the neutral script development (See section 2.4.3). Participants were then scheduled to participate in the training session and testing phase of the study in the following week. Participants were given a form outlining the

various procedures to follow on each day of each testing session in which cortisol was collected. Namely, they were given the time at which they were requested to eat their final meal and smoke their last cigarette before attending the testing session. Further, they were reminded not to consume any caffeine and asked to avoid physical exercise for 4 hours prior to testing. In addition to making these requests, we also collected their self-reported adherence to these requests, as well as exhaled carbon monoxide levels, at the beginning of each testing session in order to assess the effects of any deviations from the study procedures statistically. The order of the testing sessions was randomized across participants, and the participants were blinded to experimental condition until the time they arrived in the testing room each night.

2.3.2 Session 2 (Imagery and Relaxation Training Session)

To further reduce the variability in imagery ability, participants completed a relaxation and imagery response training session, as recommended by Sinha (unpublished manual). Imagery training has been found to reduce the effects of variability in baseline imagery ability across participants (Miller et al., 1987). The relaxation training consisted of a 20-minute progressive muscle relaxation procedure that allowed the participants to achieve a relaxed state and focus on the imagery training that followed.

The imagery training involved participants visualizing some commonplace scenes as they were presented to them. The scenes were neutral and non-emotional in content, such as reading a popular magazine. Following the imagery, the participants were asked questions about the visualization and given pointers regarding the process of imagining the scene. The participants also imagined scenes that were non-emotional but physically

arousing in nature, such as doing sit-ups in gym class. Following these scenes, participants were asked whether they noticed any changes in their physiological response, such as change in heart rate or change in breathing. Once again, pointers with regard to imagining the situation "as if it were happening right now" were presented. The participant's active participation in the imagery was emphasized. The relaxation and imagery training procedure lasted approximately one hour and ensured that all participants were trained on the method of generating an image and maintaining it for the assigned time period. After the image period for each scene, participants were administered the Imagery Vividness Scale (IVS) on which they made a rating on a 10-point visual analog scale (with 1= not at all clear, and 10=perfectly clear – "as if it were happening now") for how "clearly and vividly" they were able to imagine the situation.

2.3.3 Sessions 3, 4, & 5 (Cortisol Testing Sessions)

Testing sessions were run after dinner at the residential treatment center (See *Figure 1* for a diagram of testing session procedures). Participants were asked to smoke their last cigarette 60 minutes before each testing session commenced in order to control for the effects of acute nicotine administration. Upon arrival in the testing room, participants completed a protocol compliance interview and provided exhaled carbon monoxide levels. Next, they were walked through a 5-minute muscle relaxation exercise, followed by a 5-minute rest period during which they were asked to relax and focus on their breathing, for a total of 10 minutes of relaxation. The first saliva sample was taken immediately following the deep breathing exercise and the second was taken following another 10 minute rest period. The mean of these two samples represent the baseline, or

"pre-stress" cortisol concentration for each testing session. Participants then completed one of the three experimental conditions (PASAT, Stress Imagery Script, or Neutral Imagery Script), immediately followed by saliva sample collection. Participants were asked to fill out the PANAS before and after each task in order to measure subjective levels of distress. Exposure to the experimental condition was then followed by 40 minutes of rest, during which cortisol samples were collected every ten minutes. During this time, participants sat comfortably in a cushioned chair and read magazines. After 40 minutes passed, the participants again filled out the PANAS to ensure that all participants reported levels of distress at the end of the session that were comparable to baseline levels. Participants also filled out a Nicotine Withdrawal Scale at the beginning and end of each session in order to assess for the acute effects of nicotine withdrawal on cortisol reactivity in the final analyses. Once all measures were complete, the participants were compensated and thanked for their time, and reminded of the date and time of their next testing session visit. The order of the tasks was randomized across all participants. Participants were coded based on the order in which they received the tasks in order to analyze the final data for any potential order effects.

2.4 Experimental Conditions

2.4.1 PASAT

The computerized psychological stress task was a modified version of the computerized Paced Auditory Serial Addition Task (PASAT-C; Lejuez, Kahler, & Brown, 2003). The PASAT-C (see *Figure 2*) has been shown to increase subjective stress levels, and persistence on this task has been reported to predict length of smoking

cessation attempt (Brown et al., 2002), length of previous abstinence attempt among illicit drug users (Daughters, Lejuez, Kahler, et al., 2005), and dropout from substance abuse treatment (Daughters, Lejuez, Bornovalova, et al., 2005). For this task, numbers are sequentially flashed on a computer screen, and participants are asked to add the currently presented number to the previously presented number before the subsequent number appears on the screen. As the task is designed to limit the role of mathematical skill in persistence, the presented numbers only range from 0 to 20, with no sum greater than 20. Participants are told that their score increases by one point with each correct answer and that incorrect answers or omissions will not affect their total score. There are three levels of difficulty, lasting two minutes each. The first level begins with a 5-second latency in between number presentations and titrates this latency based on performance (correct answers reduce the latency by 0.5 seconds whereas incorrect answers or nonresponses increase the latency by 0.5 seconds). Titration in this manner allows for determination of the average latency between number presentations for each participant, which is used to limit confounds associated with differential math skill and reaction time. The second level is more difficult, as the latency between number presentations is set to 75% of the average latency that was determined in the first level. The final level utilizes an extremely difficult challenge latency, which is set to 50% of the average latency from level one. Further, the participant is inundated with constant aversive auditory feedback in the form of explosions for each incorrect answer or missed response. To make the task even more distressing, participants are told that their performance on the task influences how much money they will get at the end of the session. In previous studies, and during the baseline session of the current study, participants were given the option to quit the

task at any time during the third round, and distress tolerance was indexed as latency in seconds to task termination. However, during the cortisol testing sessions in the current study, the PASAT was used only as a means to induce cortisol reactivity to stress; therefore, participants were not given the option to quit. All participants completed the PASAT for the full task duration.

2.4.2 Stress Imagery Scripts

Prior to participating in the actual testing sessions, a personalized stress imagery script was developed for each participant, using the same script development protocol as Sinha and colleagues (unpublished manual). That is, participants were asked to recount a recent stressful situation, not involving drug use. Participants were encouraged to think of situations that were interpersonal in nature, that made them "sad, mad, or upset" and in which, at that moment, they felt as if they "could not do much to change it" (Sinha et al., unpublished manual). After describing the situation to the researcher, participants were asked to rate their level of distress during the situation on a 10-point Likert type scale, and only situations that were rated as 8 or higher were used. Examples of situations that were used for script development include a break-up with a significant other, an argument with a friend or family member, or unemployment related stress such as being fired or laid off from a job. Participants were asked to describe all of the details that they could remember about the situation, including thoughts, behaviors, and physiological reactions to the stressor (e.g., pounding heart, muscle tension, shortness of breath). A 6-minute script was then developed based on the participant's description of the situation and was recorded to audio tape for use during the testing session. For the actual task

administration, participants were provided with headphones and given the following instructions, “Close your eyes and imagine the situation being described, as if it were happening right now. Let your body and mind get completely involved in the situation, doing what you would do in the real situation. Continue imagining until I tell you to stop.” The length of each script was approximately 6 minutes followed by 30 seconds of continued imagining, for a total imagery period of 6.5 minutes. All participants completed the IVS immediately following script administration to assess their ability to participate fully in the imagery and become completely immersed in the scene.

2.4.3 Neutral Imagery Scripts

A neutral imagery script was also developed for each participant prior to participation in the testing sessions. Each participant was provided a list of common relaxing situations, such as going for a walk alone, quietly reading or listening to music, or taking a hot shower or bath. Participants chose one of the relaxing scenarios and recounted a recent time when they experienced a similar source of relaxation in their own life. Again, participants were asked to recount as many details as possible about the situation, including their thoughts, feelings, and physiological responses. Neutral imagery scripts were developed and administered using the same procedures as the stress imagery scripts.

2.5 Measures

Domain	Measure	Description
Demographics, and Screening Measures	Demographics Questionnaire	Basic information on age, gender, race, education level, marital status, and total household income
	SCID-IV-NP	Diagnostic information (All Axis I Psychopathology)
	DUH	Assessment of drug use history
	Medication Questionnaire	Frequency, dosage, and type of various medications, including psychotropic, non-psychotropic, and over-the-counter medication
	Health Screening Questionnaire	Assessment of additional variables that may influence HPA axis functioning including sleep quality, BMI, caffeine consumption, history of immune dysfunction.
Affective and Imagery Vividness Measures	PANAS	Assesses state level positive and negative affect
	IVS	Single item Likert-type scale used to assess how vividly participants imagined the scripts
Smoking	NWQ	Assesses severity of withdrawal symptoms
Biological Measures	Salivary Cortisol	Assessment of HPA functioning
	Carbon Monoxide	Assessment of expired air carbon monoxide levels

2.5.1 Clinical Interview and Questionnaires

1. Demographic Questionnaire. Subjects provided basic demographic information including age, gender, education level, occupation, home occupants, and socioeconomic status.

2. Structured Clinical Interview for DSM-IV (SCID-NP, non-patient version, First, Spitzer, Gibbon & Williams, 2002). Diagnostic inclusions/exclusions, including Axis I diagnoses and substance use disorders were determined using the SCID-NP, a measure with demonstrated reliability (First, Spitzer, Gibbon & Williams, 2002). The SCID-NP (non-patient) version was used because subjects in the study are not identified as psychiatric patients.

3. Drug Use History. As a measure of substance use frequency and severity, polydrug use was assessed with a standard Drug Use History Questionnaire (e.g., Babor & Del Boca, 1992; Grant, Contoreggi, & London, 2000; Daughters, Lejuez, Bornovalova, et al., 2005). Specifically, participants were asked if they have ever used a particular substance in their lifetime, how often they used it in the past year prior to treatment, and how often they used the substance during the period of their life when they were using it most frequently. The substance categories included: (a) marijuana, (b) alcohol, (c) cocaine (not crack), (d) crack, (e) ecstasy, (f) Methamphetamines, (g) sedatives, (h) heroin, (i) illegal prescriptions, (j) and PCP.

4. Medication Questionnaire. Self-report assessment of which medications participants were taking currently (if any), how long they had been taking these medications, as well as dosage and frequency. Medication was coded as a dichotomous variable, and divided into status on the following: selective serotonin reuptake inhibitors, SSRIs; anxiolytics; atypical antipsychotics; other psychotropic medications, and other medications including over-the-counter antihistamines, sleep aids). Patients were excluded if they endorsed current use of any psychotropic medications or corticosteroids.

5. Health Screening Questionnaire. This questionnaire was used to assess additional variables that can influence HPA axis functioning including sleep quality, BMI, caffeine consumption, and history of immune dysfunction. Further, a modified version was readministered at the beginning of each testing session to check for compliance with the study protocol.

6. Positive and Negative Affect Scale (PANAS; Watson, Clark Tellegen, 1988). This 20-item measure was used to assess both positive (PA) and negative (NA) affect. PA

reflects the extent to which a person feels enthusiastic, alert, and active. NA reflects a person's subjective distress and encompasses a number of negative mood states including anger, contempt, disgust, and guilt. NA is related to self-reported stress and poor coping (Clark & Watson, 1988) and frequency of unpleasant events (Stone, 1981). The PANAS was administered immediately before and after each task to assess the subjective level of distress experienced in response to the tasks.

7. *Imagery Vividness Scale (IVS; Sinha et al., unpublished manual).* The IVS is a single-item Likert scale that was designed to measure the extent to which participants were able to imagine the personalized imagery scripts vividly. After completing each imagery script, participants were asked to rate on a scale of 1 to 10 how clearly they were able to imagine the scene. The IVS was used after each imagery exercise during the training session, and after each personalized imagery script on the testing nights of the study.

8. Nicotine withdrawal symptoms were assessed at the beginning and end of each cortisol testing session using a reliable and sensitive, 10-item scale (Hughes & Hatsukami, 1986). This measure will be used to control for nicotine withdrawal symptoms, including craving, as they have been associated with decreases in cortisol concentration and are likely to occur over the course of the long testing session.

2.5.2 Biological Measures

1. Salivary Cortisol. Cortisol, a glucocorticoid, is the primary biological marker that is used to study the stress response in humans. In recent decades, salivary cortisol has emerged as a reliable, non-invasive, and inexpensive way of evaluating the human stress

response (Mandel, 1993). Studies have consistently shown a significant relationship between salivary cortisol levels and cortisol concentration in the blood stream (Burke et al., 1985; Chatterton et al., 1997; Fox et al., 2006; Heiser et al., 2000; Tunn et al., 1992), providing support for the use of salivary cortisol as a measure of HPA axis functioning. Cortisol secretion peaks approximately 12 minutes after a stressor (Chatterton et al., 1997; Kirschbaum et al., 1993), and makes the transit from circulation to saliva in another 5 minutes (Tunn et al., 1992). The reliability of salivary cortisol has been examined specifically in cocaine users, and has been found to correlate significantly with plasma cortisol levels at multiple time points throughout the day (Fox et al., 2006), thus providing further evidence of the utility of salivary cortisol as a reliable measure of HPA functioning in cocaine users.

In the current study, samples were collected using supplies purchased from Salimetrics®. To collect the samples, participants were asked to place a small inert polymer cylindrical swab underneath their tongue for 2 minutes. The participants then removed the saturated swab from their mouths and placed it into a labeled resealable polypropylene tube. Immediately after each testing session, all salivary cortisol samples were stored in a deep freezer at CAPER until they were shipped for analysis. All cortisol samples were sent to the Biochemistry Laboratory at the University of Trier, where they were assayed in duplicate using a time-resolved immunoassay with fluorescence detection (for technical details see Dressendörfer et al., 1992). The mean and coefficient of variance (CV) were computed for each duplicate assay. Samples that showed a CV higher than 15%, or cortisol values that were outside of a defined range (+/- 2SD), were

reanalyzed. The results of each assay were recorded in an excel spreadsheet which was emailed directly to the primary investigator from the University of Trier.

2. Expired air carbon monoxide. Carbon monoxide analysis of breath samples was assessed with a Vitalograph Breathco carbon monoxide monitor (Jarvis et al., 1987). Expelled carbon monoxide concentrations were used to assess acute cigarette exposure at the beginning of each testing session, and was examined as a potential covariate.

2.6 Statistical Analyses

To address the primary study hypotheses that cocaine dependent individuals will exhibit (1) a greater salivary cortisol response to the personalized stress imagery script relative to the neutral imagery script; (2) a greater salivary cortisol response to the PASAT as compared to the neutral imagery script; and (3) a greater salivary cortisol response to the personalized stress imagery script relative to the non-personalized PASAT, a number of steps were undertaken as outlined below. First, we conducted a manipulation check to examine whether exposure to the two experimental stressors effectively induced increased levels of subjective distress, while exposure to the neutral condition had no significant effect on subjective distress. To do this, we conducted separate repeated measures ANOVAs for each experimental condition to test for differences between pre- and post-task ratings of negative affect on the PANAS. In order to test whether participants were equally able to actively participate in the imagery procedures across both the stress and neutral imagery conditions, we conducted a repeated measures ANOVA to test for differences in IVS ratings across the two imagery sessions.

The next step included an examination of potential covariates. This included a comparison of baseline (i.e., pre-stress) salivary cortisol concentrations across the three nights of testing to test for potential differences in cortisol functioning that were not related to experimental condition exposure. Additionally, we examined the effect of testing order on cortisol concentrations. We also tested for significant differences in exhaled CO concentrations, baseline (i.e., "pre-stress") levels of self-reported emotional distress as measured by the negative affect subscale of the PANAS at the beginning of each session, and differences in nicotine withdrawal symptoms across sessions as measured by the NWQ. Any potential covariates that were found to differ significantly across the three nights of testing were included as covariates.

Next, linear mixed effects models (LME; Laird & Ware, 1982; Singer & Willett, 2003) were implemented using the PASW software package to test the study hypotheses. LME is particularly well suited for designs that call for repeated measurements within the same individual that can lead to multicollinearity between the measurements. Additionally, such models are useful when there is missing data, as they prevent exclusion of subjects with missing data points (Littell et al., 1996). Because the raw cortisol values, peak cortisol values, and AUC variables all yielded substantially positively skewed distributions, log10 transformations were used to normalize the distributions of the cortisol outcome variables (Tabachnick & Fidell, 2001). In all LME analyses that included a linear effect of time, we centered the time variable for consistency and clarity of interpretation.

2.6.1 Salivary Cortisol Concentrations across Time

The first LME was conducted with the log10 transformed cortisol concentrations as the dependent variable, and included within subjects factors of Condition (3 levels; PASAT, Stress Imagery, Neutral Imagery) and Time (centered) (5 levels; immediately post-task, +10min, +20min, +30min, +40min) as the fixed effects, and Subjects as the random effect. Between subjects factors of relevant covariates, including testing order and baseline (pre-stress) cortisol concentrations, as well as other relevant covariates, were also included as fixed effects. Post-hoc contrasts were used to assess the subhypotheses that the stress imagery condition would elicit significantly greater cortisol concentrations than neutral imagery, the PASAT would elicit significantly greater cortisol concentrations than neutral imagery, and the stress imagery would elicit significantly greater cortisol concentrations than the PASAT.

2.6.2 Peak Cortisol Response

Next, we calculated peak cortisol responses across each night of testing for all participants. Specifically, we calculated the difference between baseline cortisol concentrations (i.e., the mean of the two pre-stress cortisol assessments) and the greatest cortisol concentration recorded during the 40 minutes of rest following each task. This method was utilized in order to account for individual differences in the time it takes to reach peak response to the stressor. To test the effect of experimental condition on log10 transformed peak cortisol values, a linear mixed effects model was implemented with the within subjects factor of Condition (3 levels; PASAT, Stress Imagery, Neutral Imagery) and between subjects covariate factors included as the fixed effects, and Subjects as the

random effect. Post-hoc contrasts were used to assess the specific subhypotheses that the stress imagery condition would elicit a significantly greater peak cortisol response than neutral imagery, the PASAT would elicit a significantly greater peak cortisol response than neutral imagery, and the stress imagery would elicit significantly greater peak cortisol response than the PASAT.

2.6.3 Area Under the Curve

To test the final subhypotheses, area under the curve (AUC) values were calculated for each experimental testing session across all participants. Computation of AUC is commonly used in endocrinological research involving repeated measurements over time because it increases the power of testing compared to other methods (e.g., repeated measures ANOVA using individual cortisol samples) without sacrificing information contained in multiple measurements (Pruessner et al., 2003). Pruessner and colleagues outlined two different approaches to computing AUC. The first approach, termed "area under the curve with respect to ground" (AUC_G) is calculated based on the distance of each measurement (i.e., each cortisol concentration) from zero, and most closely represents the overall intensity of hormonal output over time. The second approach, termed "area under the curve with respect to increase" (AUC_I) is calculated based on the distance of each measurement from baseline (i.e., pre-stress), and is most closely related to the overall magnitude of change over time, with positive values representing an increase and negative values representing a decrease over time. Given that each approach emphasizes two different characteristics of the data, two separate linear mixed effects models were implemented: once with log10 transformed AUC_G

values as the dependent variable, and once with log10 transformed AUC_I values as the dependent variable. In both models, the within subjects factor of Condition (3 levels; PASAT, Stress Imagery, Neutral Imagery) and between subject covariate factors were included as the fixed effects, and Subjects as the random effect. Post-hoc contrasts were used to assess the specific subhypotheses that the stress imagery condition would elicit significantly greater AUC values than neutral imagery, the PASAT would elicit significantly greater AUC values than neutral imagery, and the stress imagery would elicit significantly greater AUC values than the PASAT.

Chapter 3: Results

3.1 Participants

A total of 22 participants were approached for recruitment in the study. Of these, 2 participants declined participation. Thus, 20 participants provided informed consent and were enrolled in the study. Of these, 4 were excluded either for (a) reporting a major medical condition that was not disclosed during the initial SCID-IV-NP interview (n = 3) or for (b) providing undetectable salivary cortisol data (n = 1). Thus, the data analysis for the current study is based on a sample of 16 participants. Participants ranged in age from 29 to 54 (M = 46.44, SD = 7.05). With regard to racial/ethnic background, all 16 participants (100% of the sample) were African American. In terms of highest education level, 25.0% (n = 4) reported less than a high school education, 43.75% (n = 7) reported completing high school or obtaining a GED, and 31.25% (n = 5) reported some college or technical school. Nearly half of the sample reported current unemployment (43.75%, n = 7), and the majority of the sample reported an average household income of less than $30,000 a year (68.75%, n = 11). Thirteen of the 16 participants (81% of the sample) endorsed smoking cigarettes on a daily basis. Demographic information is shown in *Table 1*.

3.2 Manipulation Checks

Separate repeated measures ANOVAs revealed a significant increase in distress (as measured by the negative affect scale of the PANAS) following experimental administration of the stress imagery script [$F(1, 15) = 12.49$; $p = 0.003$], but a non-significant increase in distress following experimental administration of the PASAT [F(1,

15) = 3.86; $p = 0.068$]. Notably, although the increase in distress following PASAT administration was not statistically significant, it did approach significance, with an effect size that was small, but generally considered significant in the social sciences literature (partial $\eta^2 = 0.205$) (Cohen, 1988; 1992). Additionally, we examined ratings on individual items of the PANAS negative affect scale and found significant increases in response to PASAT administration on two items including "Distress" [$F(1, 15) = 6.361$, $p = .02$] and "Upset" [$F(1, 15) = 5.993$, $p = .03$], but no significant increase in ratings on the other eight items, including "Irritable", "Guilty", "Scared", "Hostile", "Ashamed", "Nervous", "Jittery", and "Afraid". There was no significant change in negative affect in response to the neutral imagery script [$p = 1.000$]. See *Table 2* for pre- and post-task negative affect data across the three testing conditions.

A repeated measures ANOVA was also conducted to test for significant differences in imagery vividness scale (IVS) ratings across the two imagery conditions. Analyses revealed a significant effect of imagery condition on participant ratings of imagery vividness [$F(1, 15) = 9.62$; $p = 0.007$]. Specifically, participants reported significantly higher imagery vividness for the stress imagery condition ($M = 9.56$; $SD = 0.89$) as compared to the neutral imagery condition ($M = 8.94$; $SD = 1.12$). As such, imagery vividness ratings during the two imagery conditions were included as covariates in all subsequent analyses to control for the effect of imagery vividness on salivary cortisol response to the two imagery scripts.

3.3 Examination of potential covariates

First, we implemented a linear mixed effects model to test for significant differences in log10 transformed cortisol concentrations at baseline (i.e., the mean of time-points 1 and 2; "pre-stress") across experimental conditions. To do this, we implemented a separate linear mixed effects model with the within subjects factor of Condition (3; PASAT, Stress Imagery, Neutral Imagery) included as a fixed factor, and subjects included as the random factor. The results revealed no significant difference in baseline cortisol concentrations across conditions [$p = 0.17$]. We then tested for significant differences across conditions at time-point 1 and 2 individually. We implemented separate LMEs including the within subjects factor of Condition (3; PASAT, Stress Imagery, Neutral Imagery) a fixed factor, and subjects as the random factor. The results revealed a significant difference in cortisol concentrations at time-point 2 [$F(1, 15.825) = 5.610$; $p = 0.03$], reflecting significantly higher cortisol concentrations at time-point 2 in the Neutral Imagery condition ($M = 0.498$; $SD = 0.449$) as compared to the Stress Imagery condition ($M = 0.272$; $SD = 0.298$) and the PASAT condition ($M = 0.216$; $SD = 0.351$). As such, given the difference between pre-stress cortisol values at time-point 2, we took the conservative approach and chose to control for baseline (mean of time-points 1 & 2) in all subsequent analyses to insure that any differences that were found across conditions were not simply due to pre-stress differences in cortisol concentrations.

We used similar LMEs to test for significant differences in other variables that may have influenced HPA axis functioning across the three nights of testing, including exhaled CO values on each testing night, baseline (i.e., pre-stress) self-reported negative

affect as measured by the negative affect scale of the PANAS, and nicotine withdrawal symptoms at the beginning and end of each testing session. The LMEs revealed no significant differences in exhaled CO across the three nights [$p = 0.49$] and no significant differences in baseline negative affect across the three nights [$p = 0.88$]. Therefore, neither variable was included as a covariate in subsequent analyses.

Finally, we conducted separate one-way ANOVAs to test for a significant effect of testing order on each of the outcome variables. That is, testing order was included as the independent variable, and separate ANOVAs were conducted with log10 transformed cortisol concentrations, AUC_I, AUC_G, and peak cortisol response to stress as the dependent variables. Testing order was significantly associated with log10 cortisol values [$F(5, 301) = 10.861$; $p < 0.001$] and peak cortisol response to stress [$F(5, 40) = 2.527$; $p = 0.04$], as well as a small, but statistically non-significant effect on AUC_G [$p = 0.07$; $\eta^2 = 0.231$]. Additionally, there was a notable imbalance in the number of participants that were randomized to each testing order, with more than half of the sample assigned to complete the PASAT first ($n = 9$), three randomized to complete the stress imagery condition first, and four completing the neutral condition first. As such, we took the conservative approach and included task order as a covariate in all primary analyses.

3.4 Test of primary study hypotheses

3.4.1 Log10 Transformed Cortisol Values

To address the subhypotheses regarding the effects of the experimental tasks on log10 transformed cortisol values, a linear mixed effects model was implemented with within subjects factors of Condition (3 levels: PASAT, Stress Imagery, and Neutral

Imagery) and Time (centered) (5 levels; immediately post-task, +10min, +20min, +30min, and +40min), as well as between subjects covariate factors of IVS scores, baseline cortisol concentrations, and testing order as fixed factors and subjects as the random factor. The analysis revealed no significant main effect of time [$p = 0.26$] or condition [$p = 0.13$], and no significant time by condition interaction [$p = 0.11$] on log10 transformed cortisol values. See *Figure 2* for a plot of the mean baseline cortisol values and the mean log10 transformed cortisol concentrations at each of the 5 post-task time points for each experimental condition. Estimates of fixed effects are listed in *Table 3*.

3.4.2 Log10 Transformed Peak Cortisol Values

To address the subhypotheses regarding the effects of the experimental tasks on log10 transformed peak cortisol values, a linear mixed effects model was implemented with the within subjects factor of Condition (3 levels: PASAT, Stress Imagery, and Neutral Imagery), as well as between subjects covariate factors of IVS scores, baseline cortisol concentrations, and task order as fixed factors, and subjects as the random factor. The analysis revealed no significant effect of condition on peak cortisol values [$p = 0.63$]. See *Table 4* for the estimates of fixed effects, and *Figure 3* for a bar graph representing the adjusted mean log10 transformed peak cortisol values for each condition.

3.4.3 Log10 Transformed AUC_G

To address the subhypotheses regarding the effects of the experimental tasks on log10 transformed AUC with respect to ground (AUC_G) values, a linear mixed effects model was implemented with the within subjects factor of Condition (3 levels: PASAT,

Stress Imagery, and Neutral Imagery), as well as between subjects covariate factors of IVS scores, baseline cortisol concentrations, and task order as fixed factors, and subjects as the random factor. The analysis revealed no significant effect of condition on AUC_G values [$p = 0.81$]. See *Table 5* for the estimates of fixed effects, and *Figure 4* for a bar graph representing the adjusted mean log10 transformed AUC_G values for each condition.

3.4.4 Log10 Transformed AUC_I

To address the subhypotheses regarding the effects of the experimental tasks on log10 transformed AUC with respect to increase (AUC_I) values, a linear mixed effects model was implemented with the within subjects factor of Condition (3 levels: PASAT, Stress Imagery, and Neutral Imagery), as well as between subjects covariate factors of IVS scores, baseline cortisol concentrations, and task order as fixed factors, and subjects as the random factor. The analysis revealed no significant effect of condition on AUC_I values [$p = 0.89$]. See *Table 6* for the estimates of fixed effects, and *Figure 5* for a bar graph representing the adjusted mean AUC_I values for each condition.

3.4.5 Exploratory Analyses

Although the omnibus timeXcondition interaction effect that was reported in Section 3.4.1 was not statistically significant [$p = 0.11$], we conducted additional exploratory analyses of the effect of time on each of the three experimental conditions separately, in order to supplement our primary analyses and to more fully characterize the pattern of salivary cortisol response that was observed in response to each of the three conditions. To do this, we conducted three separate LME analyses (i.e., one for each

experimental condition), with log10 transformed post-task cortisol concentrations serving as the dependent variables. The analyses included the within subjects factor of Time (5 levels: immediately post-task, +10, +20, +30, and +40), as well as between subjects covariate factors of baseline cortisol concentrations and task order as fixed factors, and subjects as the random factor. IVS scores were only included as between subjects covariates in the LME analyses conducted for the two imagery conditions given that these were the only testing sessions in which IVS scores were collected. The LME analyses revealed no effect of time on log10 transformed cortisol values during the stress imagery condition [$p = 0.60$], a significant negative linear effect of time on log10 transformed cortisol values during the PASAT condition [$B = -0.03$, $SE = 0.01$, $p = 0.05$], and an even stronger significant negative linear effect of time on log10 transformed cortisol values during the neutral condition [$B = -0.04$, $SE = 0.02$, $p = 0.02$]. See *Tables 7, 8, & 9* for estimates of fixed effects for these exploratory analyses.

Chapter 4: Discussion

4.1 Summary of Main Findings

The current study examined the pattern of HPA axis response to two different previously validated psychological stressors compared to a neutral no-stress condition in a sample of 16 cocaine dependent individuals in residential substance use treatment. The current study built on previous work establishing dysregulated patterns of cortisol reactivity to psychological stress among cocaine dependent individuals (Daughters et al., 2009; Harris et al., 2005; Lovallo et al., 2000; Sinha et al., 2003; 2006) by directly comparing the pattern of cortisol reactivity to two different psychological stressors, including: 1) a personalized stress imagery script (Sinha et al., unpublished manual) and 2) a non-personalized computerized challenge task (i.e., PASAT; Lejuez et al., 2003), as compared to a neutral, no stress condition. Additionally, because there are different approaches that have been used across studies to analyze cortisol reactivity data, each of which captures slightly different aspects of the cortisol response to stress, the current study built on previous findings by utilizing three different methods of analyzing HPA axis response to the three experimental conditions. Specifically, we tested for: 1) differential change in salivary cortisol concentrations across the five post-task time points between the three conditions, 2) differences in peak salivary cortisol response to the three conditions, and 3) differences in AUC between the three conditions. Using all three approaches allowed for a potential examination of the reliability and robustness of any significant differences in cortisol response across the various analytic approaches. We hypothesized that all three approaches to analyzing the cortisol data would reveal: 1) a greater salivary cortisol response to the personalized stress imagery condition as

compared to the neutral imagery condition, 2) a greater salivary cortisol response to the PASAT as compared to the neutral imagery condition, and 3) a greater salivary cortisol response to the personalized stress imagery condition as compared to the non-personalized PASAT condition.

In conducting the primary study analyses to test for differences in cortisol reactivity in response to the stress imagery script, the PASAT, and the neutral imagery script, no significant differences in cortisol response were found across the three experimental conditions. Specifically, after controlling for confounding variables, including testing order, baseline salivary cortisol concentrations, and differences in imagery vividness across the two personalized imagery conditions (i.e., stress imagery and neutral imagery), no significant differences were found in log10 transformed cortisol concentrations, peak cortisol response values, or AUC values across the three experimental conditions. The only analytical approach that came close to approaching a statistically significant difference on cortisol response between the three conditions was the assessment of change in log10 transformed salivary cortisol concentrations across the five post-task time points. Specifically, LME analyses revealed a non-significant time by condition interaction [$p = 0.11$]. Given that our small sample size may have precluded a significant omnibus interaction effect, we conducted additional exploratory analyses to assess the linear effect of time on salivary cortisol response for each condition separately. These analyses revealed a significant negative linear effect of time on cortisol concentrations during the PASAT condition and the neutral imagery condition, but no significant effect of time during the stress imagery condition.

Although no definitive conclusions can be drawn on the basis of these exploratory findings given the absence of an omnibus interaction effect, the general pattern that was observed may suggest that under neutral, non-stressed laboratory conditions, the natural pattern of cortisol secretion among this sample is a linear decline over time; however, exposure to psychological stress may prevent this natural decline, keeping cortisol concentrations level over time rather than declining. Specifically, there was a non-significant increase in negative affect during the PASAT condition, during which there was a less robust, but statistically significant, linear decline in cortisol concentrations over time as compared to the neutral condition. Conversely, there was a significant increase in negative affect in response to the stress imagery script, and cortisol values showed no significant linear effect of time during the stress imagery condition. Although there was no significant difference in the overall pattern of cortisol secretion between the three conditions, the fact that cortisol concentrations dropped significantly over time during the neutral imagery condition, less so during the PASAT condition, and not at all during the stress imagery condition may suggest that exposure to psychological stress may function to mitigate the natural decline in cortisol that is observed among cocaine-dependent individuals in the absence of stress. Importantly, these observed patterns and interpretations are highly speculative given that the omnibus timeXcondition interaction effect was not significant.

Although the sample size in the current study was quite small, the dearth of statistically significant differences in cortisol reactivity across the three experimental conditions was highly unexpected, especially given the methodological precautions that were taken. Despite the precautions, there remain a number of possible explanations to

account for the lack of significant findings. First, there was a significant effect of testing order on log10 transformed cortisol concentrations and peak cortisol values. Although we covaried for testing order in all analyses, the imbalance in the number of participants that were randomized to each testing order (i.e., 9 participants completed the PASAT condition first, as compared to 3 who completed the stress imagery condition first and 4 who completed the neutral imagery first) may have influenced the findings.

Another potential explanation for the current study's lack of significant findings is the time of day that was chosen to conduct testing. While evening hours are ideal for controlling for the potentially confounding effects of the circadian decline in cortisol secretion that occurs during morning hours, there is some evidence in the literature that the HPA axis may be less reactive in the evening, particularly between the hours of 6:00PM and 12:00AM (Horrocks et al., 1990). However, other researchers have found no evidence for reduced HPA axis reactivity to psychological stress in the late afternoon and early evening as compared to morning hours (Kudielka et al., 2004). Thus, it is possible that the lack of cortisol response to the psychological stressors in the current study may be explained by circadian influences on HPA axis reactivity, but the magnitude of the circadian effect on cortisol reactivity during evening hours remains unclear.

The current study's null findings may also imply that HPA axis response to psychological stress among cocaine dependent individuals is not as reliable and robust as the current literature suggests. This is not to say that our null findings present a direct challenge to conventional findings; however, the current results may suggest that clinicians should be cautious when interpreting findings in the extant literature and should not jump to conclusions regarding the potential utility of developing substance use

treatments that are specifically aimed at reducing HPA axis dysfunction. This need for caution is also exemplified by the fact that the current literature exhibits a great deal of methodological heterogeneity across studies, thus increasing the difficulty of generalizing findings and drawing firm conclusions. Moreover, given the multitude of mathematical (e.g, peak cortisol response, AUC_G, AUC_I, percent change from baseline, and mean cortisol concentrations) and statistical approaches (e.g., repeated measures ANOVAs, linear regression, linear mixed effects models, and growth curve modeling) that are currently in use when it comes to examining and testing patterns of cortisol reactivity, it is somewhat troubling that the analytic methods that are used vary widely across studies of HPA axis functioning, even when examining literature emanating from a single researcher or laboratory. That is, the absence of a standardized approach to examining cortisol functioning allows for researchers to use multiple mathematical and statistical approaches to examine their data and to report findings using any method that yields a *p*-value of $<.05$, even if the other methods that were used showed no significant effect. As such, the accessibility and acceptability of a countless number of approaches to analyzing and reporting cortisol data may lead to an inflated risk of Type I error as a consequence of conducting multiple comparisons. The field could benefit greatly from an effort to standardize both experimental and statistical methods in order to clarify the specific conditions under which the HPA axis responds to stress, the reliability of HPA axis responding across methodological and statistical approaches, and the extent to which HPA axis reactivity to stress differs across different clinical and non-clinical samples.

Finally, it is also possible that the non-significant differences between cortisol reactivity to the two stressors as compared to the neutral condition may be an accurate

reflection of the severe HPA axis dysfunction that has consistently been observed among cocaine dependent individuals. Indeed the impaired cortisol responses to stress that were observed in the current study are consistent with empirical (e.g., Daughters et al., 2009; Harris et al., 2005; Lovallo et al., 2000; Sinha et al., 1999, 2000, 2003) and theoretical evidence (Koob & LeMoal, 2008) suggesting that chronic substance use leads to allostatic changes in brain reward and anti-reward (i.e., stress) circuits, which are characterized by chronic elevation in basal HPA axis functioning and blunted HPA axis response to stress. Although Sinha and colleagues have consistently reported significant (albeit blunted) cortisol responses to stress compared to non-stressed conditions among cocaine users, our findings are consistent with Lovallo and colleague's (2000) finding that only healthy control participants showed a significant effect of stress on cortisol functioning, whereas alcohol dependent and comorbid alcohol + stimulant dependent individuals showed no significant difference between the two conditions. Unfortunately, it is impossible to provide experimental support for this explanation in the current study given that we did not include a healthy control group of non-drug users to examine whether these patterns of cortisol non-reactivity to our psychological stress manipulations are specific to cocaine dependence, or if it could be explained by a failure of the experimental stress manipulations to induce a robust HPA axis response in all participants, regardless of substance use status. Importantly, the patterns of cortisol response that were observed when examining each of the experimental conditions separately may provide some evidence that Sinha and colleague's stress imagery procedure did in fact influence cortisol secretion by holding the concentrations steady over time as compared to the drop in cortisol that was observed in the PASAT condition

and more so in the neutral imagery condition. However, the non-significant omnibus interaction effect hinders our ability to conclusively interpret our data in this manner.

Overall, the small sample size and lack of a healthy control group leads to great difficulty in interpreting the nonsignificant findings reported in the current study. However, the general pattern of the data implies that there may be a natural linear decline in cortisol concentrations during the evening hours when individuals are not exposed to psychological stress (i.e., during the neutral imagery condition) and this linear decline may be reduced in the presence of a challenging working memory task (i.e., the PASAT) and may be completely eliminated in the presence of intense, personalized stressful imagery (i.e., the stress imagery condition). Future studies may determine whether this general pattern of cortisol functioning holds true among larger samples of chronic cocaine users as compared to matched samples of healthy control participants.

4.2 Limitations and Future Directions

One limitation of the current study that is important to note is the modest sample size. It has been suggested that for linear mixed effects models, sample sizes of at least 20 (and preferably 50) are most appropriate in order to obtain a level of statistical power that is adequate for detecting significant effects (Hox, 1995). It is worth noting, however, that the sample size in the current study is comparable to many of the within subjects design studies of cortisol reactivity among substance users that were described in Chapter 1. For example, Sinha and colleagues (1999) reported a significant difference in cortisol response to a personalized stress imagery script compared to a neutral script in a sample of only ten cocaine users, and Lovallo and colleagues (2000) included only twelve participants per group in his examination of cortisol response to the TSST compared to a

neutral condition among healthy controls, alcohol users, and comorbid alcohol and stimulant users, finding a significant effect of testing condition among healthy controls only. An estimate of effect size would be useful for determining whether there was a robust effect of psychological stress on cortisol functioning in the current study that simply failed to reach statistical significance; however, effect size estimation for mixed linear models is complicated given that both the fixed and random effects in the model must be estimated (Field, 2009). Moreover, few statistical software packages currently provide effect size calculators for mixed effects models. As such, it remains unclear if our non-significant findings may be explained by low statistical power due to the small sample size.

A second limitation of the current study is the absence of a significant increase in self-reported distress, as measured by the negative affect scale of the PANAS, following PASAT administration. Although the increase in distress that was exhibited in response to the PASAT administration did not reach significance at the 0.05 level, the small sample size may not have provided enough statistical power to detect a significant effect. Thus, we also examined the effect size of PASAT administration on change in distress ratings and found an effect size that was small, but generally considered significant within social science research (partial $\eta^2 = 0.205$) (Cohen, 1988; 1992). Additionally, we examined ratings on individual items of the PANAS negative affect scale and found significant increases on some items, including "Distress" and "Upset", but no significant increase in ratings of other items in the negative affect scale, including "Irritable", "Guilty", "Scared", "Hostile", "Ashamed", "Nervous", "Jittery", and "Afraid". As such, it appears that the PASAT may be more useful for inducing specific negative emotions,

including feeling distressed and upset, as opposed to the personalized stress imagery script which effectively induced a more general negative affective state.

The current study is also limited given that participants were exposed to the PASAT during their baseline assessment session, thus reducing the novelty of the task when it was administered for the second time during the PASAT cortisol testing session. Given that novelty is one factor that has been associated with the magnitude of the HPA axis response to stress (Dickerson & Kemeny, 2004), exposure to the PASAT during baseline screening may have influenced the pattern of cortisol response that was observed in response to the PASAT during cortisol testing. It is possible that repeated exposures to the PASAT may have also mitigated the negative affective response to the task upon completing it a second time, thus explaining the non-significant increase in negative affect ratings that were observed following PASAT administration during cortisol testing.

Another limitation of the current study is the significant difference in baseline "pre-stress" cortisol concentrations, such that participants exhibited significantly greater baseline cortisol during the neutral imagery condition as compared to the PASAT and stress imagery conditions. It is unclear what drove this difference in baseline salivary cortisol values; however, it is possible that an unknown confounding variable induced an elevation in cortisol secretion immediately prior to the neutral condition, but not the other two testing sessions. One possible explanation is that individuals were more nervous when they arrived for the neutral imagery sessions than they were at the beginning of the other two conditions due to the imbalance in testing order assignment. That is, the majority of participants were randomized to complete at least one of the two stress conditions during sessions that preceded the neutral imagery condition, thus potentially

triggering an anticipatory cortisol response upon returning to the laboratory setting following stress administration on a previous testing night. Despite the plausibility of this explanation, there was no significant relationship between testing order and baseline salivary cortisol values, and there was no significant difference in self-reported negative affect at baseline during the neutral imagery condition compared to the two stress conditions. Alternatively, it is possible that there may have been an unknown experimenter effect that influenced cortisol secretion at baseline during the neutral condition. For example, perhaps research assistants spent less time administering the progressive relaxation exercise during neutral imagery sessions compared to the other two conditions. Unlike experiments conducted by Sinha and colleagues, research assistants in the current study were not blinded to the experimental condition on each testing night; therefore, the possibility of an experimenter effect on baseline cortisol secretion cannot be discounted.

Finally, the current study is limited in the extent to which findings can be generalized across other samples of cocaine users. Specifically, the current study excluded women, individuals with comorbid opiate dependence and/or Axis I psychopathology, individuals on certain medications, and individuals with major medical conditions. Given the small number of participants that met inclusion criteria over the course of 16 months of study recruitment, it is clear that the current study sample is not representative of the overall population of substance users at the recruitment facility. Additionally, there is mixed evidence in the literature to suggest that some environmental factors, such as low socioeconomic status (Cohen, Doyle, & Baum, 2006; Cohen, Schwartz, et al., 2006; Dulin-Keita et al., 2010; Lupien, King, Meany, & McEwen, 2001;

for review see Dowd, Simanek, & Aiello, 2009), racial discrimination and race-related stress (Pascoe & Richman, 2009; Richman & Jonassaint, 2008; Tull, Shue, Butler, & Cornelious, 2005), and chronic stress exposure (Miller, Chen, & Zhou; Wolf, Nicholls, & Chen, 2008; Zarcovic et al., 2003) are associated with HPA axis abnormalities. Given that the current sample consisted of primarily low-income African American individuals living in or near the inner-city, all of these factors are likely to have had a significant effect on the pattern of cortisol reactivity to stress that was observed in our particular sample, thus reducing the generalizability of our findings even further.

Many questions remain in the field of HPA axis functioning and addiction. Additional research is needed to increase our understanding of the specific conditions under which drug dependent individuals exhibit abnormal cortisol reactivity to stress, and the extent to which cortisol reactivity to different types of stress is associated with differential vulnerability for stress-induced relapse. Larger scale studies that include matched samples of healthy non-drug users are needed to facilitate the further development of larger models that include individual difference factors, such as specific genetic polymorphisms, early and chronic stress exposure, gender, and personality factors that may influence both basal HPA axis functioning and reactivity to stress. It is possible that larger models of this kind may be useful for identifying individuals who are most susceptible to stress-related neuroadaptations over the course of addiction, as well as those most susceptible to stress-induced relapse. Such research could be of clinical benefit both in the assessment of relapse susceptibility and potentially by matching individuals specifically vulnerable to stress related neuroadaptations and relapse to

interventions that are specific to these addictive processes (Sinha, 2009). However, a great deal of research is still needed in order to work toward these long-term goals.

Table i. Demographic Information

Demographic Characteristic	
Age, mean (SD)	46.44 (7.05)
Marital Status	
Single, %	75.0
Living with a partner as if married, %	12.5
Married but separated, %	6.25
Married, %	6.25
Race	
Black, %	100.0
Education	
Less than high school, %	25.0
High School/GED, %	43.75
More than high school, %	21.25
Total Income < 10,000, %	56.25
Unemployed, %	43.75
Daily Smokers, %	81.0

Table ii. Pre- and Post-Task PANAS Negative Affect Scores by Condition

Condition	Pre-task *M (SD)*	Post-task *M (SD)*
PASAT	11.88 (3.12)	15.13 (6.30)
Stress Imagery**	11.34 (2.03)	21.63 (11.63)
Neutral Imagery	11.88 (4.16)	11.88 (3.69)

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

Table iii. LME analysis predicting log10 transformed cortisol concentrations

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Testing Order	-.02	.02	-.88	.40	[-.07, .03]
Baseline Cortisol	.90	.08	11.23	<.001	[.74, 1.06]
Imagery Vividness	.01	.03	.39	.70	[-.05, .07]
Time (centered)	.07	.06	1.12	.26	[-.05, .18]
Condition	.09	.06	1.54	.13	[-.03, .21]
TimeXCondition	-.04	.02	-1.60	.11	[-.08, .01]

Table iv. LME analysis predicting log10 transformed peak cortisol values

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Testing Order	-.03	.06	-.48	.63	[-.15, .09]
Baseline Cortisol	.53	.26	2.08	.05	[.01, 1.05]
Imagery Vividness	.00	.10	.02	.99	[-.20, .20]
Condition	.09	.17	.49	.63	[-.27, .44]

Table v. LME analysis predicting log10 transformed AUC_G values

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Randomization	-.02	.02	-.94	.35	[-.06, .01]
Baseline Cortisol	1.00	.07	13.70	<.001	[.86, 1.15]
Imagery Vividness	.02	.03	.61	.54	[-.04, .07]
Condition	.01	.05	.24	.81	[-.09, .11]

Table vi. LME analysis predicting log10 transformed AUC_I values

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Randomization	.01	.03	.34	.74	[-.05, .07]
Baseline Cortisol	-.03	.11	-.24	.81	[-.26, .20]
Imagery Vividness	.00	.04	.01	.99	[-.09, .09]
Condition	-.01	.08	-.14	.89	[-.17, .15]

Table vii. LME analysis predicting log10 transformed cortisol values during PASAT condition

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Randomization	.00	.02	-.025	.98	[-.04, .04]
Baseline Cortisol	1.04	.09	11.23	<.001	[.85, 1.24]
Time (centered)	-.03	.01	-1.99	.05	[-.06, .00]

Table viii. LME analysis predicting log10 transformed cortisol values during stress imagery condition

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Randomization	.02	.03	.70	.50	[-.04, .08]
Baseline Cortisol	1.22	.17	7.24	<.001	[.87, 1.58]
Imagery Vividness	.02	.05	.45	.66	[-.09, .14]
Time (centered)	-.01	.01	-.53	.60	[-.04, .02]

Table iv. LME analysis predicting log10 transformed cortisol values during neutral imagery condition

Variable	*B*	*SE*	*T*	*P*	*95% CI*
Fixed effects					
Randomization	-.04	.02	-2.36	.03	[-.08, .00]
Baseline Cortisol	1.11	.07	14.80	<.001	[.95, 1.27]
Imagery Vividness	.01	.03	.34	.74	[-.05, .07]
Time (centered)	-.04	.02	-2.62	.02	[-.08, -.01]

Figure i. Diagram of Testing Session Procedures

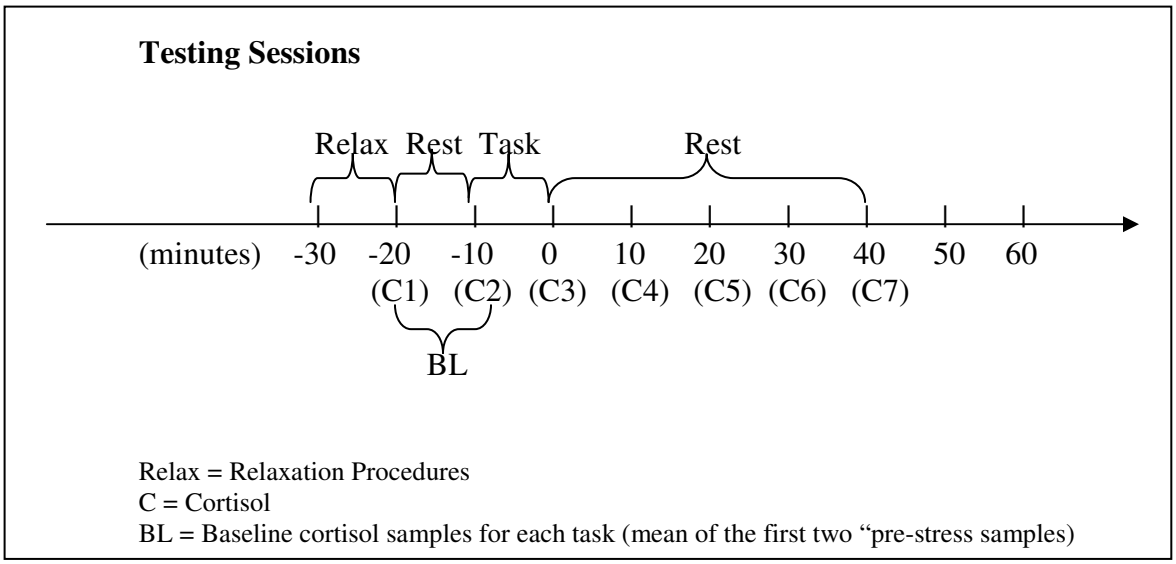


Figure ii. Computerized Paced Auditory Serial Addition Task (PASAT-C)

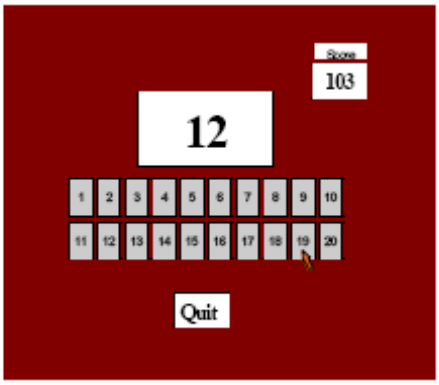


Figure iii. Plot of mean log10 transformed salivary cortisol concentrations at each time point by condition. Dotted line reflects experimental task administration. Baseline values are not connected to post-task values because they were included in the model as covariates.

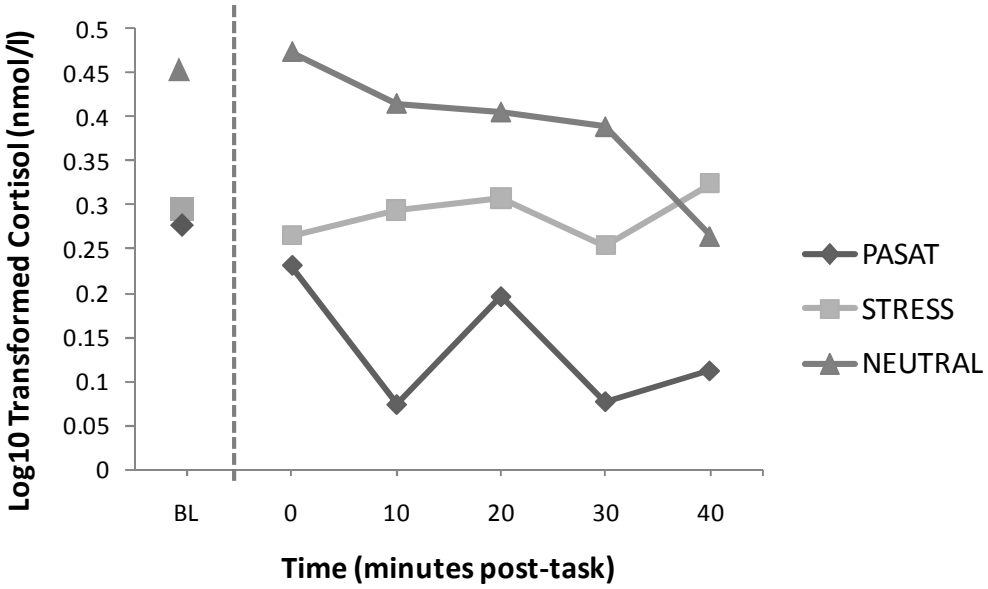


Figure iv. Mean and SE (adjusted for covariates) log10 transformed peak cortisol values by condition

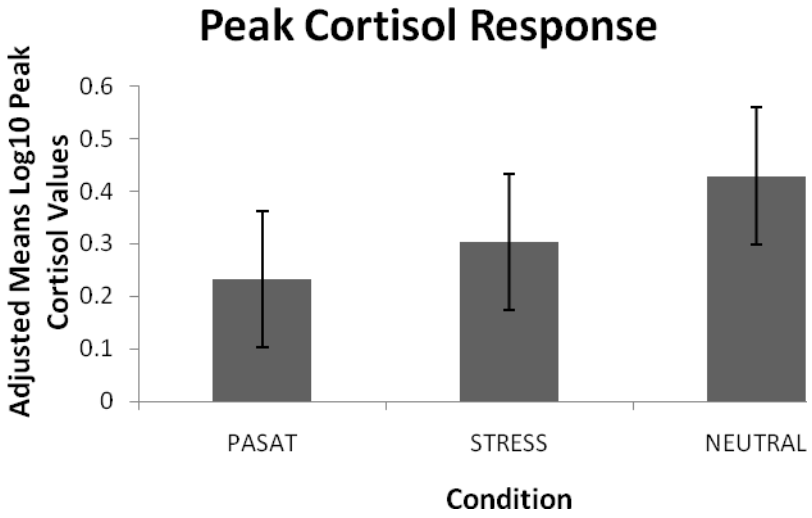


Figure v. Mean and SE (adjusted for covariates) log10 transformed AUC_G values by condition

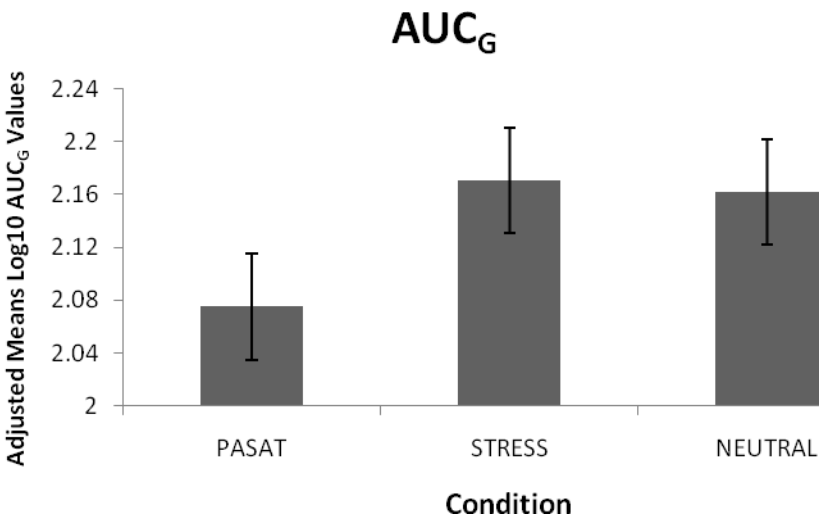
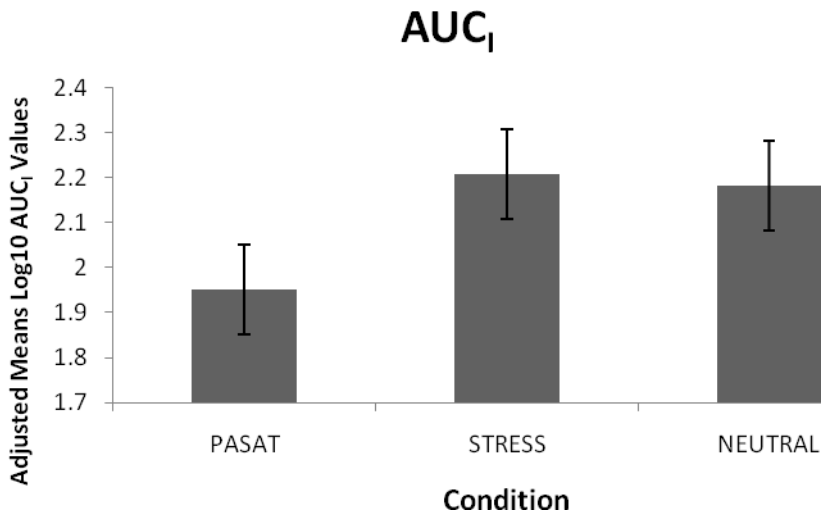


Figure vi. Mean and SE (adjusted for covariates) log10 transformed AUC_I values by condition



Appendices

Appendix I: Sample Stress Imagery Script

"Close your eyes and imagine the scene as if it were happening right now. When the scene is over, continue imagining until I tell you to stop. Let's begin."

It is a warm evening in May. You are watching television in the living room of your mother's old home in D.C. [Your sister]* walks through the front door of the house. Your heart quickens. She stands in the doorway and looks around the room. You scan her face with your eyes. You know she is about to pick a fight with you. You tense the muscles in your face and forehead. She shakes her head and turns to speak to you. "You need to think about finding a new place to live and get out of here", she says. She sounds angry. 'What is she talking about?', you think. You breathe faster. "Who the hell do you think you are? This isn't your house!", you yell. You tense the muscles in your back, arms, and legs. "This isn't your house either", she snaps back. "I can only imagine what Mom would say if she saw this place." Your hands are trembling. 'Who is she to tell me what our mother would want?' Your heart is racing. 'I'm the one that cared for Mom when she was dying', you think. You breathe faster. Your whole body is shaking. [Your sister] is yelling at you. "This place is disgusting! You can't even get yourself up to mow the damn lawn!" She screams. You clench your fists. You can't believe your own sister is treating you like this. You want to scream or smash something. 'Who does she think she's talking to?' you think. Your heart is pounding now. "It's none of your damn business what I do with this house!" you shout back. Your stomach is in a knot. How could she just storm in like this? You want to throw her out of the house. "The hell it isn't my business! [Your brother] and I both want you out". You feel hot all over. How could they team up on me like this, you think? "So this is how it's going to be?" you yell. "Well, you two will have to take me to court if you want me out of this place." You grit your teeth. My own family is turning against me, and [my brother] wasn't even man enough to tell me to my face. You feel jittery all over. "Fine!" [Your sister] shouts. "I'll see you in court!" she screams. There is a sinking feeling in your stomach. She walks out the front door and slams it behind her. "Fuck you!" you yell. Your entire body is shaking. You start to go after her, but you stop yourself. You are so angry you could strike somebody. How could my own family gang up on me like this?? Where will I go if they kick me out? You imagine yourself on the street alone, homeless. There is a heavy feeling in your stomach. You feel helpless and betrayed. You just want to get away, away from here and all of these terrible feelings. You feel empty, drained, hollow. It hurts to be alive. Tears come to your eyes.

"You can stop imagining now. Please open your eyes and remove your headphones."

*Bracketed information represents first names that have been removed to protect confidentiality

Appendix II: Sample Neutral Imagery Script

"Close your eyes and imagine the scene as if it were happening right now. When the scene is over, continue imagining until I tell you to stop. Let's begin."

It is 12 o'clock in the afternoon on a pleasant day in May. You are laying on the couch in the living room. You are alone and the house is quiet. Your stomach is full from the food you cooked this morning. You take in a deep breath as you lie back on the couch, stretching the muscles in your back and legs. When you listen closely, you can hear the hum of the air conditioning cooling the house. You reach down and pull a blanket over you, feeling warm and comfortable. Your breathing slows down. You move around to get comfortable, noticing the smooth, soft feel of the couch against your skin. You relax the muscles in your neck and shoulders as you lay your head down on the pillows. You feel the tension begin to melt out of your body. You stretch over and reach for the remote control to change the channel. You watch the bright images moving on the television set. The house is quiet and calming. You breathe in deeply and stretch the muscles in your arms, back and legs. You settle in and sink back into the couch. You notice that your clothing feels smooth and soft against your skin. You look down and notice Yodi sitting next to you on the floor. You turn your head to the side, slowly stretching the muscles in your neck. You slowly reach down and pet Yodi, feeling the soft fur in your hands. You feel the tension ease out of your body. You pull your arm back under the blanket as you snuggle more deeply into the couch. Your heart beats slower. You take in a few more deep breaths, noticing the faint smell of fried potatoes, bacon, and eggs in the air. You exhale slowly, letting out any tension remaining in your body. The tension from your body goes away and you feel comfortable and at ease. You feel at peace in the quite solitude of the house. All of your worries fade away. You feel a general sense of release. Your breathing slows down. Slowly you find your eyes closing and your mind drifts away. There is a sense of lightness inside you. You want to hold time and capture this moment. A feeling of peace comes over you.

"You can stop imagining now. Please open your eyes and remove your headphones."

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