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# Acute Stress Exposure and Expression of Instrumentally Conditioned Financial Preferences: An fMRI Study

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ACUTE STRESS EXPOSURE AND EXPRESSION OF INSTRUMENTALLY  
CONDITIONED FINANCIAL PREFERENCES:  
AN FMRI STUDY

by

William T. McCuddy, B.A.

A Thesis submitted to the Faculty of the Graduate School,  
Marquette University,  
in Partial Fulfillment of the Requirements for  
the Degree of Master of Science

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ABSTRACT  
ACUTE STRESS EXPOSURE AND EXPRESSION OF INSTRUMENTALLY  
CONDITIONED FINANCIAL PREFERENCES:  
AN FMRI STUDY

William T. McCuddy, B.A.

Marquette University, 2016

Recent research suggests acute stress exposure is associated with increased habit-based over goal-oriented decision making (e.g., Schwabe & Wolf, 2011). The current study examined whether acute stress promotes the expression of simple financial preferences “overtrained” to the point of habit in the face of a changing environment where said preferences were later rendered non-optimal.

Over three days participants ( $N = 28$ ) learned to discriminate between visual stimuli probabilistically associated with monetary gains or losses and made decisions between stimuli with real financial outcomes. On the fourth day after exposure to either an acute stressor or control procedure participants performed the same tasks during fMRI scanning, including a related task in which monetary values associated with the same stimuli were altered. Choice and fMRI data, psychophysiological measures and salivary cortisol were collected. Participants in both groups successfully made optimal decisions between stimuli on Days 1 to 3 (reaching asymptote on Day 2).

During fMRI scanning after stimuli values were altered stressed participants made significantly more decisions consistent with original stimuli values, although these decisions were now financially detrimental, than did non-stressed participants. Thus, stressed participants made decisions more consistent with their overtrained (i.e., habit-based) preferences. In the control group, differential levels of BOLD activation, relative to stimulus valence, were observed in regions associated with goal-directed (i.e., caudate and prefrontal cortex) and habit-based (i.e., putamen) behaviors during both overtrained and novel stimulus-outcome pairings. In the acute stress group, similar differential BOLD activation was limited to the putamen and was only observed for overtrained pairings. During the decision-making portion of the task, increased BOLD activation was observed in the dorsal anterior cingulate cortex and insula for incorrect relative to correct responses in both groups. Further, alterations in dorsolateral prefrontal and entorhinal cortex suggest some stress-related impairment of executive control of memory.

The current study adds to research that demonstrates a dual-process of decision-making and the propensity to resort to habitual behavior after exposure to acute stress. Further, these findings suggest stress-induced neural changes take place during both the learning and recall of reward-related information used in decision-making.

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## INTRODUCTION

Ranging from simple (e.g., deciding what to wear or what to have for lunch) to complex (e.g., managing a large portfolio on behalf of thousands in an international market or coordinating military activity on the battlefield), decisions can have important consequences in terms of the physical and mental health, and therefore well-being, of the individual and others. Just as decision-making is a fundamental process in which people engage every day, another unavoidable part of the daily human experience is exposure to stress. Many environmental stimuli can trigger the cascade of physiological changes collectively termed the “stress response” including some that are physiological in nature, such as physical trauma or exposure to extreme temperatures, and others that are psychological, such as work or interpersonal relationship pressure. It is also clear that situations often occur in which decisions must be made under stressful conditions. Whether it is the stockbroker making far-reaching financial decisions in the chaotic global market or a military official coordinating multiple units on the battlefield under adverse and extreme conditions, sound decisions must be made under moderate to severe levels of stress. Therefore, the extent to which stress might influence decision-making is a critical topic of interest across many research domains including, but not limited to, the fields of psychology, economics, and medicine.

The research proposed here is meant to advance our understanding of how stress influences decision-making, and to examine the neural correlates of stress-related alterations in that process. While individuals are capable of making decisions using precise logic and deliberation, their behavior can also be guided by intuitive judgments based on past experiences (Reyna, 2004). The latter necessitates repeated exposure to

environmental stimuli in order to form a habitual response to specific cues (i.e., conditioning), perhaps leading to decreased reliance on logic and deliberation to guide decision-making. At times this may be beneficial, as in situations with limited time to make decisions in an environment that matches the context in which the habit was developed (e.g., a well-trained surgeon treating a gun-shot victim, or a first responder to the scene of a natural disaster). That said, over-reliance on habitual behaviors can also have adverse consequences (e.g., a military official carrying out a routine strike plan without adequately considering the most recent intelligence or changes in the location of the battlefield).

Importantly, this research will add to the current literature through examination of a stress-induced shift from deliberative and logical to habitual decision-making. By conducting such an experiment in a functional magnet resonance-imaging (fMRI) paradigm, it is possible to examine the neural substrates subserving both types of decision-making. This may provide additional evidence for how the brain recruits various regions involved in cognition and processing of reward-related information to carry out decisions. Further, an understanding of the broad impact of stress on this neural circuitry may inform other researchers about the specific role of neuromodulators known to be involved in the stress response (e.g., corticosteroids and catecholamines) in the modulation of decision-making's locus.

Additionally, a greater understanding of the neural basis of stress and decision-making could provide vital insight into the neural basis, development, and treatment of disorders influenced by stress. For example, one long-standing hypothesis underlying the etiology of many psychological disorders is the stress-diathesis model (Monroe &

Simons, 1991). This research has the potential to initiate interdisciplinary investigation by examining the relationship between stress, brain activation, and cognition, providing direct clinical implications for the development of certain psychological disorders (such as PTSD and major depression) and for exacerbating existing disorders such as relapse in drug addiction. Research examining this intersection may elucidate interventions aimed at changing individuals' maladaptive cognitive, emotional, and behavioral habits while enhancing adaptive habits. Whether the goal is to inform theoretical and experimental neuroscience, or to provide novel clinical interventions, investigation into the effects of stress on decision-making should start with a basic understanding of the difference between controlled versus automatic decision-making processes.

## **LITERATURE REVIEW**

### **Dual-Process Theories of Decision-Making**

Researchers of a wide range of academic disciplines have studied the topic of decision-making, at times originating in entirely different perspectives based on different assumptions. Thus, multiple theories of reasoning have been developed (resulting at points in varied and confusing terminology). Across disciplines, however, a common trend has emerged: to conceptualize reasoning and decision-making in a dual-process manner involving two separable but interacting systems.

Dual-process theories of decision-making differentiate between systems supporting styles of decision-making that are (I) habitual, stimulus-bound, automatic, and less effortful versus (II) deliberative, flexible, controlled, more effortful and resource-dependent. Though each theory possesses unique characteristics, they all share an

approach involving a portrayal of decision-making as dichotomous. In social psychology, this dichotomy is divided into automatic and controlled processes (Shiffrin & Schneider, 1977). In economics, individuals are thought to make decisions based on System 1 *gut instincts*, or System 2 processes that are more deliberate (Kahneman & Frederick, 2002). Finally, in behavioral neuroscience, decision-making is generally described as being habit-based or goal-directed (Dickinson, 1985). It should be noted that some have raised important concerns with respect to this dichotomy being an oversimplification (Evans, 2008), yet as an experimental tool the dichotomy remains useful and thus it is adopted here.

The current project takes a behavioral neuroscience approach, the focus of which exists towards the center of a progression of research that sprouted from the early learning experiments of Thorndike (1911) and Tolman (1948), and has since led to advanced computational models explaining the relative contributions of each form of decision-making in different situations (Daw, Niv, & Dayan, 2005). Situated at the center point of this progression, the current project aims to examine the influence of stress on decision-making and the neural systems involved. In keeping with the traditional taxonomy of the early behavioral neuroscience work upon which this study is directly based, the terminology “goal-directed” and “habit-based” will be adopted throughout to describe each system.

A goal-directed system supports decision-making that is characterized by awareness, intentionality, controllability and increased cognitive effort (Bargh, 1996; Shiffrin & Schneider, 1977). Goal-directed behaviors are derived from predictions about future consequences regarding some action and are therefore mediated by action-outcome

(A-O) contingencies (i.e., a casual relationship between behaviors and their resulting consequences; Dickinson, 1985) The habit system, on the other hand, promotes decision-making characterized by unawareness, unintentionality, lack of control, and decreased cognitive effort (Bargh, 1996; Shiffrin & Schneider, 1977). Habitual behaviors persist even in a changing environment as they are controlled by environmental stimuli, which have been repeatedly paired with a response. Therefore, the habit system is thought to be guided by stimulus-response (S-R) associations (i.e., a casual relationship between the environmental context and the production of a behavioral response; Dickinson, 1985). Accordingly, decisions can be characterized on a continuum of automaticity ranging from completely controlled to completely automatic (Bargh & Chartrand, 1999). In the current proposal, our goal is to examine the effects of acute stress on decisions manipulated to be closer to the “poles” of that continuum.

Underlying both goal-directed and habitual behaviors is the concept of instrumental conditioning, the process of learning the association between behaviors and their consequences (Dickinson, 1985). Although both systems are thought to be concurrently active and competing for behavioral control (Kahneman & Frederick, 2002), a temporal progression from goal-directed to habitual decision-making throughout the process of learning has been observed (Adams, 1982; Dickinson, Balleine, Watt, Gonzalez, & Boakes, 1995). That is, early during the learning process, behaviors are generally goal-directed and contingent on a behavioral outcome. After repeated and consistent training, however, behaviors can become more habitual. They can be elicited from contiguously related environmental cues and are relatively independent of behavioral outcomes (Dickinson, 1985). This automatization of routine behaviors may

serve an adaptive function, as it frees cognitive resources that can be allocated to other, non-routine, behaviors (Bargh, 1994). However, as habits can influence behavior in ways of which one is unaware (e.g., Bargh & Morsella, 2008), understanding the factors involved in a shift from goal-oriented to habitual decision-making processes is important.

### **Goal Devaluation Studies: Measuring the Shift between Systems**

Using an experimental procedure known as outcome devaluation, researchers have been able to examine factors that contribute to a dissociation between the goal-directed and habit-based systems. Originally utilized in animal research (e.g., Adams & Dickinson, 1981; Balleine & Dickinson, 1998; Dickinson, 1985), the general design of this procedure begins by training hungry rats to press a lever for a food reward (e.g., sucrose pellets). After sufficient training, the food reward is devalued and responses for the reward (now devalued) are measured under extinction. The process of devaluation originally involved pairing consumption of the food reward with a noxious drug (Adams & Dickinson, 1981). More recently, however, devaluation has been achieved through the method of selective satiety, in which subjects are allowed free access to consume the food reward until satiated prior to the extinction phase (Rossi & Yin, 2012).

A hallmark of goal-directed action is that it is guided by a learning system that is sensitive to the behavior's outcome or teleological goal (Adams & Dickinson, 1981). Therefore, goal-directed behaviors can be examined by the extent to which outcome devaluation affects responding during extinction. That is, if behaviors are guided primarily by the prediction of future outcomes, responses for devalued rewards should decrease during the initial phase of extinction (a behavioral response that is opposite of the typically examined extinction burst). While the existence of flexible, goal-directed

behaviors may not be unexpected in humans, the results from Adams and Dickinson (1981) demonstrating a similar capacity for learning in animals contradicted the prevailing theory of that time. In their experiment, two groups of rats were trained to make a lever press for one type of food, while a different type of food was delivered non-contingently. Next, the contingent reward was devalued for one group, while the non-contingent reward was devalued for the other. During the initial extinction phase, the group that experienced the devaluation of the contingent reward responded less frequently than the group whose contingent reward remained unaltered. This lack of responding demonstrates some knowledge about the association between the action of pressing a lever and the outcome of a particular food (i.e., the A-O contingency).

Habitual responding has also been demonstrated using the same outcome devaluation method described above. That is, after sufficient overtraining, some subjects continued to respond for the devalued reward at the same rate as subjects whose reward value remained unchanged. For example, Adams (1982) devised an experiment in which one group of rats were trained to respond for a food reward for ten days, while another group was trained for only two days. For both groups training consisted of 50 rewards per day. After training, the food reward was devalued for half of each group by pairing its consumption with a noxious stimulus. The resulting groups consisted of a moderately trained devaluation (100-D) and non-devaluation (100-N) group, and an overtrained devaluation (500-D) and non-devaluation (500-N) group. During the subsequent extinction test, the moderately trained rats whose food reward was devalued decreased responding compared to rats with the same amount of training whose reward remained unchanged (100-D < 100-N). Contrarily, overtrained rats whose food reward was



devalued did not reduce their responding for the devalued reward. Instead, this group lever pressed at a similar rate as the groups whose reward remained unchanged (500-D  $\approx$  500-N). This suggests behaviors can be controlled by the stimuli associated with the reward, rather than the reward itself, consistent with the idea of habit formation. A similar shift from goal-directed to habitual responding, as a result of overtraining, has also been demonstrated in humans (Tricomi, Balleine, & O'Doherty, 2009).

Other factors that may contribute to the dominance of either the goal-oriented or habit system in a specific context have been investigated. Of particular interest here is the impact of stress. While both systems provide unique advantages which promote adaptive responding, overreliance on either system may lead to undesirable consequences (Bargh, 1994). Several animal and, more recently, human studies have demonstrated stress-induced shifts from goal-oriented to habitual responding using paradigms similar to the goal devaluation studies just discussed (Dias-Ferreira et al., 2009; Schwabe & Wolf, 2010). Notably, stress may promote this shift by altering the brain's reward processing circuitry (Schwabe, Tegenthoff, Hoffken, & Wolf, 2012). Therefore, before discussing the finer details of these studies, it is important to briefly review the peripheral and neural pathways involved in the stress response and decision-making.

### **Major Stress Pathways**

In order to properly respond to stress (i.e., changing environmental demands or threat of/actual harm), an organism's well-being is contingent on its ability to recruit and manage resources while maintaining physiological homeostasis. Two major systems critical for maintaining homeostasis are the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis. SAM activation and its precipitating

events are fast acting, producing functional changes in the body within seconds (McEwen & Sapolsky, 1995). The SAM axis mediates cardiac output by means of post-ganglionic neurons innervating the heart, as well as through release of epinephrine from the adrenal medulla of the hypothalamus (Seals & Esler, 2000). Activation of the SAM axis has also been demonstrated to stimulate the release of catecholamines such as epinephrine and norepinephrine, as well as dopamine neurally (Arnsten, 2009). Due to the accelerated cardiac functioning and the release of catecholamines, SAM activation is responsible for increasing arousal in order to prepare the body to respond to threatening or aversive stimuli (e.g., fight or flight Cannon, 1932). These catecholamines have a concentration-dependent influence over neuronal firing that can be characterized as an inverted U-shape relationship. That is, moderate levels of catecholamines are necessary for optimal neural processing, but hypo- or hyper-activity of the system under- or over-excites neurons respectively leading to disorganized firing in the latter case as when the system is exposed to acute stress (Arnsten, 2009). For example, it has been observed that excessive stress-related release of catecholamines is associated with decrements in working memory performance (Arnsten, 2009; Arnsten & Goldman-Rakic, 1998).

A parallel system, the HPA axis, also mediates homeostasis in response to stress. Under conditions of acute stress the hypothalamus sends signals (i.e., corticotrophin releasing hormone) to the anterior pituitary gland that in turn activates (via adrenocorticotrophic hormone) the cortex of the adrenal glands, stimulating the release of corticosteroids, such as cortisol, into the bloodstream. This complex cascade of events occurs relatively slowly, with effects reaching peak levels approximately 15-20 minutes post-stress (Herman et al., 2003). Once in the bloodstream, corticosteroids play a critical

role in returning the body to a state of homeostasis. Corticosteroids bind to many of the body's nucleic cells and play a role in metabolizing carbohydrates, increasing blood glucose levels. Increases in blood glucose provide the necessary fuel to meet metabolic demand after excess consumption of energy resources (e.g., after responding to a stressful situation, Miller & O'Callaghan, 2002). At the same time, however, corticosteroids can influence multiple psychological systems including learning and memory (McEwen & Sapolsky, 1995) after brief exposure, and have been associated with several psychological disorders after chronic exposure (Herman et al., 2003). The influence of these stress systems on decision-making will be discussed further in later sections.

### **Acute Laboratory Stress Techniques**

In order to induce activation of physiological stress systems in a laboratory setting, various forms of acute stress have been utilized in past research. These range from physiological to psychosocial to cognitive stressors. Importantly, different forms of stress may affect brain functioning through separable, but overlapping, pathways (Herman & Cullinan, 1997), resulting in varying degrees of activation from each stress system. Various stress induction approaches can be categorized into two broad categories: processive and systemic.

Processive stressors, such as fear conditioning and restraint in animals or public speaking in humans, require a sequence of higher order processing to integrate multiple sensory inputs with past experiences (Herman & Cullinan, 1997). Therefore, the amount of stress produced by these stressors is directly related to the quality and quantity of individuals' previous exposure. Evidence for such higher-order processing and integration has been demonstrated by lesion studies in which the ability of these stressors

to evoke a stress response was inhibited by degradation of prefrontal cortex (PFC), amygdala, and hippocampus (Diorio, Viau, & Meaney, 1993; Feldman, Conforti, Itzik, & Weidenfeld, 1994; Sapolsky, Krey, & McEwen, 1984, respectively). For example, lesions to the medial prefrontal cortex (mPFC) significantly increased adrenocorticotropin and corticosterone plasma levels following a restraint procedure (i.e., a processive stressor) but not after exposure to ether (i.e., a systemic stressor; see below) in rats (Diorio et al., 1993).

Systemic stressors, on the other hand, engender an immediate threat to homeostatic functioning. This category includes physiologic stressors such as ether and hypoxia in animals and exposure to extreme heat or cold in humans. These stressors are more likely to evoke respiratory distress and to be interpreted as threatening survival. Additionally, the stress response elicited by these stimuli is not affected by lesions to PFC, amygdala, and hippocampus (Diorio et al., 1993; Feldman et al., 1994; Sapolsky et al., 1984, respectively). This provides evidence for a more direct pathway to the paraventricular nucleus of the hypothalamus, a major originating source of cortisol release (Herman & Cullinan, 1997).

One of the most commonly employed systemic stressors is the cold-pressor test (CPT), which involves immersion of the participants' hand into ice water for a matter of minutes (described by Hines & Brown, 1932). This procedure was originally developed for cardiovascular research due to its ability to reliably produce a pressor response (i.e., an increase in arterial blood pressure). CPT has been shown to reliably activate the SAM axis (as measured by increased skin conductance [Buchanan, Tranel, & Adolphs, 2006] and blood pressure [al'Absi, Petersen, & Wittmers, 2002]), as well as the HPA axis (as

measured by mild-to-moderate increases in salivary cortisol [McRae et al., 2006]).

Perhaps the most frequently used processive stressor is the Trier Social Stress Test (TSST). TSST typically involves participants' preparing a short speech, followed by delivery of said speech, and subsequent verbal performance of difficult mental arithmetic in front of a panel of multiple evaluators (often in white lab coats with audio and/or visual recording equipment as well; Kirschbaum, Pirke, & Hellhammer, 1993). Thus, creating a situation of social evaluation is critical for the successful implementation of the TSST. Of note, the TSST has been shown to reliably evoke a larger cortisol response compared to the CPT (McRae et al., 2006). That said, it requires greater cost in terms of personnel and facility demands making it a difficult protocol to implement. Completion of the full protocol can take 10-25 minutes and requires multiple laboratory personnel and space. The extended time needed to complete the TSST may also present a number of methodological confounds. Further, with an extended stressor it is plausible that individual differences in self-regulatory processes may be more likely to increase while the ability to disassociate the impact of the SAM and HPA axes on a subsequent behavioral task may be reduced. While the social evaluative component of the TSST has been cited as a critical element of its success in evoking strong HPA activation (Dickerson & Kemeny, 2004), the TSST is subject to high inter-individual variation as a function of age (Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004) and sex (Kudielka, Hellhammer, & Kirschbaum, 2007). Additionally, individual differences in comfort level with public speaking may also contribute to individual differences in cortisol variations. While research examining this idea has not yet been conducted, representing a gap in the literature, it is consistent with the notion that processive

stressors require higher-order processing to trigger the stress response.

### **The Brain's Reward Processing Circuitry**

Notably, some research indicates that stress exposure may influence brain function in regions involved in decision-making. Therefore, it is important to discuss the functional anatomy of decision-making, with special attention paid to overlap in stress effects on such regions. As discussed previously, behavior may be guided by two distinct systems: one that supports habitual responding (i.e., S-R associations) and one that produces goal-directed action, (i.e., A-O associations). Whether rewards are delivered contiguously to bolster S-R associations, or predictably in accordance with interpretable contingencies, it is necessary for the organism to possess the capacity to interpret stimulus and outcome valence in order to properly direct behavior. Research indicates that reward-related information is detected and processed by diverse brain regions that comprise the brain's "reward processing circuitry" (Rolls, 2000; Schultz, 2000).

That specific brain regions are important for processing rewarding stimuli was first demonstrated by Olds and Milner (1954), after observing persistent self-stimulation of several limbic structures in rats. Since that time, researchers have developed a functional schematic of the brain's reward processing functions (the meso-limbic dopamine system; Pierce & Kumaresan, 2006). Though variations in roles attributed to specific anatomy exist in the literature, this system is generally comprised of dopamine pathways linking together the ventral tegmental area (VTA), ventral and dorsal striatum, septum, hippocampus, amygdala, and prefrontal cortex (Ikemoto, 2007). For the purposes of the current study, primary attention is given to the prefrontal cortex and striatum. That said, both of these regions can be divided into independent but

overlapping areas, demarcated either by structural or functional characteristics, and play critical roles in reward processing.

**Prefrontal cortex.** The prefrontal cortex (PFC) is a large and functionally heterogeneous portion of cortex with multiple anatomical subdivisions. In the broadest sense, PFC is implicated in higher-order processes and executive functioning such as planning, flexible thinking, working memory, and decision-making (among others; Wood & Grafman, 2003). While the PFC can be divided along many structural and functional lines, given their well-documented role in reward processing and decision-making this proposal will focus primarily on the subdivisions that comprise the anterior cingulate cortex (ACC), medial PFC (mPFC), and orbitofrontal cortex (OFC).

The ACC is a relatively large brain region comprised of multiple sub-regions, which have been implicated in various cognitive and emotional processes (for review see Bush, Luu, & Posner, 2000). More specifically, the ACC has been consistently implicated in multiple functions involving processing of reward-related information. ACC activation has been observed during monitoring or correcting errors on various cognitive tasks (Botvinick, Braver, Barch, Carter, & Cohen, 2001), as well as during *punishment* trials (e.g., the loss of a monetary reward) during an incentive delay task (Knutson, Westdorp, Kaiser, & Hommer, 2000). The ACC has also been implicated for differential neuronal firing for positive and negative visual stimuli (i.e., increased responding for positive and decreased responding for negative stimuli), as well as for behaviors that led to painful (e.g., shock) or pleasant (e.g., food) consequences (Nishijo et al., 1997). Studies aimed at identifying functional differences within the ACC have implicated the dorsal portions of this region in higher cognitive functioning, while the

ventral ACC has been associated more with emotional processes (see Drevets & Raichle, 1998). Additionally, the processing of reward-related information (using a design similar to those discussed above) has also been linked more specifically to dorsal ACC (Bush et al., 2002).

The mPFC and OFC play a similar, yet distinct, role in reward processing. Though the anatomical boundaries between these two regions are somewhat blurred, functional heterogeneities may allow for their division (Ongur & Price, 2000). Within the OFC, distinct regional activation is observed as a result of positive (glucose) and aversive (salt) taste (O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001). Similar findings have been demonstrated using smell (Rolls, Kringelbach, & de Araujo, 2003), touch (Rolls, O'Doherty, et al., 2003) hearing (Blood, Zatorre, Bermudez, & Evans, 1999) and vision (O'Doherty et al., 2003). Studies have also demonstrated OFC activation in response to more abstract rewards, such as money (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). These results highlight the role for this region in processing rewarding and aversive environmental stimuli. Interestingly, several reports suggest spatial segregation between responses to rewards and punishments within OFC. Specifically, medial activation to rewards and lateral activation in response to punishment have been observed (for review see, Haber & Knutson, 2010; Kringelbach & Rolls, 2004; Porcelli & Delgado, 2009).

While OFC appears to play a role in differentiating stimuli valence (i.e., differential activation for positive versus negative stimuli), the mPFC may be more associated with predicting rewards and planning action based on reward outcome (Amodio & Frith, 2006; Knutson & Cooper, 2005). In one study, activity in mPFC



increased when monetary rewards were delivered consistent with expectation, and decreased when expected rewards were withheld (Knutson, Fong, Bennett, Adams, & Hommer, 2003). Studies also suggest that mPFC is sensitive to anticipated magnitude and probability of rewards (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Yacubian et al., 2006), as well as reward immediacy (Ballard & Knutson, 2009). It is noteworthy that the functional demarcation between OFC and mPFC is a source of ongoing research. Multiple studies have demonstrated the aforementioned mPFC characteristics in medial OFC as well (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Plassmann, O'Doherty, & Rangel, 2007; Rolls, McCabe, & Redoute, 2008).

The PFC has also been implicated as being particularly vulnerable to the effects of acute stress (i.e., increases in catecholamines and glucocorticoids). This effect has been demonstrated by stress-induced impairment on behavioral tasks requiring cognitive flexibility (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007) and working memory (Luethi, Meier, & Sandi, 2008). This negative impact is likely due to a synergistic interaction between catecholamines (e.g., dopamine, noradrenaline, and serotonin) and glucocorticoids (e.g., cortisol; Arnsten, 2009). In experiments measuring single neurons during a spatial working memory task, acute stress disrupted typical neuronal firing in PFC (Funahashi, Bruce, & Goldman-Rakic, 1989). At the same time, researchers have demonstrated stress-induced dopamine increases in PFC (Finlay, Zigmond, & Abercrombie, 1995) and pharmacological dopamine antagonists successfully ameliorate stress-induced impairment (Arnsten & Goldman-Rakic, 1998). Evidence for stress related impairment of PFC functioning also originates in studies employing multiple imaging modalities. For example, deactivation of mPFC after a psychosocial stressor has

been demonstrated using both positron emission topography (PET) and functional magnet resonance imaging (fMRI; Pruessner et al., 2008). Given influence of acute stress on PFC activity as represented in these studies, it is not surprising that PFC-based cognitive functions could be altered under conditions of acute stress.

**Striatum.** Another brain region critical for coding subjective value of external stimuli is the striatum. The striatum, along with globus pallidus, substantia nigra, and subthalamic nucleus, is a collection of subcortical nuclei that comprises the basal ganglia (Graybiel, 2000). The striatum receives most of the input from the neocortex. Other basal ganglia output information to the thalamus, which is relayed to PFC and other frontal regions, creating a series of parallel loops (Graybiel, 2000; Knutson, Delgado, & Phillips, 2008). The anatomy and function of these loops remain an exciting topic of interest for many researchers (for review see Pennartz et al., 2009), however, the current study focuses primarily on the various subdivisions of the striatum. The degree to which the striatum may be sub-divided in terms of structures is dependent on the spatial resolution of the chosen imaging technique (e.g., PET versus fMRI), as well as the particular species being observed. In human fMRI studies, the striatum is generally divided into a ventral region, comprised of the nucleus accumbens (NAcc), and a dorsal region, comprised of the caudate (dorsomedial) and putamen (dorsolateral).

The ventral striatum has been consistently implicated in the anticipation or prediction of monetary gains (Knutson et al., 2008), whereas the dorsal striatum may be more important for processing rewarding versus non-rewarding outcomes (Delgado, Locke, Stenger, & Fiez, 2003; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). The degree to which the outcome of a decision is congruent with the prediction is known as a

prediction error (Schultz, Dayan, & Montague, 1997). Interestingly, time course analyses of prediction errors for gain-related stimuli demonstrate earlier activation of ventral striatum, followed by activation of dorsal striatum up to four seconds later (Knutson et al., 2008). This temporal pattern of activation may represent a spatial-temporal flow of information. That is, basic reward information may first be processed by NAcc before being gradually integrated with other information via the striatal-hypothalamus-PFC loop, which moves dorsally through the striatum in a spiral fashion (Knutson et al., 2008).

Similar to OFC, stress-induced changes to striatum have also been observed. For example, in an animal model, acute stress (intermittent tail shock) is related to increased extracellular dopamine in ventral and dorsal striatum (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989) and chronic stress led to hypertrophy (i.e., increased neuronal density and dendritic length) in dorsolateral and atrophy in dorsomedial striatum (Dias-Ferreira et al., 2009). These studies demonstrate sensitivity of striatum to stress and provide evidence for the implicating role of dopamine. The functional differences between dorsolateral and dorsomedial striatum are of particular importance to this proposal and will be discussed further in the next section.

**Other reward-related regions.** Three other reward-related brain regions, while not a primary focus here, are noteworthy. First, the VTA, located near the midline of the ventral portion of the midbrain, serves as the origin of many excitatory pathways that comprise the reward network (Oades & Halliday, 1987). In addition to its excitatory projections to various reward regions, the VTA also receives information from the hippocampus (Lisman & Grace, 2005). In contrast to the frontal regions, which may be

important for the *processing* of rewarding and punishing stimuli, the hippocampus is important for *storing* information regarding the environmental contexts for which positive and negative stimuli are experienced (Fuchs, Eaddy, Su, & Bell, 2007). This information is then transmitted to VTA in order to activate or inhibit further excitation of the reward network (Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011). A final region of the reward circuitry worth mentioning is the amygdala. Located deep and medially within the temporal lobe, this almond-shaped region has consistently been associated with negative (for review see Calder, Lawrence, & Young, 2001) and positive states of arousal (Hamann & Mao, 2002). Stress hormones, such as noradrenaline and cortisol, have been associated with greater amygdala activation and enhanced memory consolidation for emotionally arousing event (for review see, Roozendaal, McEwen, & Chattarji, 2009). Therefore, the extent to which learning from environmental rewards and punishments evokes an emotional response, the amygdala plays a crucial role in the reward network. While all of the above brain regions play a critical role in decision-making, for the purpose of the current project the next section will look only at research implicating the PFC and striatum.

### **Learning and Decision-Making in the PFC and Striatum**

The PFC and striatum's role in processing pleasant and aversive stimuli make these regions especially critical for learning and decision-making. Associations between flexible, adaptive decision-making and OFC have been consistently demonstrated using experimental paradigms including single neuron recordings in non-human primates (Tremblay & Schultz, 2000) and a variety of PET and fMRI techniques in humans (Kringelbach & Rolls, 2004; Schoenbaum, Setlow, Saddoris, & Gallagher, 2003;

Tremblay & Schultz, 2000). The OFC has also been implicated in the learning of contingencies related to complex decision-making tasks (Bechara, Tranel, Damasio, & Damasio, 1996) and appropriately altering behavioral responses in reversal learning tasks (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999). In OFC-lesioned animals, the Pavlovian association between cues predictive of food (CS) and approach behavior (UR) was inhibited (Chudasama & Robbins, 2003). In the same study, OFC lesions also produced more maladaptive perseverative responding in a behavioral paradigm in which previously learned reward contingencies were altered (Chudasama & Robbins, 2003).

Within the striatum, various aspects of learning and decision-making can also be disassociated. Action-outcome learning and flexible, goal-directed decisions have been demonstrated to be associated primarily with dorsomedial striatum/caudate nuclei, while rigid and habitual behaviors, characteristic of stimulus-response relationships, are primarily associated with the dorsolateral striatum/putamen (Graybiel, 1998; Hikosaka, Takikawa, & Kawagoe, 2000). In rodents, lesion and pharmacological inactivation of dorsolateral striatum have been shown to render habit-based decisions sensitive to contingency manipulations (Yin, Knowlton, & Balleine, 2004; 2005, respectively). Similarly, pharmacological GABA agonists injected into the caudate region of non-human primate subjects inhibited acquisition of learning new motor tasks, while suppression of putamen disrupted previously overtrained responses (Miyachi, Hikosaka, Miyashita, Karadi, & Rand, 1997). Additionally, electrical stimulation of caudate immediately after a correct behavioral response has been shown to augment learning (Nakamura & Hikosaka, 2006).

Possessing dual circuitry that enables habitual and goal-directed systems allows

for maximum reward gains across many situations with varying degrees of certainty (Daw et al., 2005). However, it is plausible that over-reliance of either system would lead to disadvantageous outcomes (Bargh, 1996). Recent evidence suggests that acute stress may disrupt the natural interaction between these two systems. The overarching hypothesis of the current study is that exposure to acute stress will elicit a shift toward habitual decision-making, leading to negative outcomes in this particular context (i.e., rather than making goal-directed decisions based on new information that will lead to some reward, participants will rely on outdated information that is no longer relevant). Similar designs have revealed stress-induced shifts toward habitual responding in animals (Dias-Ferreira et al., 2009) and humans (Schwabe & Wolf, 2009, 2010) using food reinforcement. Specifically, these studies trained subjects to perform two instrumental responses, associated with specific stimuli, in order to gain two separate food rewards. After sufficient training, one of the two food rewards was devalued through selective satiety (i.e., subjects are allowed free access to one of the foods until that food is no longer wanted). Next, responses to the individual stimuli are measured in the absence of any reward. Results showed that when stress preceded instrumental conditioning, subjects responded equally to the stimuli associated with both the devalued and the non-devalued food reward. That is, stress facilitated habitual behavior by decreasing subjects' sensitivity to the changes in the value of food outcomes.

To the researcher's knowledge, this project is the first to examine a similar effect using a potent secondary reinforcer (i.e., money). Instead of using selective satiety to devalue a food reward, previously learned monetary values associated with task stimuli were altered via contingency reversal. Effectively this operationalizes the manner in

which real-world decisions can be associated with an ever-changing environment, necessitating that individuals alter their decision-making style to function optimally. Participants were then given the opportunity to make decisions for actual money based on these recently learned values, but they must abstain from responding in a way that would have been optimal pre-reversal in order to maximize their winnings. Thus, the current study pits participants' responses previously overtrained to the point of habit against newly acquired information requiring utilization of goal-directed decision-making. If acute stress promotes a shift in decision-making from goal-oriented to habitual, the current design should be able to detect this change.

There are three central aims to this project. First, *to develop evidence for the hypothesis that stress exposure promotes expression of habitual financial decisions over logical and deliberative ones*. It is expected that the results of the proposed experiment will support this hypothesis. If supported, this will add to the growing body of stress research and help to inform researchers and clinicians of the behavioral tendencies induced by stress. Similar designs have reliably shown stress-induced reliance on habit performance in animals. Few studies, however, have been designed to test the same principles in humans. Importantly, the current design is the first known attempt to examine stress-induced shift from goal-oriented to habit-based using a potent secondary reinforcer (i.e., money). Results from this study would likely spur future research designed to explore, more specifically, how to manage increased stress to make more advantageous decisions.

Second, this project aims *to determine the neural basis of stress' promotion of habitual financial behaviors using fMRI*. Toward this end, two specific hypotheses are

tested. First, it is hypothesized that regions of PFC and dorsomedial striatum will exhibit reduced responses to stimuli in those participants exposed to acute stress. Second, stressed participants will demonstrate enhanced dorsolateral striatal activation consistent with a shift from goal-directed to habitual decisions whereas non-stressed participants' decision-related striatal activation will be dorsomedially centered with additional reward-related activation in OFC. While multiple studies have examined neural activation of stress' effects on memory, the results from the current research would add to the dearth of imaging literature related to decision-making.

Third, this research aims *to examine the extent to which neuropsychological measures of executive functioning impacts the effects of habitual financial responding under conditions of acute stress*. The current study also examines various neuropsychological constructs (e.g., working memory, attention, and inhibitory control) in order to assess potential risk/protective factors related to stress-induced changes in decision-making behavior. While there is recent evidence implicating greater working-memory capacity as protecting goal-oriented decision-making after stress (Otto, Raio, Chiang, Phelps, & Daw, 2013), this idea is largely exploratory. It is hypothesized that higher functioning in these executive domains will attenuate the shift from controlled, to automatic decision-making processes under stress. These domains of executive functioning have been implicated to play a vital role in the development of substance use disorder and relapse is often brought about by acute stress. Therefore, the effect of individual differences in executive functioning on stress' impact on decision-making is of particular interest.



## METHOD

### Overview

The current study took place over four days. On day one, participants arrived at Marquette University and completed a cognitive test battery, questionnaires, and began learning an instrumental conditioning procedure. Baseline physiological measures were also collected during this time. On days two and three, participants engaged in the same instrumental conditioning task in order to facilitate a habitual pattern of responding. On the fourth and final day, participants arrived at the Medical College of Wisconsin and participated in a short stress (or control) procedure before completing two instrumental conditioning tasks in an MRI paradigm. The first task was the same conditioning task completed on days one through three. The second task was similar, except it required participants to reverse their now overtrained pattern of responding. Physiological measures (e.g., heart rate, blood pressure, skin conductance, and salivary cortisol) were collected before and after the stress procedure, and during the conditioning task inside the scanner. All study procedures were approved by the Medical College of Wisconsin Institutional Review Board.

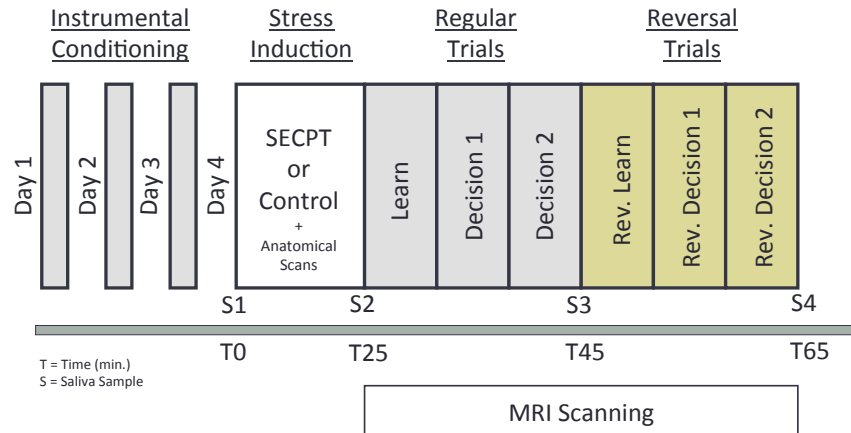


Figure 1. Visual depiction of procedural time line.

## Participants

Participants were solicited through a variety of means including flyer postings around Milwaukee and surrounding areas, newspaper ads, Internet postings, and word of mouth. In order to control for numerous environmental, behavioral, medical, and psychological conditions that could have a negative impact on the interpretation of study results, participants were excluded if they reported a history or evidence of: 1) neurological illnesses/conditions, such as motor or vocal tics (including a diagnosis of Tourette's syndrome), head trauma with significant loss of consciousness (>30 min), cerebral ischemia, vascular headache, carotid artery disease, cerebral palsy, epilepsy, brain tumor, dementia (including Alzheimer's disease and Mild Cognitive Impairment), chronic meningitis, multiple sclerosis, pernicious anemia, normal-pressure hydrocephalus, HIV infection, Parkinson's disease, and Huntington's disease; 2) severe medical illnesses/conditions that may affect brain function, such as untreated hypertension, cardiac disease, insulin-dependent diabetes mellitus, endocrine disorders, renal disease, glaucoma, and chronic obstructive pulmonary disease; 3) major psychiatric

disturbance meeting DSM-5 criteria; or 4) substance abuse meeting DSM-5 criteria. Additionally, participants were excluded from the study if they indicated taking prescribed psychoactive medications, or if they reported a history of cigarette or nicotine use. Participants were also excluded if they refused to refrain from alcohol use for 24 hours and caffeine use for 12 hours prior to testing.

In order to insure the safety of all participants and study personnel, additional exclusionary criteria were adopted specific to magnetic resonance (MR) scanning. These included: pregnancy, weight inappropriate for height, ferrous objects within the body, low visual acuity, and a history of claustrophobia. In addition, children ages 17 and younger are excluded from this study.

Finally, given the role of stress in the proposed study, additional exclusionary criteria apply in order to ensure participants' safety. These include: a history of cardiovascular illness (including but not limited to aneurysm, heart attack, congenital heart abnormalities, untreated hypertension), chronic rheumatologic disease, diabetes, Reynaud's Disease, and Cold Urticaria. Also, because prescribed contraceptives influence endogenous hormone levels (including cortisol – a major dependent variable in the proposed study), women taking prescription birth control were excluded.

Of 90 total individuals screened, 31 met all eligibility requirements and provided informed consent. One participant failed to complete the MRI scanning protocol due to scheduling limitations. Two participants' data were excluded due to initial MRI technical errors. The resulting sample of 28 participants (14 men and 14 women) ranging in age from 18-53 ( $M = 23.21$ ,  $SD = 6.93$ ) and all right-handed successfully completed the entire study protocol.

In order to retain participants, they were contacted via email or phone messages to remind them of their scheduled time. As compensation for their time, participants were paid \$10 per hour for participation on Days 1-3 and \$15 per hour on day 4 (i.e., involving MRI scanning). Total participation time was approximately 6 hours over 4 days. In addition, participants had the opportunity to earn bonus monetary compensation (between \$1 and \$15) based on choices made in the financial decision-making task. This is a standard in economic research, because if participants enter into a financial decision they know is hypothetical (i.e., not resulting in actual monetary outcomes), their decision-making is altered.

### **Sample Size Justification**

A power analysis was conducted using G\*power (G\*Power 3.0: Erdfelder, Faul, & Buchner, 1996) assuming a small effect size, (0.25, less than observed in similar work; e.g., [Schwabe & Wolf, 2009]), 2 experimental groups (Stress vs. No Stress) and 2 symbol valences (Reward vs. Aversive). Results indicated that in order to attain an effective power of 0.8 in decisions made for an experimental group x symbol valence interaction during day 4 tasks (i.e., those performed during MRI scanning), a minimum sample size of 34 would be required, though this is a conservative estimate as we expect a moderate effect size.

### **Procedures**

**Informed consent.** When participants arrived on day one they were given an overview of the study purpose and a detailed description of the study procedures. The researcher then walked through each part of the consent form, explaining each step.

During each of these procedures the researcher solicited questions and answered any that arose. Afterward, the researcher asked them to read it in its entirety and ask any remaining questions. The researcher and participant then signed and study procedures began afterward. Informed consent and study instructions took place again at the Medical College of Wisconsin on day four (prior to MRI scanning). Following the signature, participants were screened for (a) MRI Safety Exclusions (using the official MCW metal screening form), and (b) Stress Safety Exclusions, prior to continuing with additional cognitive testing, surveys, questionnaires, as well as behavioral tasks and MRI scanning.

**Cognitive test battery and other measures (Day 1).** Day one procedures included safety screening to protect participants from MRI and stress related injuries. After meeting the proper safety criteria, informed consent was completed. Next, participants were administered a brief neuropsychological test battery, which is briefly outlined below.

**Digit span.** In order to examine working memory, the forward (DF), backward (DF), and sequencing (DS) digit span tasks from (WAIS-IV) were administered. These tasks require participants to manipulate information for a brief period of time and are widely used in neuropsychological research and clinical assessment (Wechsler, 1939).

**Color-word inference.** In order to assess inhibition and cognitive flexibility, participants were also asked to complete a computerized color-word inference task based on the original Stroop procedure (Stroop, 1935). A series of words were displayed on the screen, one at a time, in various hues. The relationship between the word's hue and its semantic meaning was either congruent (e.g., the word "yellow" displayed in a yellow

hue), incongruent (e.g., the word “blue” displayed in a red hue), or neutral (e.g., the word “jacket” displayed in a green hue). The participants were asked to identify the color of each word presented on the screen by selecting a corresponding key on a number pad. A model of the response possibilities and their representative locations on the keypad (e.g., Digit 1 – Yellow; Digit 2 = Red; Digit 3 = Blue; Digit 4 = Green) remained at the bottom of the screen throughout the task.

**Conners continuous performance test, 3<sup>rd</sup> edition (CPT3).** The CPT3 was administered to assess sustained attention, vigilance, and impulsivity (Conner, 2014). In this computerized program, a series of letters are displayed on a computer screen one at a time. The participant was instructed to make a space bar response for every stimuli presentation except if the stimulus is an “X”. The task takes 15 minutes to complete and uses a variable inter-stimulus-interval (ISI) and inter-stimulus-event rate.

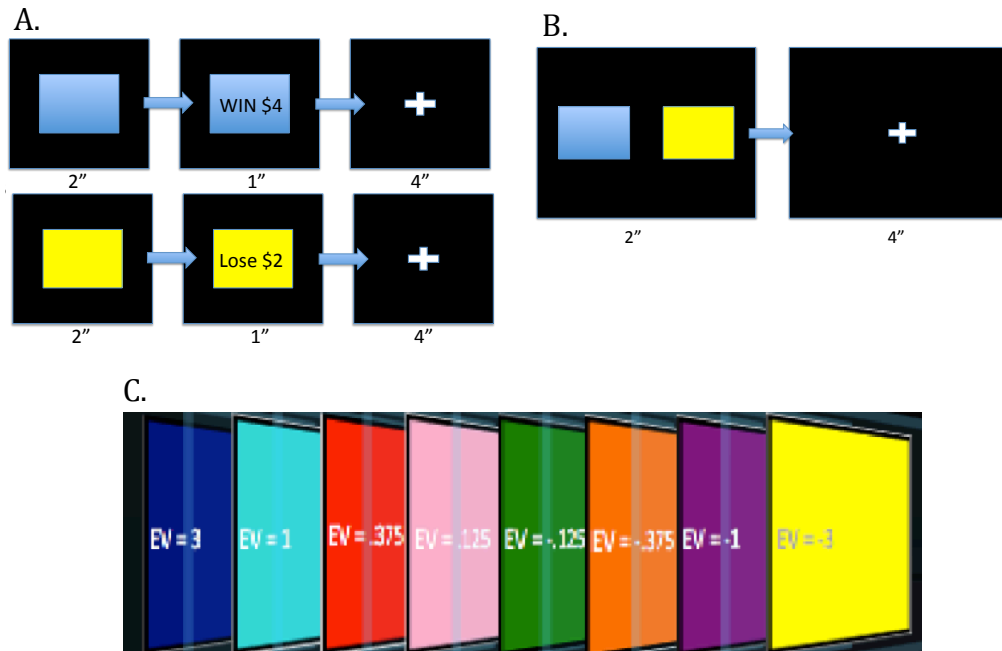
**Symbol-digit modalities test.** In order to measure processing speed, visual scanning, and applied nonverbal learning, the Symbol-digit Modalities Test and Digit Copy Test was administered (Smith, 1982). The former task required participants to substitute numbers for randomly presented symbols as quickly as possible.

**Trail making test (TMT) A & B.** TMT B assesses visual scanning, processing speed, and mental flexibility (Tombaugh, 2004). TMT-A requires participants to draw a line connecting 12 letters and 13 numbers randomly distributed numbers in sequential order, alternating between numbers and letters (e.g., 1-A-2-B-3-C, etc.).

The purpose of the neuropsychological battery is to gather information regarding individual differences in cognitive flexibility generally and working memory, impulsivity and processing speed specifically. These differences might serve as moderators of habit

acquisition and stress-induced changes observed during the reversal instrumental conditioning task.

**Instrumental conditioning task procedures *Days 1-3*.** The instrumental conditioning procedure requires participants to form preferences regarding multiple visual stimuli (e.g., colored squares presented on a computer screen) that are associated with specific monetary values (i.e., gains or losses of money; see Figure 2). Days one through three consisted of alternating “Learning” and “Decision” phases for a total of four phases. During the learning phase, participants were shown a single stimulus and had three seconds to make a button press. The button press reveals the monetary value associated with that stimulus. There are 8 total stimuli and each are presented eight times during each learning phase.



*Figure 2.* Visual representation of learning and decision phases. A) Two learning trials in which the stimulus is presented for two seconds, follow by one second of feedback, and a variable ITI with an average presentation of four seconds. B) Decision trial in which participants have two seconds to respond (via keyboard button press or scanner button box) followed by a variable four second ITI. C) List of each stimuli and associated pre-reversal EVs.

Importantly, each stimulus differs in terms of the magnitude, as well as, the probability of reward (Table 1). Participants were informed that no winnings or losses would occur during the learning phase. Next, during the decision phase, participants were asked to make decisions between counterbalanced pairs of the same visual stimuli in the absence of feedback. The purpose of the decision phases is to assess how well the participants have learned the reward/cost associated with each stimulus. Participants were told that responses made during the decision phase would result in real-life financial outcomes.



Table 1

*Summary Of Probability, Magnitude, and Expected Value for Each Stimulus*

Stimulus	pWIN	pLOSS	Payoff-Win (x)	Payoff-Loss (y)	EV
Blue Square	0.875	0.125	4	2	3
Aqua Square	0.625	0.375	4	2	1
Red Square	0.875	0.125	0.5	0.25	0.375
Pink Square	0.625	0.375	0.5	0.25	0.125
Green Square	0.375	0.625	0.5	0.25	-0.125
Orange Square	0.125	0.875	0.5	0.25	-0.375
Purple Square	0.375	0.625	4	2	-1
Yellow Square	0.125	0.875	4	2	-3

*Note.* The first four stimuli have a positive expected value (EV) and the last four have a negative EV. Stimuli with positive EV are considered advantageous, as they are more likely to result in a win compared to a loss.  $EV = (pS+ * x) - (pS- * y)$  where pS+ = probability of a gain; pS- = probability of loss; x = magnitude of win; and y = magnitude of loss. The pairings between EV and stimuli are reversed for the reversal task.

**Day 4 (Scan Day).** The fourth and final day took place during scanning at MCW.

Participants underwent an acute stress procedure (see Stress Induction section below), followed by the instrumental conditioning task (20-30 minutes later) inside the scanner. While in the scanner, participants completed one learning phase followed by two decision phases according to the same probability schedule as days one through three. Next, participants were informed that the stimulus-associations were altered. They completed one learning phase in which the associated reward-stimulus pairings were reversed (i.e., the stimuli previously associated with rewards were then associated with losses and vice versa). Following the reversal-learning phase, the participants completed two “reversal decision phases.” At no time did the financial outcomes of this task detract from

participants' compensation for participation in the study. Rather, they had the opportunity to win additional bonus compensation (e.g., \$0-\$15) based on the choices they make during financial tasks (via randomly selected trials that were given to the participant at the completion of the study).

### **Physiological Measurements**

Prior to entry into the scanner (e.g., before, during, and after the stress induction procedure, see below), participants' blood pressure and heart rate were recorded using an Omron automatic blood pressure monitor. Similarly, continuous HR, skin conductance, and respiration were recorded using a Biopac MP150 system. A GE scanner system was used to continuously record blood oxygen content via pulse oximetry and respiration. A Biopac MP150 system using MRI-safe amplifiers, leads, and electrodes were also used to continuously collect skin conductance levels during scanning from two sensors on the non-dominant hand and heart rate (via electrocardiogram using standard 3-lead with MRI-safe disposable electrodes).

Further, saliva samples were acquired prior to and during MRI scanning (e.g., a baseline sample before stress induction and a series of 5 samples over the remainder of the protocol) in order to measure salivary cortisol and alpha amylase levels. Samples were collected using a Salimetrics Oral Swab (Salimetrics, LLC, State College, PA) placed in a swab storage tube. All samples were placed in freezer storage (identified by number only) in a locked room in the psychology department at Marquette University prior to assaying. Saliva samples were assayed by study key personnel at Marquette's Biochemical and Immunoserological Core Laboratory. A competitive enzyme immunoassay technique was used to determine salivary cortisol concentration. The test

uses 25  $\mu$ l of saliva with a lower limit sensitivity of 0.19 nmol/L and a standard curve range of 0.33 to 82.77 nmol/L. Assays were conducted in duplicate and average cortisol concentrations were obtained. Intra- and inter-assay coefficients were 8.26% and 7.38%, respectively.

### **Stress Induction**

On the fourth day, approximately 20 minutes prior to task performance [as cortisol levels have been shown to peak 20-30 minutes after acute stress (Duncko, Cornwell, Cui, Merikangas, & Grillon, 2007)], participants randomly allotted to the experimental condition underwent a physiological stressor with a social evaluative component: the socially evaluative cold pressor, a novel variant of the cold pressor test (Schwabe, Haddad, & Schachinger, 2008). This task involves the participant placing their hand in ice-cold water (2-4 degrees Celsius) for a period of three minutes. Additionally, participants were instructed to stare into the lens of a camera while being observed by study key personnel as part of the social evaluative component. The combination of physiological and social stress has been shown to have a cumulative effect on the body's stress response and was used in the current study to maximize stress. The no-stress control group was asked to immerse their hand in room temperature water, with no evaluation or camera, for a similar period of time.

## **DATA ANALYSIS**

### **Psychophysiological Data**

**Hypothalamic-pituitary-adrenal axis (HPA) measures.** A 2 (Stress Group) x 4 (Sample) mixed ANOVA was used to examine main effects and interactions in salivary

cortisol levels.

**Sympathetic-adrenal medullary (SAM) axis measures.** Skin conductance levels (SCL) were calculated as the average waveform (in microsiemens [ $\mu\text{S}$ ]) during a 3-min period of baseline activity before the start of the conditioning task on Day 2. On the fourth day, SCL was calculated in the same manner during three, 3-minute bins in the mock scanner room at MCW. The first bin was collected after a minimum of 20 minutes of habituation. The second bin was collected during the 3 minutes of the socially evaluative cold pressor test (vs. control). Finally, SCL was measured for 3 minutes immediately following the stress procedure. Heart rate (HR) and blood pressure measures were collected in the same manner. Data were analyzed using a mixed ANOVA along the variables of interest specific to each task (as above).

### **Behavioral Data**

For decision-making portions of the task, where participants were presented with a choice between two stimuli per trial, choice of the stimulus that optimizes financial gains (i.e., associated with a higher monetary gain or lower loss than the other stimulus in the pair) are considered “good” whereas the opposite choice are considered “bad”. For example, if presented with two stimuli where the first was associated with +\$1 and the second -\$1, choice of the first would be “good” and the second “bad”. Similarly, faced with a choice between a stimulus associated with -\$5 versus -\$1, choice of the second would be considered “good”. The proportion of “good” and “bad” choices participants made over the course of each task was the primary dependent variable, and was examined via 2-way mixed-design ANOVA incorporating experimental group and participant decision quality (i.e., good/bad). Greenhouse Geisser adjustments were applied to

degrees of freedom as necessary to correct for sphericity violations if needed.

Additionally reaction time was analyzed via a 2-way mixed-design ANOVA incorporating the factors of experimental group and outcome valence. The independent variables for this analysis consisted of stress group (SECPT or control) and reversal phase (pre-reversal versus post-reversal).

### **Neuropsychological Measures**

The total number of errors for all incongruent trials on the color-word inference task was used to measure inhibitory control and cognitive flexibility. In order to measure impulse control, commissions – erroneous responses to target stimulus, X, were examined. Additionally, total time for completion on the symbol-digit modalities test was collected, yielding a measure of processing speed and WAIS-IV scores for Digit Span (total) measured working memory. Finally, total time to complete Trails B, was computed to obtain a measure of visual scanning and cognitive flexibility.

### **fMRI Analysis**

fMRI data were generated and analyzed using BrainVoyager QX (Goebel, 2012). Preprocessing involved motion correction (six-parameter, three-dimensional motion correction), spatial smoothing (4-mm FWHM), voxel-wise linear detrending, high-pass filtering of frequencies (3 cycles per time course) and normalization to Talairach stereotaxic space (Talairach & Tournoux, 1988). The number of activated voxels, whole brain and functionally defined regions of interest (ROI), was then calculated. Each voxel time series was temporally shifted to account for time differences in slice acquisition and spatially registered to reduce effects of motion using a rigid body iterative linear least

squares method. Motion parameters assessed during functional scans were incorporated as nuisance regressors.

Our rapid event related design consisted of trials spaced closely together in time, leading to a significant overlap of the hemodynamic response function. Relying on the assumption that the hemodynamic response function follows the principle of linearity, however, the overlapping responses can be dissociated using deconvolution analysis (or finite-impulse responding; FIR). First, general linear models (GLM) were defined at the single-subject level in which a set of shifted stick functions associated with each of the 10 TRs from stimulus onset was generated for predictors of interest (e.g., specific predictors for each stimuli associated with a particular EV in the learning phase, participants' decision quality in the decision phase, etc.). Thus, each stick function covered a span of 20 seconds after trial onset. These were regressed onto the dependent variable of blood-oxygen-level dependent (BOLD) changes within the brain (i.e., fMRI's dependent measure of "brain activity"). Next, participants' whole-brain time-course data were z-transformed, prior to entry into a second-level random effects group GLM. Finally, contrasts were performed to examine variations in BOLD associated with the fourth and fifth stick functions of predictors of interest (6-10 seconds after stimulus onset, approximating the potential temporal peak of the HRF).

If possible, contrasts were corrected for multiple comparisons by false discovery rate (FDR; Forman et al., 1995). When no clusters survived FDR correction, cluster-level corrections (Goebel, Esposito, & Formisano, 2006) were implemented. Specifically, the voxel level threshold was set to  $p = .005$  and a minimum cluster size threshold was calculated based on a Monte Carlo simulation procedure. This procedure quantifies the

minimum cluster size necessary to achieve false positive rates of less than 5% at the cluster level. Based on this whole brain analysis, parameter estimates were extracted and analyzed using contrasts which parallel the central variables of the task: (a) stress vs. no stress, (b) rewarding vs. aversive visual stimuli, and, (c) participants' decisions during the decision phase of the task. Additional whole-brain analysis included examination of variations in BOLD via stimuli valence (i.e., reward – aversive) contrasts and a 2 (Stress Group: Stress vs. No Stress) x 2 (Stimuli Valence: Reward vs. Aversive) mixed-design ANOVA for the learning phases. Similarly, BOLD variations derived from the decision phases were examined via decision quality (i.e., good – bad) contrasts and a 2 (Stress Group: Stress vs. No Stress) x 2 (Decision Quality: Good vs. Bad) mixed-design ANOVA. Beta weights from activation clusters that survived either method of correction stated above were extracted and post-hoc analyses were performed along the lines of stress group and reversal phase (i.e., pre- vs. post-reversal) in the case of simple contrasts and only along the lines of reversal phase for the mixed-design ANOVA. Given the absence of a behavioral baseline task and the nature of the aforementioned z-normalization procedures, the fMRI "baseline" around which all data are presented represents a whole-brain (i.e., global) z-score of 0.

## **RESULTS**

### **Subjective Ratings of Stress**

Post-experimental subjective ratings of perceived stress were examined between the acute stress and control groups via independent *t*-tests. These included ratings of how the SECPT procedure made participants feel (good to bad) and how stressful their

experience was (not at all to very much). Relative to the control group, the stress group rated their experience during the procedure as being a significantly worse,  $t(26) = 4.38, p < .001, d = 1.66$  and more stressful,  $t(18) = -6.66, p < .001, d = -2.52$  (see Figure 3).

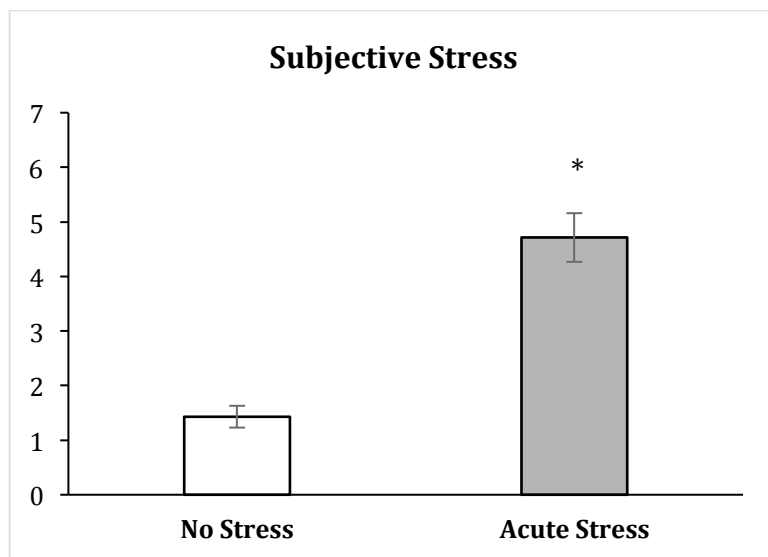


Figure 3. Participants in the acute stress group reported higher levels of subjective stress compared to the control group; \*  $p < .05$ .

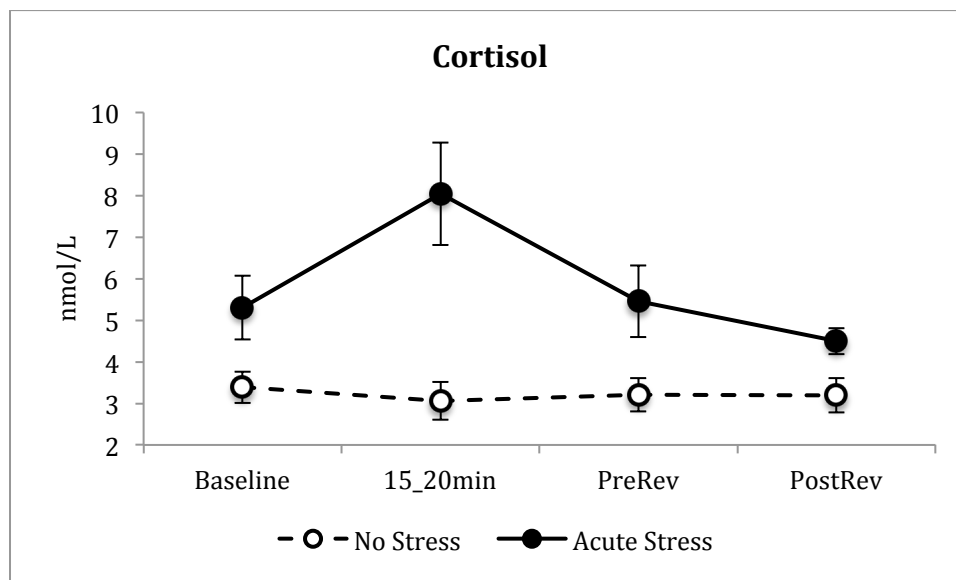
## Psychophysiological Measures

**Hypothalamic-pituitary-adrenal axis (HPA) Measures.** Salivary data were excluded from one participant due to insufficient saliva collection during MRI. Thus, cortisol analyses were conducted on 27 of the 28 participants (13 control and 14 acute stress). Mean salivary cortisol levels for all four samples are displayed in Table 2. The results of a 4 (Sample 1, 2, 3, or 4)  $\times$  2 (Experimental Group: Control vs. Stress) repeated measures ANOVA revealed a significant interaction,  $F(3, 23) = 3.37, p < .05, \eta_p^2 = 0.32$  (see Figure 4). In order to examine the effects of the interaction, post-hoc independent samples  $t$ -tests were conducted between groups for each sample. Results demonstrated



significantly higher levels of cortisol for the stress group for each sample, including baseline. These baseline differences are likely an effect of having a small sample.

Importantly, post-hoc paired samples *t*-tests revealed a significant increase from Sample 1 (Baseline) to Sample 2 (~30 minutes post-stress) for the stress group only,  $t(13) = -2.85, p < .05, d = -.75$ .



*Figure 4.* Mean cortisol concentration (nmol/L) for the acute stress and control groups across four time points. Only the acute stress demonstrated a significant cortisol response 15-20 minutes post SECPT or control.

Table 2

*Mean Salivary Cortisol Measurements*

Sample (nmol/L)	Experimental Group	
	Acute Stress	Control
Baseline	5.31 ± 0.77	3.35 ± 0.36
~30 Min Post-Stress	8.05 ± 1.23	3.00 ± 0.44
Pre-Reversal	5.45 ± 0.86	3.20 ± 0.40
Post-Reversal	4.50 ± 0.32	3.38 ± 0.44

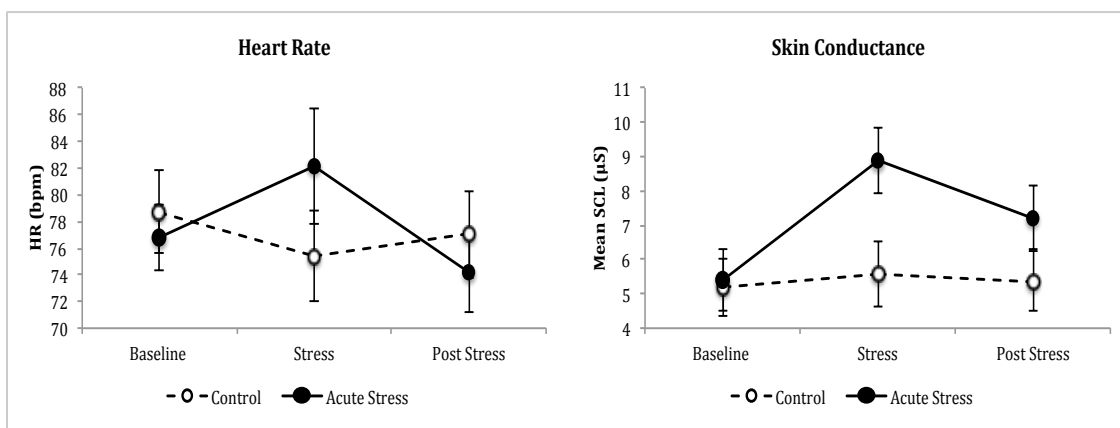
*Note.* Mean salivary cortisol and standard error of the mean (SEM).

**Sympathetic-adrenal medullary (SAM) axis Measures.** Mean HR measures during each phase of the acute stress procedure are displayed in Table 3. To examine SAM activation during the stress procedure, a 3 (Phase) × 2 (Experimental Group: Control vs. Stress) was conducted. Results revealed a significant interaction  $F(2, 52) = 8.34, p < .001, \eta_p^2 = 0.24$  (see Figure 5). Post-hoc comparisons demonstrated a significant increase in HR for the acute stress group only,  $t(13) = -2.42, p < .05, d = -0.46$ , followed by a significant reduction after the removal of the stressor,  $t(13) = 2.94, p < .05, d = 0.57$ .

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also collected during each phase of the stress procedure as additional markers of SAM activation. Blood pressure data were excluded from ten participants due to technical error, thus the following analyses were carried out on from 18 (9 Acute Stress and 9 Control) participants. A 3 (Phase) × 2 (Experimental Group: Control vs. Stress) ANOVA was conducted for both blood pressure measures. This resulted in significant phase by stress interactions for both SBP and DBP  $F(2, 32) = 17.77, p < .001, \eta_p^2 = 0.53$ , and  $F(2,$

32) = 21.29,  $p < .001$ ,  $\eta_p^2 = 0.57$ , respectively. Post-hoc comparisons between groups during stress manipulation revealed significantly higher SBP and DBP in acute stress group [SBP:  $t(16) = -5.25$ ,  $p < .001$ ,  $d = -3.26$ ; DBP:  $t(16) = -5.71$ ,  $p < .001$ ,  $d = -2.69$ ].

Mean SC levels during each phase of the acute stress procedure are displayed in Table 3. A third 3 (Phase)  $\times$  2 (Experimental Group: Control vs. Stress) ANOVA was conducted to assess SC response, yet another marker of sympathetic activation. Results demonstrated a significant interaction effect,  $F(2, 52) = 14.99$ ,  $p < .001$ ,  $\eta_p^2 = 0.37$  (see Figure 5). Follow-up independent  $t$ -tests demonstrated significantly higher SC levels for participants in the acute stress group  $t(26) = -2.4$ ,  $p = < .05$ ,  $d = .91$ .



*Figure 5.* Mean HR and SCL for each experimental group capturing response to SECPT or control procedure. Only the acute stress group demonstrated a significant increase in HR and SC response to the experimental manipulation.

Table 3

*Mean Sympathetic Measurements During Acute Stress Procedure*

	Experimental Group			
	Acute Stress		Control	
	HR	SC	HR	SC
Baseline	76.08 ± 2.5	5.41 ± 0.9	78.47 ± 3.1	5.2 ± 0.84
Stress	82.18 ± 4.36	8.87 ± 0.96	75.41 ± 3.39	5.59 ± 0.96
Post Stress	74.17 ± 2.96	7.21 ± 0.92	77.02 ± 3.29	5.35 ± 0.87

*Note.* Heart rate (HR; bpm) and skin conductance (SC;  $\mu$ S) were collected in 3-minute bins.

**Behavioral Data**

**Days 1-3 reaction time (learning trials).** A 3 (Day)  $\times$  8 (EV) repeated measures ANOVA revealed a significant interaction  $F(14, 378) = 1.80, p < .05, \eta_p^2 = 0.06$ . In order to simplify interpretation, a follow-up 3 (Day)  $\times$  2(EV) ANOVA was conducted in which only the most positive (EV = 3) and most negative (EV = -3) stimuli were assessed. Due to their association with the most extreme EVs, these stimuli were likely most salient during learning. Results from the follow-up ANOVA also demonstrated a significant interaction,  $F(2, 54) = 4.36, p < .05, \eta_p^2 = 0.14$ . This interaction was characterized by a decrease in RT for the most positive stimulus from day 1 to day 3,  $t(27) = 2.86, p < .01, d = .59$ , but no change in RT for the most negative stimulus.

**Days 1-3 decision quality (decision trials).** Data regarding decision quality were examined by identifying trials in which the subject chose the square that was most advantageous (or less disadvantageous) during the decision trials. Once the data were corrected for null trials, the number of good to bad trials were exactly proportional, thus

analyses here were performed on good choices only. The percentage of good decisions was measured for each of the three training days using repeated measures ANOVA (see Figure 6). Results indicated a significant main effect of Day,  $F(1.40, 37.83) = 24.21, p < .001, \eta_p^2 = 0.47$ . Post-hoc  $t$ -tests revealed a significant increase in correct responses from Day 1 ( $M = 66.27\%$ ,  $SD = 12.22\%$ ) to Day 2 [ $M = 76.30\%$ ,  $SD = 11.13\%$ ;  $t(27) = -4.62, p < .001, d = -.86$ . Notably, decision quality reached asymptote on Day 2 with non-significant improvement on Day 3 ( $M = 78.1\%$ ,  $SD = 10.29\%$ ).

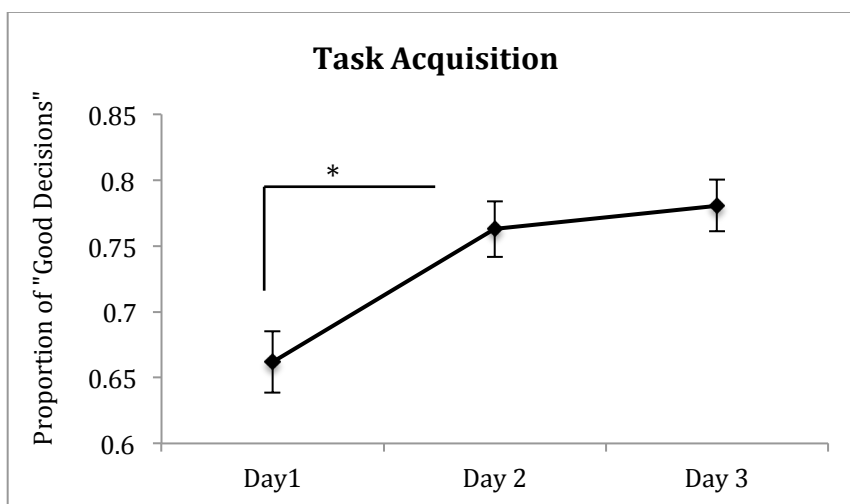


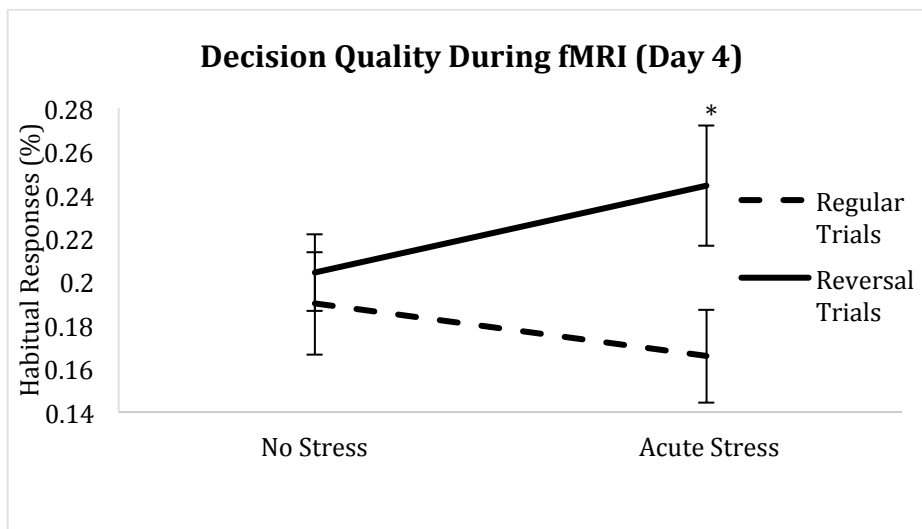
Figure 6. Proportion of good decisions across the first three days of instrumental conditioning, combined across groups; \*  $p < .05$ .

**Scan day reaction time (learning trials).** A 2 (Reversal Phase) X 8 (EV) X 2 (Stress Condition) mixed design ANOVA revealed a main effect of EV,  $F(7, 182) = 2.09, p < .05$  that failed to maintain significance after accounting for a violation of sphericity. No other within or between group findings were observed.

**Scan day decision quality (decision trials).** When examining decision quality, one subject in the control condition performed significantly worse (more than 2 SD from

the control group mean). Additionally, this particular participant reported difficulty staying awake during this portion of the task. Importantly, removal of this individual did not alter the significance of the results below. Thus, this subject's average post-reversal bad decision score was windzORIZED.

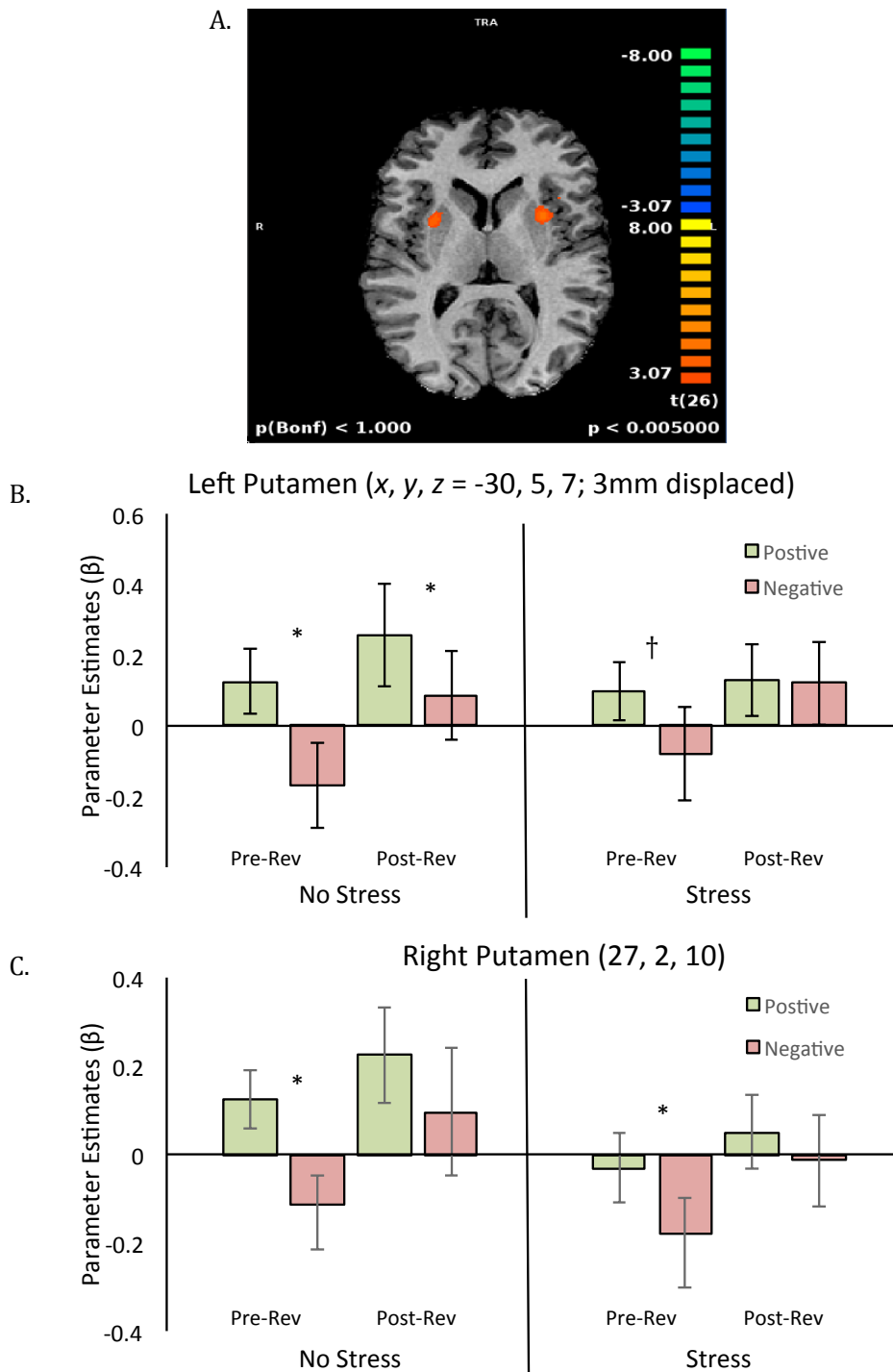
The proportion of good decisions from the two pre-reversal trials was averaged separately from the post-reversal trials to compose a pre- and post-reversal decision quality score. In order to examine the effect of acute stress on habitual decisions, a 2 (Bad decisions for Pre- vs. Post-Reversal)  $\times$  2 (Acute Stress vs. No Stress) mixed ANOVA was conducted (see Figure 7). Results demonstrated a significant main effect of Reversal  $F(1, 26) = 10.06, p < .005, \eta_p^2 = 0.28$ , as well as significant reversal-stress group interaction  $F(1, 26) = 6.88, p < .05, \eta_p^2 = 0.21$ . Post-hoc paired samples  $t$ -tests were used to examine significant changes in bad decisions from pre- to post-reversal within each experimental group. Results indicated a significant increase in Bad decisions for the stress group only [pre-reversal bad decisions:  $M = 16.51, SD = 6.62$ ; post-reversal bad decisions:  $M = 24.50, SD = 10.22; t(13) = -4.1, p < .005, d = -.93$ ]. No significant between group differences for bad decisions post reversal were observed,  $t(26,) = -1.20, p = .24$ .



*Figure 7.* Proportions of “Bad” decisions for overlearn stimuli (regular trials) and after probabilistic stimuli associations were reversed (reversal trials) for acute stress and control group. Stress group participants made decisions more “in line” with the original overtrained (i.e., habitual) values post-reversal; \*  $p < .05$ .

## fMRI Results

**Stimuli valance (Learning): positive EV – negative EV contrast.** Functional ROIs were generated by applying a positive EV – negative EV contrast for all learning trials [(Pre-Reversal Positive EV + Post-Reversal Positive EV) - (Pre-Reversal Negative EV + Post-Reversal Negative EV)]. This whole-brain contrast yielded significant activation in the right putamen and a relatively large activation cluster in the left putamen (slightly displaced) that extended into the claustrum and anterior insula. Parameter estimates were extracted from the whole ROI in the right putamen, but limited to 8 cubic mm<sup>3</sup> around the peak voxel of left putamen ROI. In this case, limiting extraction around the peak voxel allowed the researcher to minimize the contribution of the claustrum and to exclude the anterior insula from post-hoc analyses (see Figure 8).

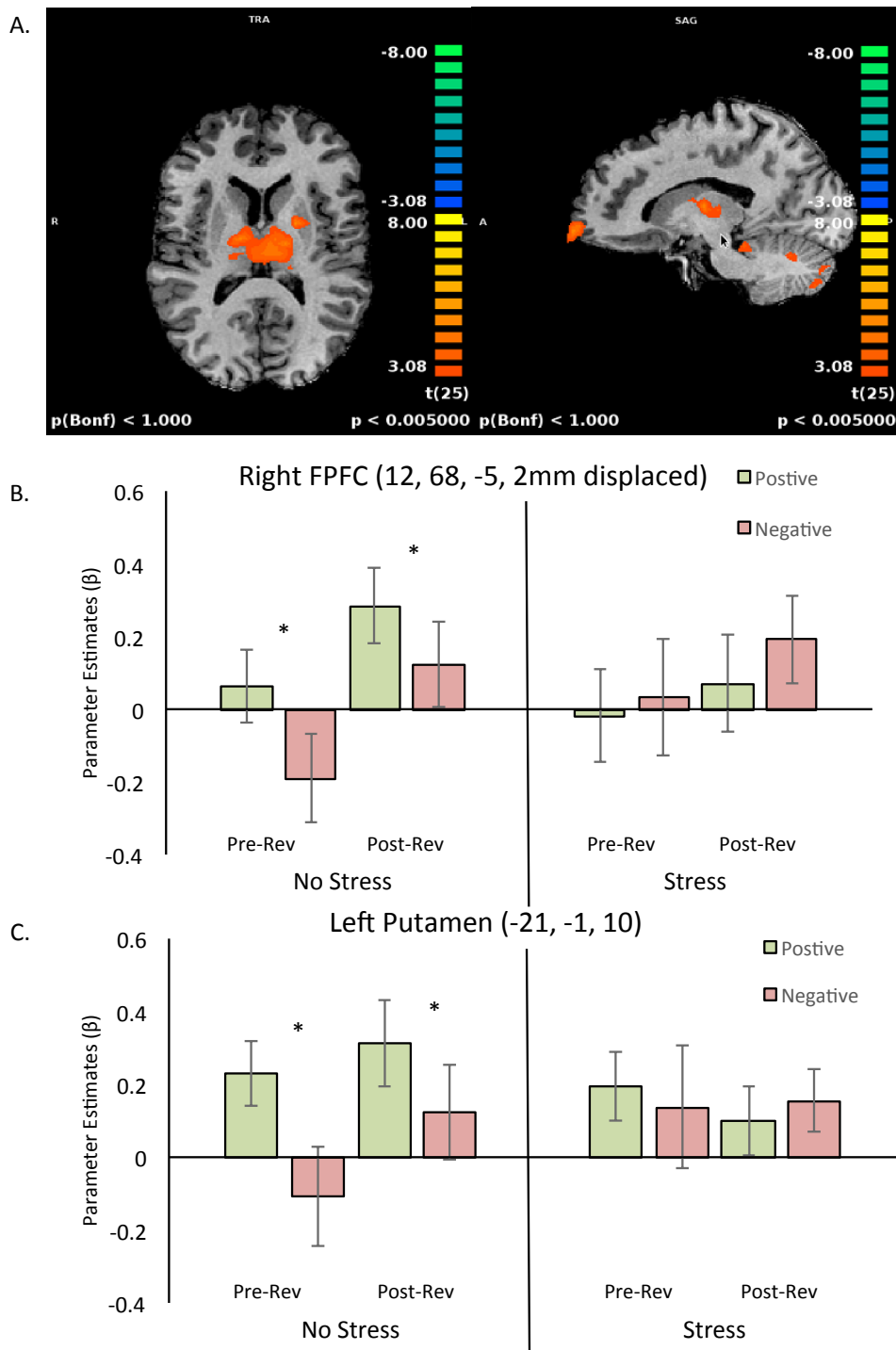


*Figure 8.* A) Activated ROIs for positive EV – negative EV contrast during learning trials. B and C) Post-hoc examination of ROIS along the lines of stress group and reversal phase; differential activation between positive and negative stimuli was maintained in the putamen for the pre-reversal trials in both acute stress and control groups; \*  $p < .05$ ; †  $p = .05$ .



In order to examine differences in putamen activation between over-trained and novel stimuli, parameter estimates for pre- and post-reversal were compared within and between experimental groups. In the right putamen, differential activation for positively and negatively valenced stimuli was significant for the pre-reversal stimuli only. This significant differential activation was observed for both the control,  $t(12) = 3.96, p < .005, d = .90$  and acute stress group,  $t(13) = 2.22, p < .05, d = .34$ . In the left putamen, the same significant differential activation was also observed for the pre-reversal stimuli in the control group,  $t(12) = 3.82, p < .005, d = .69$ , and trended in the same direction for the acute stress group,  $t(13) = 2.11, p = .05, d = .56$ . Unlike the results from right putamen, the differential activation between positively and negatively valenced stimuli in the left putamen was significant for novel stimuli during the reversal trials, but only for the control group,  $t(12) = 2.85, p < .05, d = .43$ . *Post-hoc t*-tests comparing activation in both right and left putamen did not reveal significant differential BOLD responses within the stress group.

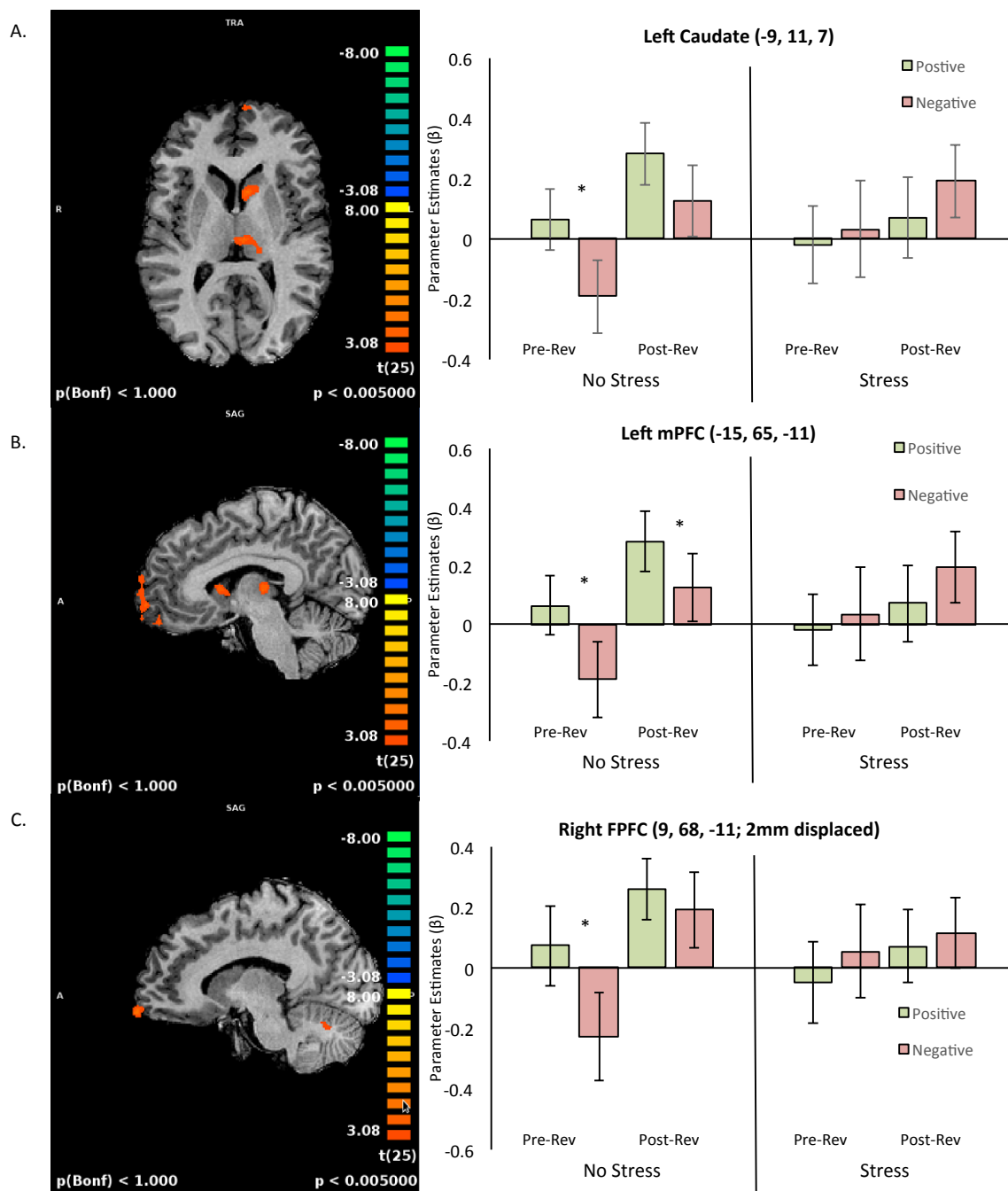
**Stimuli valance (Learning): positive EV – negative EV by experimental group contrast.** To examine differences in differential responses to positively versus negatively valenced stimuli between stress groups, a contrast of positive EV – negative EV was computed along the between-subjects factor of stress group [(No Stress Positive EV – No Stress Negative EV) - [(Stress Positive EV – Stress Negative EV)]]. This contrast yielded significant clusters in right frontopolar prefrontal cortex (FPFC) and left putamen, as well as broad activation of thalamus (see Figure 9).



*Figure 9.* A) Activated ROIs for positive EV – negative EV by experimental group contrast. B and C) Post-hoc examination of ROIS along the lines of stress group and reversal phase; differential responding for positive and negative stimuli during pre- and post-reversal was achieved in the left putamen and FPPFC for the control group only; \*  $p < .05$ .

To further examine the nature of this interaction, parameter estimates for positive and negative stimuli were divided along the lines of pre- and post-reversal trials within each experimental group. In the control group, the right FPFc exhibited significant differential activation for positive and negative stimuli during pre- and post-reversal learning,  $t(12) = 4.49, p < .01, d = .63$  and  $t(12) = 2.33, p < .05, d = .40$ , respectively. In the acute stress group, however, significant differential activation between stimuli valence was not observed during either pre- or post-reversal condition,  $t(13) = -.68, p = .51$  and  $t(13) = -1.72, p = .12$ , respectively. A similar pattern of activation was detected in the left putamen cluster. That is, significant differential activation between stimuli valence during both pre- and post-reversal was observed in the control group,  $t(12) = 6.02, p < .001, d = 1.02$  and  $t(12) = 2.35, p < .05, d = .46$ , respectively, but not the acute stress group,  $t(12) = -.47, p = .65$  and  $t(12) = -1.23, p = .23$ , respectively. No significant between group differences were observed in either the FPFc or putamen.

**Stimuli valance (Learning): positive EV – negative EV by experimental group contrast (Pre-Reversal Only).** Next, a positive EV – negative EV contrast for pre-reversal trials only was computed along the between-subjects factor of stress group [(No Stress Pre-Reversal Positive EV – No Stress Pre-Reversal Negative EV) - [(Stress Pre-Reversal Positive EV – Stress Pre-Reversal Negative EV)]. This was limited to pre-reversal trials only. An independent examination of pre-reversal activation provides a more robust analysis of functional activation associated with overtrained stimulus-response associations. This contrast yielded activation clusters in right PFC (2mm displaced), left mPFC and left caudate (see Figure 10).



*Figure 10.* Activated ROIs during the pre-reversal learning trials only based on a positive EV – negative EV by experimental group contrast and associated post-hoc analyses along the lines of stress group. The same ROIs were also applied to the post-reversal learning trials for both experimental groups. Regions associated with goal-directed behaviors displayed differential activation for positively and negatively valenced stimuli, but only in the control group. Only mPFC maintained differential activation during the reversal trials; \*  $p < .05$ .

In the left mPFC, the differential activation between positively and negatively valenced stimuli was significant in the control group only,  $t(12) = 5.04, p < .001, d = .69$ . Interestingly, higher levels of activation corresponding to negatively valenced stimuli were observed for the control group, while lower BOLD levels were observed for the acute stress group. This difference trended toward significance,  $t(25) = -1.89, p = .07$ .

In the control group only, significant differential activation between positively and negatively valenced stimuli was also observed in the left caudate;  $t(12) = 5.85, p < .001, d = .89$  and right PFC,  $t(12) = 6.07, p < .001, d = .60$ . There were no significant between group differences in either the caudate or PFC. When these three ROIs (mPFC, left caudate, and right PFC) were applied to the reversal-learning data, only the mPFC for the control group demonstrated continued differential responding,  $t(13) = -2.24, p < .05, d = -.31$ .

**Stimuli valance (Learning): positive EV – negative EV by experimental group contrast (Post-Reversal Only).** When computing the positive EV – negative EV contrast along the between-subjects factor of stress group [(No Stress Post-Reversal Positive EV – No Stress Post-Reversal Negative EV) - [(Stress Post-Reversal Positive EV – Stress Post-Reversal Negative EV)]], a single activation cluster was observed near the posterior portion of the superior frontal gyrus, a portion of the supplementary motor area (SMA).

First, to directly assess the specific nature of this significant interaction cluster paired samples t-tests were conducted between positively and negatively valenced stimuli in both the control and acute stress group. Results demonstrated significantly greater activation for negatively valenced, compared to positively valenced stimuli in the acute

stress group,  $t(13) = -4.91, p < .001, d = -.73$ , but not the control group,  $t(12) = 1.48, p = .17$ . This was the only analysis that yielded significant differential activation between positively and negatively valenced stimuli in the stress group during post-reversal learning. Between-group differences for activation associated with either positive or negative stimuli were not observed. Interestingly, when applying this ROI to pre-reversal learning trials, the differential activation was observed in the control group only,  $t(12) = 2.28, p < .05, d = .60$ .

For a review of functional ROIs associated with differential BOLD activation for positive versus negatively valenced stimuli, refer to Table 4.

Table 4

*ROIs Indicating Significant Differential Activation Between Positively and Negatively Valenced Stimuli During Learning*

Contrast	Pre-Reversal		Post-Reversal	
	Control	Stress	Control	Stress
1	R Putamen	R Putamen	L Putamen	-
	L Putamen	L Putamen		
2	FPFC	-	FPFC	-
	mPFC	mPFC		
3	L Caudate	-	-	-
	R PFC			
4	SMA	-	-	SMA

*Note:* Contrast 1: Positive EV – Negative EV; Contrast 2: Positive EV – Negative EV X Experimental Group; Contrast 3: Positive EV – Negative EV (pre-reversal only) X Experimental Group; Contrast 4: Positive EV – Negative EV (post-reversal only) X Experimental Group

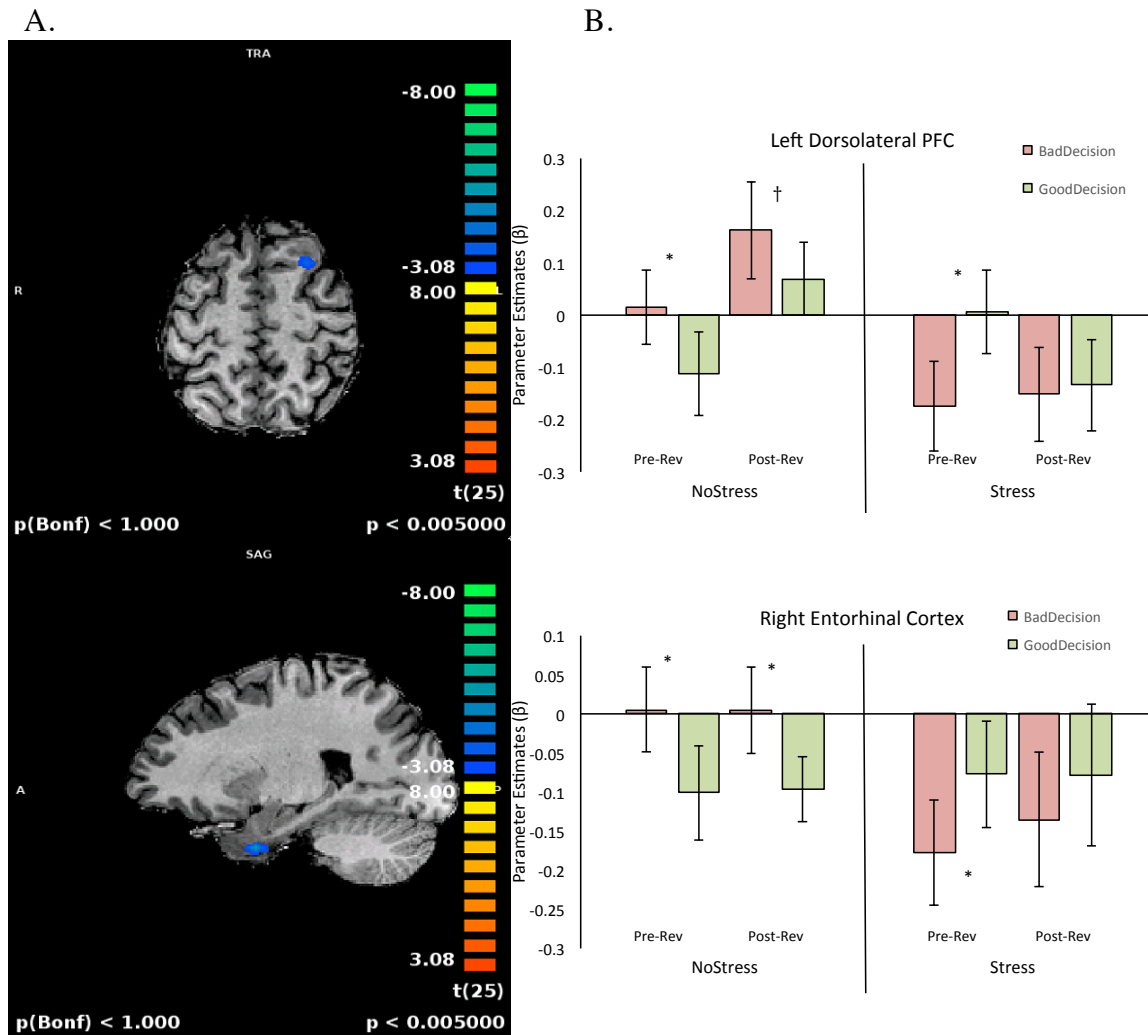
**Decision quality: Composite Good Choice – Bad Choice.** In order to assess neural function during the decision phase, a simple good choice – bad choice contrast was applied to the whole brain [(Pre-Reversal Good Decision + Post-Reversal Good Decisions) - (Pre-Reversal Bad Decisions + Post-Reversal Bad Decisions)]. To increase power, good choices from both pre- and post-reversal trials were averaged together, as were bad choices. This contrast yielded significant activation in the left and right anterior insular cortex, as well as the dorsomedial anterior cingulate cortex. Beta values were extracted from these three regions and post-hoc analyses performed. In both the left and right anterior insular cortex, greater activation was observed in the context of bad decisions compared to good decisions. In the left anterior insula of the control group, this difference was observed in both the pre- *and* post-reversal decision phase,  $t(12) = 3.87, p < .01, d = .90$  and  $t(12) = 3.28, p < .01, d = .77$ ; respectively.

Likewise, the same differences were also observed in the acute stress group for both the pre- and post-reversal decision phases,  $t(13) = 4.84, p < .001, d = .90$  and  $t(13) = 3.01, p < .05, d = .54$ ; respectively. Similar findings were observed in the right anterior insular cortex. While there were no between experimental group differences, there was a significant reduction in overall insular activation from pre- to post-reversal decision, regardless of decision quality, in the stress group only. This difference was observed in both the left and right insula,  $t(13) = 2.83, p < .01, d = .90$  and  $t(13) = 3.01, p < .01, d = .81$ ; respectively. In the ACC, greater activation was associated with bad decisions compared to good decisions. There was no effect of decision phase or stress group.

**Decision quality: Composite Good Choice – Bad Choice by experimental group contrast.**

Next, a Good Decision – Bad Decision contrast for pre-reversal trials only was computed along the between-subjects factor of stress group [(No Stress Good Decision – No Stress Bad Decision) - [(Stress Good Decision – Stress Bad Decision)]]. This contrast yielded significant activation clusters in the right entorhinal cortex (EC) and left dorsolateral PFC (DLPFC; see Figure 11).





To further examine the nature of this interaction, parameter estimates for good and bad decisions were divided along the lines of pre- and post-reversal trials. In the control group, the right EC exhibited significantly less activation for good decisions compared to bad decisions during pre- and post-reversal learning,  $t(12) = -2.25, p < .05, d$

= -.51 and  $t(12) = -2.87, p < .05, d = -.57$ , respectively]. In the acute stress group, differential activation was characterized by significantly less activation for bad decisions during the pre-reversal decision task,  $t(12) = -4.73, p < .001, d = .40$  and a similar non-significant pattern of responding post-reversal,  $t(12) = -1.28, p = .22$ . Between group analyses demonstrated significantly greater activation of the EC in the control group during pre-reversal decisions,  $t(25) = 2.11, p < .05, d = .82$ . A similar post-reversal finding trended in the same direction,  $t(25) = 1.34, p = .19$ .

In the left prefrontal cortex, parameter estimates for good and bad decisions were divided along the lines of pre- and post-reversal as above. During the pre-reversal decisions, post-hoc analyses revealed higher BOLD activation for bad decision in the control group,  $t(12) = 2.78, p < .05, d = .44$  and lower BOLD activation for bad decisions in the acute stress group,  $t(13) = -4.24, p < .005, d = -.58$ . During the post-reversal decisions, the control also exhibited higher levels activation for bad decisions that trended toward significance,  $t(12) = 1.50, p = .16$ , while no differential activation was observed in the acute stress group. Interestingly, when averaging across decision quality the DLPFC activation was significantly higher in the control group compared to the acute stress group,  $t(25) = 2.26, p < .05, d = .88$ . No between group differences were observed for pre-reversal decisions. See Table 7 for a full listing of all activated ROI clusters for each contrast reported above.

### **Neuropsychological Results**

In order to examine the impact of baseline neuropsychological functioning, Day 1 scores on 5 tests (i.e., Trails B, SDMT, Digit Span, Stroop, and CPT Commissions) measuring various aspects of executive functioning (e.g., working memory, attention,

processing speed, and impulsivity) were selected for analysis (See Table 5 for means and standard deviations of raw and standardized scores). These measures were selected based on their theoretical relation to executive functioning and a suitable amount of common variance (coefficients of .3 and above) necessary to conduct the planned factor analysis. In assessing the factorability of the above measures, the Kaiser Meyer-Olkin value was .59, approaching the recommended value of .6 (Kaiser 1970, 1974) and Bartlett's Test of Sphericity (Bartlett 1954) reached statistical significance. Together, these findings broadly support the factorability of the correlation matrix.

Table 5

*Description of Raw and Standardized Neuropsychological Test Scores*

Test	n	Raw		Standardized	
		Mean	SD	Mean	SD
Trails B	28	53.29 sec.	15.93 sec.	102.64	12.12
SDMT	28	54.82 ct.	8.96 ct.	90.54	12.58
WAIS IV-Digit Span Total	28	29.89	5.03	103.21	13.42
Computerized Stroop*	27	93.81	3.8	Z 0	Z 1
CPT Commissions <sup>^</sup>	28	T 49.25	T 7.84	98.92	11.66

*Note:* \*Raw score represents percent correct during incongruent trials. These scores were then z-transformed. All other scores were standardized using Heaton (Trails B and SDMT) or manualized normative data. <sup>^</sup>T-scores generated by Conners's CPT 3 computer scoring program are listed in lieu of raw scores.

Principal component analysis (PCA) revealed two components with eigenvalues exceeding 1, explaining 43.04% and 27.13% of the variance, respectively. To aid in the

interpretation of the two components, oblimin rotation was performed. The rotated solution revealed the presence of a simple structure (Thurston 1947), with both components showing strong loadings and each variable loading substantially to only one component. The interpretation of the first component, which is made up of Digit Span, Trails B, and Symbol Digit, relates to a global working memory/attention construct. The second component, containing CPT Commissions and Stroop, is can be interpreted as a measure of impulsivity.

To further examine the appropriateness of this 2 factor solution, the initial eigenvalues were compared to eigenvalues generated from random data using the parallel analysis technique originally developed by Horn (1965). Specifically, 1000 random data sets containing the same number of cases ( $n = 28$ ) and variable (5) were generated according to the constraints of O'connor (2000) in order to compute a series of random eigenvalues. While the initial researchers who developed this approach compared the actual eigenvalues to the mean values derived from the random data (Horn, 1965), currently it is more common to compare obtained eigenvalues to the 95<sup>th</sup> percentile of random eigenvalues (Glorfeld, 1995 as cited in Hoelzle & Meyer, 2013), limiting the likelihood of over extraction. Both the obtained and randomly generated (i.e., mean and 95<sup>th</sup> percentile) eigenvalues are displayed in Figure 12. The obtained eigenvalue of the first factor (2.11) was greater than both the mean and 95<sup>th</sup> percentile of randomly generated eigenvalue (1.57 and 1.82, respectively). The obtained eigenvalue of the second factor (1.36) was greater than the randomly generated mean eigenvalue (1.21) but fell short of the randomly generated 95<sup>th</sup> percentile eigenvalue (1.39). Nevertheless, the obtained eigenvalue of 1.36 is greater than 1.3 standard deviations above the randomly

generated mean, which when combined with theoretical understanding for the proposed two-factor solution, extraction of the second factor is not unwarranted.

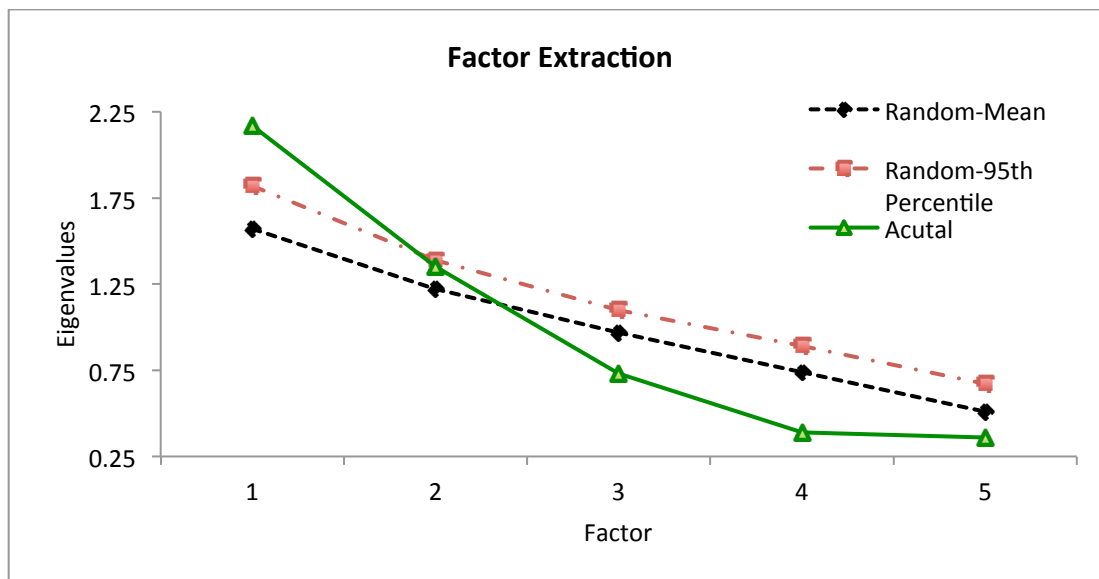


Figure 12. Original eigenvalues for Day 1 scores on 5 tests (i.e., Trails B, Coding, Digit Span, Stroop, and CPT Omissions) measuring various aspects of executive functioning (e.g., working memory, attention, and processing speed) plotted against randomly generated eigenvalue means and 95<sup>th</sup> percentile.

Next, correlations between the two resulting factor scores and the post-reversal bad decisions were computed for the stress group only. Neither the attention/working memory component, nor the impulsivity component significantly correlated with post-reversal bad decisions, [ $r(12) = -.425, p = .15$  and  $r(12) = -.01, p = .97$ , respectively]. Because neither factor was significantly correlated with the dependent variable, the planned regression analysis was not performed. Instead, a simple set of correlations was conducted to examine the potential for relationship between the primary dependent variable and each individual neuropsychological measure. Because these variables were no longer being compiled, raw scores were used for these correlations. Raw scores

provide a “clean” measure of the tested construct, independent from factors of sex, ethnicity, and age. The results from these correlations are listed in Table 6. Notably, only Trails B scores were significantly correlated with post-reversal bad decisions in the stress group ( $n = 14, r = .68, p < .01$ ).

Table 6

*Correlations Between Five Cognitive Variables and Habitual Decisions Post Stress*

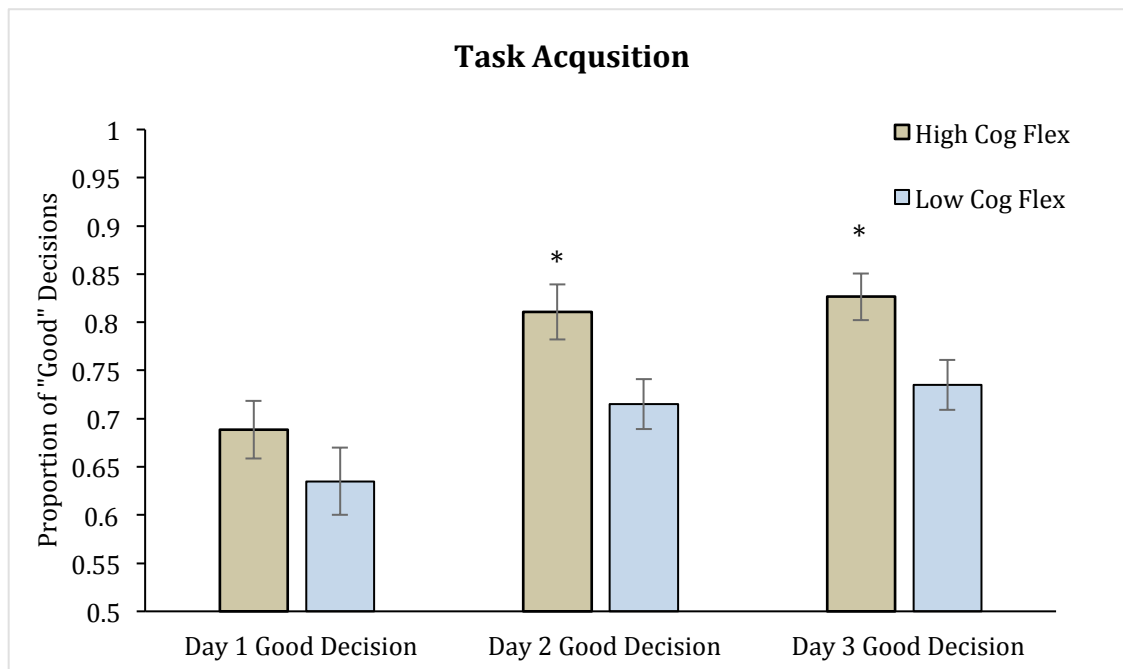
Measures	1	2	3	4	5
1. Trails B	-				
2. Stroop	0.2	-			
3. Symbol Digit	-0.42	0.15	-		
4. Digit Span	-.78*	-0.25	0.44	-	
5. Conner's Commissions	-0.34	0.32	0.23	-0.02	-
6. Habitual Decisions	.68*	-.11	-0.31	-0.42	-.52 <sup>^</sup>

*Note.* These data reflect correlations obtained in the acute stress group only ( $n = 14$ ) \* $p < .01$ , <sup>^</sup> $p = .06$ .

## **Trials B**

**Days 1-3.** In order to better understand the relationship between individual differences in executive function and habit-based decision-making under stress, Trails B scores were assessed in relation to learning on days 1-3 as well as during fMRI scanning. A median split was performed on raw Trails B to divide the sample into a high cognitive flexibility group (H-CogFlex;  $n = 14, M = 41.79, SD = 6.08$ ) and a low cognitive flexibility group (L-CogFlex;  $n = 14, M = 64.79, SD = 14.32$ ), based on their raw score

in seconds. Compared to the L-CogFlex group, the H-CogFlex had significantly more correct responses on Days 2 and 3,  $t(26) = 2.43, p < .05, d = .86$  and  $t(26) = 2.50, p < .05, d = .84$ , respectively, demonstrating improved learning and better task acquisition (see Figure 13).



*Figure 13.* Learning as measured by proportion of “Good” decisions during the first three days of instrumental conditioning examined as a function of cognitive flexibility; \*  $p < .05$ .

**Decision quality during imaging.** Using the three ROIs generated from group level ( $n = 27$ ), whole brain good – bad contrast (i.e., bilateral anterior insula and right dorsomedial anterior cingulate cortex), additional post-hoc analyses were conducted along the lines of cognitive flexibility established by the aforementioned median split. The purpose of this analysis was to assess the impact of cognitive flexibility on decision quality in both the acute stress and control group (i.e., to examine the third and final aim

of this project). Within the stress group, the right dorsal anterior cingulate cortex demonstrated differential activation between good and bad decisions that reached significance during both pre-reversal,  $t(7) = 4.32, p < .005, d = 1.55$  and to a lesser extent post-reversal decision trials,  $t(7) = 2.60, p < .05, d = .43$ , in the H-CogFlex group only. In the L-CogFlex group, the level of differential activation was not significant during pre- or post-reversal decisions. Separate examination of H-CogFlex and L-CogFlex groups within the control condition yielded a different pattern of results. That is, the level of differential activation between good and bad decisions was significant or trending for both pre- and post-reversal trials regardless of cognitive flexibility [H-CogFlex: pre-reversal,  $t(4) = 3.06, p < .05, d = .99$ ; post-reversal,  $t(4) = 2.78, p = .05, d = 1.02$  and L-CogFlex: pre-reversal,  $t(7) = 3.67, p < .01, d = .90$ ; post-reversal,  $t(7) = 2.34, p = .05, d = .67$ ].

Similar findings were observed in the bi-lateral insula. That is, in the left anterior insula of the stress group, significant differential activation between good and bad decisions was observed during both pre-reversal,  $t(7) = 3.38, p < .05, d = .88$  and post-reversal,  $t(7) = 3.19, p < .05, d = .77$  phases in the H-CogFlex group only. In the L-CogFlex group, significant differential activation was observed only in the pre-reversal phase,  $t(5) = 3.71, p < .05, d = 1.04$ . This pattern was not observed in the control group, as differential activation was significant or trending independent of cognitive flexibility [H-CogFlex: pre-reversal,  $t(4) = 2.73, p = .05, d = .94$ ; post-reversal,  $t(4) = 2.13, p = .10, d = .85$  and L-CogFlex: pre-reversal,  $t(7) = 2.88, p < .05, d = .86$ ; post-reversal,  $t(7) = 2.51, p < .05, d = .64$ ].



Finally, the same pattern of activation was also observed in right anterior insula. That is, after exposure to acute stress, the H-CogFlex group demonstrated differential activation between good and bad decisions that reached significance during both pre- and post-reversal trials,  $t(7) = 5.06$   $p < .005$ ,  $d = 1.17$  and  $t(7) = 2.75$   $p < .05$   $d = .53$ , respectively. In the L-CogFlex group, significant differential activation was observed in the pre-reversal phase,  $t(5) = 2.59$   $p < .05$ ,  $d = 0.54$ , but failed to reach significance post-reversal (See Figure 14 for a summary of these findings). The potential implications of these findings, with respect to flexibility and decision-making are discussed below. Consistent with previous findings in the ACC and insula, this pattern was not observed in the control group. Irrespective of cognitive flexibility, differential activation was observed for pre-reversal decisions, but not post-reversal [H-CogFlex: pre-reversal,  $t(4) = 3.10$ ,  $p < .05$ ,  $d = .87$ ; post-reversal,  $t(4) = 2.13$ ,  $p = .17$  and L-CogFlex: pre-reversal,  $t(7) = 2.84$ ,  $p < .05$ ,  $d = .85$ ; post-reversal,  $t(7) = .98$ ,  $p = .36$ ].

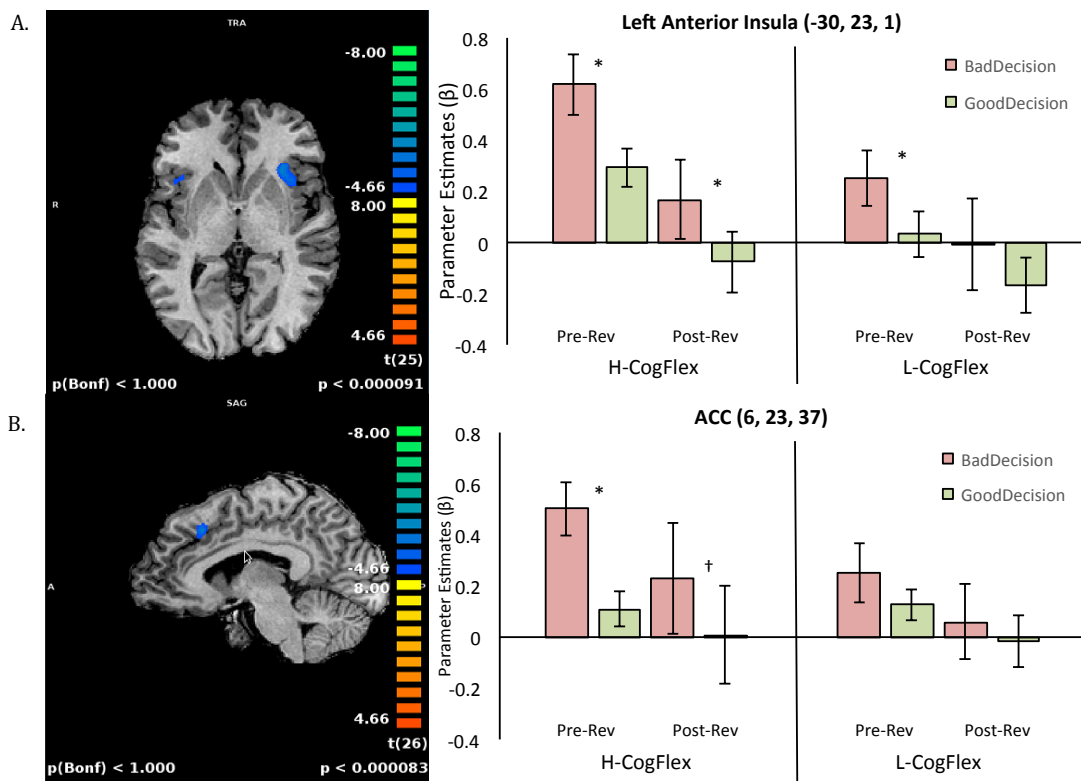


Figure 14. ROIs obtained from Good Choice – Bad Choice for the whole sample ( $n = 28$ ). Graphs display differential activation for good and bad decisions as a function of cognitive flexibility and along the lines of reversal phase in the stress group only ( $n = 14$ ). Individuals with higher baseline cognitive flexibility demonstrated greater activation for bad decisions during both pre- and post-reversal decisions; \*  $p < .05$ .

Table 7

*Brain Regions Demonstrating Significant Activation For Each Experimental Contrast (p < 0.005, corrected).*

Activated Region	Laterality	Talairach Coordinates			Voxel Count (mm <sup>3</sup> )	T-value
		x	y	z		
<b>Learning: positive EV – negative EV contrast</b>						
Dorsolateral prefrontal cortex (BA 6)*	L	-24	21	58	830	4.37
Putamen (dorsal striatum)	R	27	2	10	1431	4.59
Putamen (dorsal striatum)*	L	-30	5	7	1811	4.67
Anterior Cerebellum	L	-3	-55	-20	1000	4.37
<b>Learning: positive EV – negative EV by experimental group contrast</b>						
Prefrontal cortex (BA 10)*	R	12	68	-5	962	5.03
Putamen (dorsal striatum)	L	-21	-1	10	675	4.73
Thalamus	R/L	-15	-13	7	6370	5.22
Anterior Cerebellum	R	9	-34	-14	598	4.69
Posterior Cerebellum	L	0	-70	-20	3247	4.82
Posterior Cerebellum	R	21	-73	-26	4772	4.91
<b>Learning: positive EV – negative EV by experimental group contrast (Pre-Reversal Only)</b>						
Prefrontal cortex (BA 11)*	R	9	68	-11	905	4.67
Medial prefrontal cortex (BA 11)	L	-15	65	-11	639	4.31
Caudate	L	-9	11	7	473	4.19
Thalamus	R	-6	-19	7	634	4.20
Anterior Cerebellum	R	12	-64	-23	744	4.21
<b>Learning: positive EV – negative EV by experimental group contrast (Post-Reversal Only)</b>						
Supplemental motor area (BA 6)*	R	6	11	55	966	4.44
Posterior Cerebellum	L	-39	-70	-39	4129	5.05
Posterior Cerebellum	R	36	-64	-29	1151	4.72
<b>Decision quality: Composite Good Choice – Bad Choice<sup>^</sup></b>						
Anterior insula (BA 13)	R	33	23	4	699	-6.03
Inferior frontal gyrus (BA 47) <sup>†</sup>	L	-34	26	1	929	-6.06
Anterior cingulate cortex (BA 32)	R	7	23	37	528	-6.00
Lingual Gyrus (BA 18)*	L	-15	-67	4	6	-4.82
<b>Decision quality: Composite Good Choice – Bad Choice by experimental group contrast</b>						
Entorhinal Cortex (BA 28)	R	21	2	-29	929	-5.62
Dorsolateral prefrontal cortex (BA 6)	L	-24	14	52	605	-4.42

*Note.* \*  $\leq 3$  mm displacement; <sup>^</sup> multiple comparisons corrected for by false discovery rate (FDR); <sup>†</sup> activation extends primarily into left anterior insula.

## DISCUSSION

The goal of the current study was to assess the impact of stress on the neural correlates of instrumentally conditioned stimulus-response associations and the ability to flexibly acquire and make-decisions based on novel action-outcome contingencies using monetary gains and losses. Specifically, participants learned to discriminate between visual stimuli that were probabilistically associated with gains or losses for three days. Decision quality for the entire sample significantly improved over the course of training reaching asymptote on day two. On the fourth day, participants were exposed to an acute laboratory stressor (or control condition) prior to completing instrumental conditioning and decision tasks during fMRI scanning. The efficacy of the stress procedure was confirmed through multiple objective measures including increases in salivary cortisol, HR, blood pressure, and SCL as well as subjective measure of perceived stress.

The functional task incorporated two broad components. First, participants completed a set of learning and decision trials identical to trials on days 1-3. Second, the contingencies associated with the stimuli were reversed such that stimuli originally associated with wins more often than losses were now associated more with losses rather than wins. After reversal, participants engaged in a novel acquisition phase in order to learn the new values associated with each stimulus, followed by a set of decision trials. Importantly, just as in the original decision trials, feedback was not provided.

Consistent with Hypothesis 1 of Aim 1, exposure to acute stress increased the frequency of habit-based decisions during the reversal trials. That is, participants who were exposed to acute stress made more decisions in line with the overtrained stimuli even after those stimuli were rendered financially detrimental. While the increase in

habitual responding was significant for the stress group, it is important to recognize that both groups were able to acquire the new stimuli contingencies. For example, even the acute stress group was able to manage advantageous responding (i.e., goal-directed behavior) for 75.5% of the reversal trials (compared to 80.2% in the control group). This suggests that exposure to acute stress did not completely interfere with acquisition during the novel learning trials, nor did it fully inhibit goal-directed behavior during the novel decision trials. Further demonstrating some degree of learning, the proportion of “good” decisions for the reversed stimuli was significantly greater than the proportion of “good” decisions made on day 1, with no differences between groups. The fact that some learning continued to take place after stress exposure will be important when discussing the imaging data below.

Several studies have demonstrated similar findings in animal and human models (Dias-Ferreira et al., 2009; Schwabe & Wolf, 2009, 2010). Specifically, these studies trained subjects to perform two instrumental responses, associated with specific stimuli, in order to gain two separate food rewards. After sufficient training, one of the two food rewards was devalued through selective satiety. Testing during extinction showed that when stress preceded instrumental conditioning, subjects responded equally to the stimuli associated with both the devalued and the non-devalued food reward. That is, stress facilitated habitual behavior by decreasing subjects’ sensitivity to the changes in the value of food outcomes. While stress effects have been observed in the context of Pavlovian conditioning (Lewis, Porcelli, & Delgado, 2014), to the researchers knowledge this is the first study to utilize monetary gains and losses to assess stress induced habitual behavior in this way. Thus, this is a potentially important addition to the literature for

several reasons. First, the ability to assess habits using a financial decision-making task, rather than food devaluation, allows for more flexible design creation. Second, the use of monetary rewards arguably has greater ecological validity for assessing decision-making in a broad sense. That is, many everyday decisions are likely to involve secondary reinforcers as compared to primary reinforcers such as food and the feeling of satiety typically associated with food devaluation studies.

At the neural level, several lines of inquiry were pursued. First, several contrast-based analyses were performed involving examination of differential BOLD responses to positive and negative stimuli during the learning phases. These contrasts yielded clusters in multiple striatal and prefrontal areas. Importantly, activation during exposure to the overtrained (i.e., pre-reversal) stimuli consisted of both medial and lateral dorsal striatum, mPFC, and FPF. The caudate and prefrontal regions, which are thought to be associated with goal directed behavior, were activated during the original learning phases despite overtraining. This suggests that both the goal-directed and habit-based systems can indeed be concurrently activated and competing for behavioral control as described by Kahneman and Frederick (2002). Additionally, in a 3-day imaging study assessing neural changes associated with habit formation, Tricomi et al. (2009) observed sustained activation of medial PFC, despite clear dorsolateral striatum activation that gradually increased overtime and was linked to S-R associations. Further, when the habit system is disrupted (as in animal lesion studies) goal-oriented behavior resumes. This suggests that goal-directed neural systems remain operational despite overlearning (Yin & Knowlton, 2006).

The idea that both habit and goal-directed systems can be concurrently activated is also demonstrated by bilateral putamen and FPFPC activation during the novel acquisition phase (post-reversal). While no specific hypothesis was proposed regarding changes in brain activation during the “learning” of overtrained associations and the acquisition of novel associations, it is notable that the putamen but not the caudate remained engaged during novel stimuli contingency acquisition (i.e., post-reversal). This is likely a consequence of the experimental design itself. Stimuli presented during the reversal phase were identical to the overtrained stimuli with the exception of the contingencies probabilistically associated with each. Therefore, it is plausible that said similarities resulted in continued activation of the putamen when participants were encoding new information (i.e., at reversal) without negatively impacting behavioral performance. A similar finding was demonstrated by Foerde, Knowlton, and Poldrack (2006), in which putamen activation was associated with classification learning during a dual task procedure in the absence of habitual behavior.

Consistent with Hypothesis 1 of Aim 2, neural functioning in regions of the PFC and dorsomedial striatum that typically differentiate between gains and losses exhibited reduced discriminative sensitivity only in participants exposed to acute stress. That is, BOLD responses associated with positively and negatively valenced stimuli in caudate, mPFC, and FPFPC failed to reach significance in the acute stress group. Interestingly, discriminability with respect to reward-related information during the learning phase tasks was maintained in the putamen even after exposure to acute stress. This finding is significant in that it supports the broad notion that the putamen is important for the maintenance of “habits” (Balleine & Dickinson, 1998; Killcross & Coutureau, 2003; Yin

et al., 2004). It is important, however, that this finding be viewed in the context of experimental paradigm as the continued putamen discriminability responses after stress was only observed during exposure to the overlearned stimuli. The persistence of putamen activation during the learning of post-reversal stimuli in the control group supports the notion that regions associated with both the habit and goal-based system can be concurrently activated (Kahneman & Frederick, 2002).

Direct support for Hypothesis 2 of Aim 2 was not achieved in the current study. Specifically, data failed to support the occurrence of a stress-induced shift from prefrontal and dorsal medial striatal to dorsal lateral striatal processing during the reversal decision trials. This was likely due to the fact that feedback was withheld during the decision phase (McClure, York, & Montague, 2004). Previous research suggests that the striatum is particularly sensitive in discriminating *outcomes* (O'Doherty et al., 2004; Tricomi, Delgado, & Fiez, 2004) or outcome anticipation (Knutson, Adams, Fong, & Hommer, 2001; O'Doherty, Deichmann, Critchley, & Dolan, 2002). Therefore the lack of feedback (i.e., outcomes) likely limited the role of striatal activation during learning.

While this design choice limited our ability to assess shifts in striatal activation, it allowed for exploration of dorsal ACC and bilateral insula which are often implicated in *higher order* processes such as decision-making under uncertainty, and cognitive control (Craig, 2009). In both regions, increased activation for bad decisions was observed in both pre- and post-reversal decisions regardless of stress group. As stated previously, the ACC has been implicated in multiple functions involving processing of reward-related information such as monitoring or correcting errors on various cognitive tasks (Botvinick et al., 2001), as well as during *punishment* trials (e.g., the loss of a monetary reward;



Knutson et al., 2000). Additionally, consistent with the findings of the current study processing of reward-related information has been linked more specifically to dorsal ACC (Bush et al., 2002).

Previous research has demonstrated that the insula is also implicated in decision-making and is particularly sensitive to the uncertainty of the outcome (Rolls et al., 2008). Activation of the anterior portion of the insula has also been observed when individuals receive an unfair monetary offer (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). These findings are consistent with the present study, where increased activation of the anterior insula was observed when participants chose the least advantageous stimulus upon decision. Specifically, it is possible that participants felt more uncertain about their “bad” decisions. Further, some decision trials were designed such that both options had a relatively high probability of resulting in a monetary loss, and it is possible that this led participants to feel they were given an unfair option.

That the ACC and anterior insula continued to display similar differential activation to that observed during learning for both the stress and control group supports the behavioral finding that both groups acquired the new stimuli values after reversal. If the stress group was not able to sufficiently learn the new values after the reversal and insula activation is associated with uncertainty and unfairness (Rolls et al., 2008), it is unlikely that their bad decisions would be associated with increased insular activation. That is, if the new stimuli values were never learned, participants would be working under the assumption that they were making “good” decisions when in reality the opposite was true. Instead, the similar activation patterns between the stress and control

group suggest that the post-reversal values were learned at the cortical level, despite the tendency to revert to habitual behavior in the stress group.

Importantly, some differences in neural activation between groups might have gone unobserved in the current study simply due to a lack of power. This is reflected behaviorally in that most participants were able to successfully adjust their decision-making post-reversal, regardless of stress condition. That is, both groups made more good decisions compared to bad decisions overall effectively reducing the number of bad decision trials available for imaging analyses. This may have limited the researcher's ability to observe changes in neural function between the stress and control group during the decision trials.

In any case, these data demonstrate that the important role of striatum and FPFC in assessing reward value may not occur in the absence of feedback, even for stimuli with over-trained associations. This leads one to speculate how decisions are made in the absence of feedback. In an effort to address this specific question, Daniel and Pollmann (2012) devised a fMRI design aimed at measuring neural function during a four day observational learning task in the complete absence of feedback. On day one, bilateral putamen displayed greater activation for right compared to wrong decisions. On day four, however, neural patterns shifted to display greater activation for wrong compared to right answers in bilateral insula and mPFC, similar to the current study. While this pattern of activation (i.e., as seen in the bilateral insula) has been observed in the early stages of feedback learning (Daniel & Pollmann, 2010; Grinband, Hirsch, & Ferrera, 2006) it has been suggested that similar activation may only be observed in the absence of feedback after sufficient training. While this helps to explain the bilateral insula and

dorsal ACC activation in the current study, it does not offer an explanation for the neural mechanisms underlying the stress-induced reliance on overlearned behaviors.

Stress-induced changes in activation patterns emerged in the right EC and left DLPFC after adding the factor of stress group to the original good – bad contrast. Located in the medial temporal lobe, the EC relays information between the hippocampus and the neocortex (Lavenex & Amaral, 2000) and has been implicated in multiple aspects of learning and memory (Suzuki & Eichenbaum, 2000). For example, reward related information is thought to gain access to the hippocampus via excitatory projections that originate in OFC and other reward areas terminating in the EC (Avital, Ram, Maayan, Weizman, & Richter-Levin, 2006; Rolls & Xiang, 2005). Further, EC functioning has been directly linked to memory recall (Steffenach, Witter, Moser, & Moser, 2005) and stress has been shown to negatively impact EC functioning (Avital et al., 2006). Additionally, DLPFC has been implicated in both reward detection (Watanabe, Hikosaka, Sakagami, & Shirakawa, 2002) as well as episodic memory (Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). Evidence also suggests that DLPFC, specifically, is responsible for maintaining reward-related information over short delays in order to guide future behavior (Krawczyk, 2002). DLPFC has also been implicated in working memory (Goldman-Rakic, 1993; Mayer, 1999) task switching (Brass & von Cramon, 2004; Dias, Robbins, & Roberts, 1996), and decision-making (Robin & Holyoak, 1995).

In the current study, increased EC activation was associated with bad decisions in the control group and decreased activation in the stress group. Given that bad decisions increased with decision difficulty, the pattern of activation observed in the control group suggests increased activation for difficult decisions. Additionally, DLPFC activation was

significantly reduced in the stress group during reversal decisions compared to the control group. Given the roles of EC and DLPFC in reward related memory function and attentional control, it is likely that stress-induced habitual behaviors arise from stress-related disruption of the executive control of memory for newly acquired information. The role of cortical regions, as opposed to dorsal striatum, may be especially important modulators of stress-induced habitual behaviors in the absence of immediate feedback.

The final aim of this project sought to explore the relationship between executive functioning and stress-related reliance on instrumentally conditioned associations. Several executive tests measuring various aspects of working memory (e.g., attention, working memory, inhibition, processing speed, and cognitive flexibility) were factor analyzed into two components, attention/working memory and impulsivity. While the planned regression could not be conducted due to insufficient correlation with the proportion of stress-induced habitual decisions, the relationship between the attention/working memory composite and proportion of habit decisions trended toward significance. This trend was expected given prior research demonstrating the link between goal-directed behaviors and working memory generally (Otto, Gershman, Markman, & Daw, 2013) and the extent to which working memory protects against a stress induced reliance on habit-based behaviors (Otto, Raio, et al., 2013). Given the strong link between working memory and goal-oriented processes established by prior research, the non- significant trend reported here would likely reach significance in a repeat study with a larger sample.

Examination of the raw neuropsychological data for each test of executive functioning demonstrated that baseline cognitive flexibility, as assessed by Trails B,

positively correlated with habitual decisions. That is, individuals who demonstrated higher baseline cognitive flexibility were better able to appropriately adjust their way of responding during the reversal decision task. One explanation for this finding is that individuals with greater cognitive flexibility are better able to acquire novel stimulus-response associations. In the current sample, individuals who performed better on trails B made better decisions during learning on days two and three compared to those who performed worse.

Alternatively, increased cognitive flexibility may also improve one's ability to utilize goal-directed systems regardless of exposure to acute stress. For example, within the stress group individuals who scored highest on Trails B made significantly more goal-directed decisions. At the neural level, participants in the stress group that demonstrated greater cognitive flexibility exhibited differential activation between good and bad decisions that reach significance in bilateral insula and ACC. The same pattern of activation was not reliably observed in the control group. Cognitive flexibility, when specifically assessed with Trails B, has consistently implicated the anterior insula (Dosenbach et al., 2007; Mutschler et al., 2009; Nelson et al., 2010) as well as the ACC (Carter, Botvinick, & Cohen, 1999). Further, both of these regions have also been related to bioregulatory processes such as nociception (Apkarian, Bushnell, Treede, & Zubieta, 2005; Büchel et al., 2002) and autonomic arousal (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000) (Critchley & Mathias, 2013). Therefore, it is likely that these regions serve an important link between cognitive and behavioral flexibility after exposure to acute stress.

## Limitations

While the behavioral results presented here offer a provocative demonstration of stress-induced reliance on instrumentally conditioned financial associations, consideration of several limiting factors are warranted. First these results should be viewed within the context of a relatively small sample size. While the current sample size of  $N = 28$  is sufficient for whole group analyses, the ability to explore individual differences within the stress group ( $n = 14$ ) is limited. Further, although the decision to withhold feedback during decision trials provided an opportunity to dissociate the effects of learning from “pure” decision-making, this appears to have stymied our ability to assess medial to lateral dorsal striatal shifts in brain functioning.

Additionally the financial decision task, specifically the reversal phase, may have been somewhat easy. By simply reversing the probabilistic associations with each stimulus, learning was readily acquired by both experimental groups. Increasing the complexity of novel learning and decision phases might yield more variability in which to find stress differences during the elicitation of a habit-based or goal-directed behavior. Finally, the timing of the stress procedure could be improved. While the goal was to assess the potential for habit behaviors 25-30 minutes after exposure to acute stress, technical limitations extended the post-stress window for an additional ~28 minutes. This led to a cortisol peak during the regular learning and decision trials, rather than during the post-reversal trials.

## **Future Directions**

Future investigations should explore the impact of acute stress on the direct role of feedback during habitual decision-making. This can be accomplished by adjusting the current behavioral design to include a portion of decision trials that incorporate feedback. Given a sufficient number of trials, it would be possible to examine differences in habitual decisions made with and without feedback. Additionally, instrumental-conditioning designs similar to the one used in this study could be expanded to assess the impact of stress on the role of habit formation, rather than just habit expression. This can be achieved by extending the number of learning days and increasing the number of scans performed. Not only would this allow investigators to examine neural changes throughout the development of habitual behaviors, the impact of acute, even chronic, stress could be examined at various time points throughout habit formation.

The role of habitual behaviors, especially under stressful conditions, is wrought with clinical implications including surgical (Vitek et al., 1998), pharmacological (Corbit, Chieng, & Balleine, 2014), psychotherapeutic, (Watkins & Nolen-Hoeksema, 2014) and mediation interventions (Witkiewitz et al., 2014). Experimental paradigms that are able to assess stress-induced changes in reward salience that impact overtrained behavior can be applied to any clinical population marked by the development of undesirable habits such as substance use disorder, eating disorder, obsessive compulsive disorder and more. The ability to examine these conditions using experimental paradigms designed to assess relative contributions of habit versus goal-oriented behavior will help researchers and clinicians gain a more detailed understanding of the underlying mechanisms associated with maladaptive behaviors.

The specific effects of stress on instrumental learning and decision making also has implications for disorders that are by definition triggered by stress, such as post-traumatic stress disorder (PTSD) as well as disorders often related to stress such as anxiety and depression. Each of these conditions can be characterized as a tendency to rely on habitual patterns. In the case of PTSD, there exists habitual pattern of avoidance from stimuli associated with the traumatic event (Olf, Langeland, & Gersons, 2005). Indeed anxiety and depression can also be characterized as a tendency to rely on habitual cognitive processes known as maladaptive automatic thoughts (Beck, 1979) such as worry and rumination. Investigating common pathologies across various disorders has the potential to elucidate commonalities in the underlying neural mechanisms and offer new insights for possible re-categorization of mental health disorders along mechanistically determined criteria in line with current trends in psychiatry (Insel et al., 2010).

Finally, the link demonstrating protective effects of executive functioning with regards to goal-directed behavior after acute stress (Otto, Raio, et al., 2013) combined with connections between executive and autonomic functioning (Jennings, Allen, Gianaros, Thayer, & Manuck, 2015; Thayer & Lane, 2000) suggest that therapeutic strategies targeting autonomic regulation (Adamson, Kleckner, VanHout, Srinivasan, & Abraham, 2003) may be effective for reducing pathological symptoms associated with habitual behavior. Future research should investigate the degree to which such autonomic therapy impacts goal-directed and habitual behaviors and underlying neural function.



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