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Interactions Between the Basolateral Amygdala and Ventral Striatum During Probabilistic Learning in Children and Associations with Individual Differences in Free Cortisol

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INTERACTIONS BETWEEN THE BASOLATERAL AMYGDALA AND VENTRAL STRIATUM DURING PROBABILISTIC LEARNING IN CHILDREN AND ASSOCIATIONS WITH INDIVIDUAL DIFFERENCES IN FREE CORTISOL

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by

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Abstract

Stress can drastically alter the behavioural and functional correlates of feedback learning; however, the functional correlates of these effects are poorly understood, particularly in children. In the present study, typically developing children between the ages of 9- and 11-years-old completed a probabilistic learning task with both appetitive and aversive outcomes in a magnetic resonance imaging scanner. Anticipatory stress to the experimental environment was measured via salivary cortisol at baseline and prior to completion of the task. Although baseline and pre-MRI cortisol values were not reliably different at the group level, subsequent analyses revealed that the basolateral amygdala was less responsive to positive feedback in children with higher pre-MRI cortisol levels. Furthermore, individual differences in feedback-related basolateral amygdala activity were positively associated with differences in striatal activity. Thus, the basolateral amygdala may be particularly sensitive to individual differences in active cortisol levels, and may also modulate striatal feedback sensitivity.

Keywords

Probabilistic Learning, Amygdala, Ventral Striatum, Stress, fMRI, State Incentive, Children

Dedication

To my Family,

for their infinite encouragement and understanding.

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Chapter 1

1 Introduction

Cognitive and behavioural self-regulation refers broadly to the ability of an individual to dynamically adjust behaviours such that optimal outcomes are maximized and adverse outcomes are avoided. Making use of both positive and negative feedback to update previously held outcome expectancies is a central component of cognitive and behavioural self-regulation, and children vary considerably in their capacity to do so. For example, some children are impulsive, and show a heightened sensitivity to rewards and a relative insensitivity to the prospect of failure, while others are more reticent and are more concerned with avoiding negative outcomes. The neurobiological substrate of cognitive and behavioural self-regulation is the mesocorticolimbic system, which encodes both positive and negative discrepancies between observed and expected outcomes through complex interactions within a variety of both cortical and sub-cortical networks. Individual differences in cognitive and behavioural self-regulation likely reflect structural and functional differences within the mesocorticolimbic system, which can arise as a consequence of both genetic and environmental factors.

Dysregulation within the mesocorticolimbic system has been associated with a variety of adverse psychological outcomes, including heightened risk for substance abuse and addiction (Schneider et al., 2012; Tanabe et al., 2013), attention-deficit hyperactivity disorder (Furukawa et al., 2014; Shaw et al., 2014), schizophrenia (Slifstein et al., 2015; Wolf et al., 2014), and depression (Connolly, Gollan, Cobia, & Wang, 2015; Goya-Maldonado et al., 2015). Importantly, longitudinal studies have identified cognitive and behavioural self-regulation in childhood as a predictor of academic and social competence, psychological well-being, physical health, socioeconomic status and criminality measured in adolescence and adulthood (Mischel, Shoda, & Peake, 1998; Moffitt et al., 2011; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013; Shoda, Mischel, & Peake, 1990). As such, understanding the complex interactions between factors that influence the mesocorticolimbic system and how those interactions may contribute to the ontogeny of individual differences in self-regulation is imperative.

One exciting avenue of research that has emerged with regards to individual differences in self-regulation focuses on the influence of physiological and psychological arousal on self-regulation. Importantly, decision-making does not occur in a vacuum. A variety of state-level factors, such as whether the individual is hungry or satiated, nervous or excited, exhausted or invigorated, can all influence how they perceive and respond to environmental inputs. For example, individuals may be more likely to seek anxiolytic substances like alcohol when they are feeling overwhelmed by a particularly stressful workday, or to run a yellow light when they are in a rush to the airport and are at risk of missing an important flight. Thus, the subjective value assigned to a particular outcome may not be stable across time. Importantly, just as individuals vary in self-regulatory capacity, they also vary quite substantially in terms of how physiologically and psychologically reactive they are to particular environmental contexts. These differences can have protective or deleterious consequences for many of the behavioural outcomes commonly linked to dysregulation within the mesocorticolimbic system (Andersen & Teicher, 2009; Buydens-Branchey & Branchey, 2004; Matthys, Vanderschuren, & Schutter, 2013; Stadler et al., 2011; Tyrka et al., 2012).

Advances in animal research as well as imaging technologies in humans have begun to unravel the intricate relationships between the stress response system and the mesocorticolimbic system; however, there is presently a large amount of conflict in the human literature regarding the consequences of stress on the neural and behavioural correlates of self-regulation. While some evidence seems to suggest that stress enhances learning about rewarding outcomes and inhibits learning about negative outcomes (Mather & Lighthall, 2012), other evidence suggests the opposite (Montoya, Bos, Terburg, Rosenberger, & van Honk, 2014). Despite these conflicting accounts, all agree that there are marked individual differences in terms of how reactive subjects are to laboratory stressors.

One factor that is often overlooked in research protocols is the potential influence of the experimental environment itself. While few studies have directly assessed the consequences of the experimental environment on the output of the stress response system, there is evidence that participation in protocols involving magnetic resonance

imaging (MRI) can induce a physiological stress response, especially in adolescents (Eatough, Shirtcliff, Hanson & Pollak, 2009) and scanner naïve adults (Tessner, Walker, Hochman, & Hamann, 2006). No studies have directly assessed how the observed influences on the stress response system may impact task performance and task-related profiles of brain activity. The mesolimbic circuit of the mesocorticolimbic system may be particularly sensitive to these effects, but is relatively understudied in the field of self-regulation in humans. The present study aimed to identify the relationship between two components of the mesocorticolimbic system, the ventral striatum and the basolateral amygdala, during feedback processing. Specifically, the study sought to determine whether individual differences observed in self-regulatory behaviour as well as underlying task-related response profiles of the ventral striatum and basolateral amygdala were associated with individual differences in physiological arousal elicited by the imaging environment in a sample of typically developing children.

1.1 Components of Feedback Learning: The Mesocorticolimbic System

The mesocorticolimbic system consists of various nuclei within the basal ganglia, including the striatum, sub-thalamic nucleus, globus pallidus, and the substantia nigra, as well as afferent and/or efferent connections with various cortical and sub-cortical regions including the ventral tegmental area, prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex, thalamus, amygdala, hippocampus and hypothalamus (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Two main projection pathways from the striatum and proposed to go through basal ganglia nuclei expressing predominately either dopamine type I (DRD1) or dopamine type II (DRD2) receptors, which have opposing effects (excitatory and inhibitory, respectively) on the motoric output of the thalamus (Frank et al., 2007). The competing activity within these sub-nuclei is hypothesized to be responsible for identifying prediction errors and facilitating appropriate motoric responses. The thalamus, in turn, communicates bi-directionally with the cortical regions, facilitating the active maintenance of current information and the top-down modification of ongoing behaviour (Frank et al., 2007).

While the striatum is thought to be integral in identifying prediction errors and accordingly updating expectancies, the amygdala is thought to provide important information to the striatum regarding the overall affective and motivational significance of the information being processed, referred to as the 'state value' (Morrison & Salzman, 2010). The amygdala has been studied quite extensively in conditioned fear and aversion learning (Pare, Quirk, & LeDoux, 2004; Quirk, Repa, & LeDoux, 1995; Wilensky, Schafe, & LeDoux, 1999); however, the importance of the amygdala for reward learning has become increasingly evident (Morrison & Salzman, 2010). Furthermore, the amygdala can facilitate (Feldman & Weidenfeld, 1998) activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and interacts extensively with the autonomic nervous system, which makes it highly sensitive to changes in physiological arousal. As such, the present study focused on interactions between the striatum and the amygdala during the processing of positive and negative feedback, and sought to establish whether individual differences in physiological arousal elicited by the scanning environment influenced these interactions in a population of typically developing children.

1.1.1 Striatum

The striatum is a component of the mesocorticolimbic system that resides within the basal ganglia. The striatum is further divided anatomically and functionally into the dorsal striatum, which is primarily involved in motoric aspects of learning, and the ventral striatum (synonymous with nucleus accumbens in human neuroimaging studies), which is primarily involved in motivational aspects of learning, and is the focus of the present study (Robbins & Everitt, 1992). The striatum receives excitatory (glutamatergic) inputs from areas within the prefrontal cortex, as well as limbic structures such as the amygdala (Schultz, 2002). It also receives dopaminergic inputs from midbrain nuclei, including the substantia nigra and the ventral tegmental area (Grace, 1991; Schultz, 1997). Within the striatum, two distinguishable populations of neurons expressing predominantly either DRD1 or DRD2 receptors are associated with facilitating and preventing responding, respectively (Frank & Hutchison, 2009; Frank et al., 2007). Dopamine serves as a neuromodulator within these subpopulations of neurons, either increasing or decreasing the capacity of pre-synaptic glutamatergic inputs to elicit post-

synaptic action potentials (Surmeier, Ding, Day, Wang, & Shen, 2007). Importantly, DRD1 neurons and DRD2 neurons respond differentially to dynamic changes in synaptic dopamine.

At baseline, dopamine is tonically released into the striatum, which corresponds with tonic stimulation of high affinity DRD2 neurons (Dreyer, Herrik, Berg & Hounsgaard, 2010). In the face of rewarding outcomes, dopamine is phasically released in large bursts, which has opposing influences on DRD1 and DRD2 neurons (Dryer et al., 2010). The DRD1 receptors have a relatively low affinity for dopamine, and have minimal excitability at baseline (Surmeier et al., 2007). During phasic dopamine bursts, dopamine binding to DRD1 receptors elicits a rapid cascade of events that ultimately leads to increased excitability of DRD1 expressing neurons; conversely, saturation of DRD2 receptors leads to reduced excitability of DRD2 expressing neurons (Surmeier et al., 2007). In the face of adverse outcomes, the rate of tonic release of dopamine is reduced, and as a consequence, levels of synaptic dopamine also decrease (Surmeier et al., 2007). Reduced dopamine binding to DRD2 receptors leads to increased excitability of DRD2 neurons (Surmeier et al., 2007). These changes in synaptic dopamine, and subsequent modulation of neuronal excitability by DRD1 and DRD2 receptor binding, are predicted to underlie the rapid and dynamic learning of approach and avoidance behaviours. In humans, naturally occurring variations in the functioning of the dopaminergic system have been associated with concomitant differences in an individual's capacity for self-regulation (Frank et al., 2007), and pharmacological manipulations in both human and animal models have supported the distinct functions of these sub-populations of neurons (Garu, Govoni, Stefanini, Trabucci, & Spano, 1978; Pessiglione, 2006)

Functional magnetic resonance imaging (fMRI) studies in humans have been used extensively to understand the role of the ventral striatum in feedback learning. Functional magnetic resonance imaging techniques measure temporal and spatial changes in the blood-oxygen level dependent (BOLD) response within various tissues. Because increased activity in a particular brain region is associated with increased metabolic demands, and subsequently requires an increased supply of oxygenated hemoglobin, task-related regional patterns of change in BOLD response can be used as an indirect measure

of patterns of neural activity in the brain. Evidence from fMRI studies suggests that the ventral striatum responds robustly to positive feedback, especially when that feedback is unexpected; less is known about the ventral striatum response to negative feedback, although preliminary evidence suggests that it may be relatively deactivated in this context (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Seymour, Daw, Dayan, Singer, & Dolan, 2007). When feedback is expected, a temporal shift in ventral striatum activity is observed, such that the ventral striatum response becomes predictive, and occurs at stimulus onset as opposed to feedback onset (Delgado, Nystrom, Fissell, & Fiez, 2000; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003).

A variety of learning tasks, both classical and instrumental, are commonly employed to interrogate the neural and behavioural correlates of feedback learning. In classical conditioning contexts, a neutral stimulus (conditioned stimulus; CS) precedes an inherently positive (appetitive) or negative (aversive) outcome stimulus (unconditioned stimulus; UCS) that elicits a particular behavioural or physiological response. Over time, the CS becomes predictive, and elicits the UCS associated response prior to the delivery of the actual UCS. During instrumental learning, subjects learn to respond to a CS in order to obtain an appetitive UCS or avoid an aversive UCS. Responses can be strengthened or weakened as a consequence of dynamic changes in the strength of associations between the CS and the UCS. Instrumental learning can further be divided into two main phases: anticipation of a particular outcome following an operant response and feedback processing. These phases likely involve slightly different neural processes, as anticipation involves holding a representation of the expected outcome, whereas consumption involves updating previously held expectations based on the convergence between the expected outcome and the perceived value of the actual outcome.

There is a general consensus in the literature that the ventral striatum is recruited during the anticipation of rewarding outcomes, and although less frequently studied, evidence indicates that it is also recruited during the anticipation of adverse outcomes. Striatal activation to anticipation of both gains and losses was observed in an fMRI study conducted by McKell, MacInnes, Huettel, and Adcock (2009). The authors employed a monetary incentive delay task using fMRI in a sample of healthy adults. Briefly,

participants learned to associate particular cues with the potential for either monetary gain or loss (gain and loss trials occurred in separate experimental runs to avoid cue conflict) or no potential for monetary gain or loss. Following the cue, a response target appeared on the screen, and participants were required to press a button as quickly as possible in order to either gain money, or avoid losing money. Results of the imaging analysis revealed increased BOLD response in the ventral striatum during anticipation of both rewards and in the anticipation of losses when compared with trials in which no money was at stake. Furthermore, using positron emission tomography (PET) combined with fMRI, Schott and colleagues found that the magnitude of the striatal BOLD response during reward anticipation was positively correlated with the amount of dopamine released into the striatum. Due to the similar nature of the response profiles of the ventral striatum during anticipation of both appetitive and aversive outcomes, it is likely that the ventral striatum represents the motivational value of the anticipated outcome within this context, as opposed to the valence (positive or negative).

During feedback processing, the ventral striatum appears to respond bivalently to positive and negative outcomes, although there is some evidence to the contrary (see Seymour, Daw, Dayan, Singer, & Dolan, 2007). For example, during a card guessing game, the BOLD response in the ventral striatum was found to increase following feedback indicating a correct guess, and to decrease following feedback indicating an incorrect guess (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). The magnitude of the bivalent response in the ventral striatum has also been found to correlate positively with the level of unexpectedness of the feedback (Pessiglione, 2006), and is predictive of individual differences in sensitivity to rewarding and negative feedback measured behaviourally (van Duijvenvoorde et al., 2014).

Pharmacological manipulations that target the striatal dopaminergic network can also disrupt or enhance the magnitude of ventral striatum responding to both positive and negative feedback (Pessiglione, 2006). In particular, administration of the dopamine precursor L-DOPA prior to the completion of a probabilistic learning task wherein participants were required to learn to select stimuli that elicited positive feedback more frequently than other stimuli, and to avoid selecting stimuli that elicited negative

feedback more frequently resulted in an increase in the magnitude of the ventral striatum response to both positive and negative prediction errors when learning from positive feedback (Pessiglione, 2006). Participants in the L-DOPA group were also found to have higher estimated affective valuations of the rewarding outcome than those in a control group. Conversely, administration of the dopamine receptor antagonist haloperidol reduced the magnitude of the positive and negative prediction errors when learning from positive feedback, and was associated with reduced estimated affective valuations of the rewarding outcome. Taken together, these results suggest that during feedback processing, the ventral striatum responds bivalently to positive and negative outcomes, a process which is mediated, at least in part, by dynamic changes in dopamine. The prevailing view of the role of the ventral striatum in the feedback phase of learning is that of an error detector, and the differential response to positive and negative feedback is thought to underlie subsequent adaptive behavioural modification.

1.1.2 Amygdala -Ventral Striatum Interactions

The ventral striatum does not function as an independent entity during feedback-guided learning. As mentioned previously, the ventral striatum receives inputs from cortical regions including the medial prefrontal cortex and orbitofrontal cortex, as well as limbic inputs, including the amygdala and hippocampus. These inputs can effectively modulate both baseline and response-related aspects of ventral striatum function, and may subsequently contribute to observed inter-individual variability. The amygdala, which has received relatively less attention in human models of feedback learning than other identified ventral striatum inputs, may be particularly important in relaying information about the current environmental context to the ventral striatum in order to adaptively adjust perceived incentive value. In particular, the importance of the basolateral amygdala in facilitating appropriate striatal responding has been documented extensively over decades in animal models of both classical and operant conditioning.

For example, in a series of experiments in rats, Ambroggi, Ishikawa, Fields, and Nicola (2008) found that enhancement of reward-seeking behaviour by the ventral striatum was dependent upon input from the basolateral amygdala. In one series of experiments,

pharmacological inactivation of the bi-lateral basolateral amygdala following classical conditioning drastically reduced responding to reward-related stimuli. The level of inactivation observed from basolateral amygdala inhibition was similar to that observed when the ventral striatum was directly inhibited in an independent session. Furthermore, in a separate series of experiments, the authors found that cue-evoked potentials in the basolateral amygdala temporally preceded evoked potentials in the ventral striatum, and direct stimulation of basolateral amygdala neurons lead to excitation of ipsilateral, but not contralateral, ventral striatum neurons. Additionally, in rhesus macaques, inhibition of the basolateral amygdala during satiation with a previously rewarding stimuli prevented stimulus devaluation (Wellman, Gale, & Malkova, 2010), and inhibition of the basolateral amygdala prior to the learning phase of an operant conditioning paradigm was found to impair learning of avoidance behaviours in rabbits (Proemba & Gabriel, 1999).

In human neuroimaging studies, the role of the basolateral amygdala in feedback-guided learning has not been investigated as thoroughly as the role of the ventral striatum, especially during the feedback phase. This is likely because the basolateral amygdala was previously associated more heavily with fear and avoidance learning, and most human research focused on the role of the basolateral amygdala in emotional processing and fear-related behaviours (Williams et al., 2001; for a review see LeDoux, 2003). Very few studies have directly assessed the role of the basolateral amygdala in instrumental learning, particularly during feedback processing. A majority of human investigations have employed passive learning tasks, focusing on the response of the amygdala to a CS after initial acquisition of CS-UCS associations, and how it may relate to the subjective value assigned to the UCS itself. In these contexts, the magnitude of the CS elicited basolateral amygdala response has been shown to be positively associated with the extent to which a CS effectively elicits an anticipatory response in both aversive (Gottfried, O'Doherty & Dolan, 2002; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998) and appetitive (Gottfied, O'Doherty & Dolan, 2002) forms of classical conditioning. Few human neuroimaging studies have directly assessed response profiles in the basolateral amygdala during instrumental learning, either during anticipatory or feedback phases; however, results suggest that basolateral amygdala activity may be potentiated during

both phases, and subsequently influence task-related activity within the ventral striatum as well as behavioural correlates of decision making.

With respect to the anticipatory phase, De Martino, Kumaran, Seymour and Dolan (2006) assessed the influence of BOLD response measured in the amygdala during framed decision-making in a gambling task. In framing tasks, researchers are interested in assessing whether changing the presentation of an outcome, but not the outcome itself, influences how the outcome is processed. Briefly, participants began the task with a particular sum of money and throughout the task made decisions regarding whether to opt to lose a fixed amount of money, or to gamble with the possibility of either keeping all of the money or losing all of the money. Importantly, the amount of money that participants could knowingly lose by selecting the sure option was framed differently throughout the task. In the gain condition, the sure option was framed in terms of how much of the original sum of money participants could keep, whereas in the loss condition, the sure option was framed in terms of how much of the original sum of money participants could lose. The probability associated with losing or keeping everything was displayed in each trial. The framing effect was associated with an increased propensity towards going with the sure option in positively framed trials, and with an increased propensity towards going with the gamble in negatively framed trials. Importantly, basolateral amygdala activity was found to be higher following risky decisions than safe decisions in negatively framed trials, whereas activation was greater following safe decisions as opposed to risky decisions in positively framed trials. Additionally, a recent study employing a probabilistic learning task in an MRI scanner by Watanabe, Sakagami, and Haruno (2013) found that the presentation of fearful emotive stimuli prior to reward-predicting cues increased prediction error-related activity within the ventral striatum, and that this effect was modulated by changes in activity within the amygdala. These results support incentive value models of basolateral amygdala function in instrumental learning, and suggest that the primary function of the basolateral amygdala is to adjust the dynamics of mesocorticolimbic system such that different behavioural strategies can be adaptively employed in particular motivational contexts.

1.2 Stress and Feedback Learning

The stress response is a highly adaptive physiological mechanism for rapidly mobilizing the body's resources to adaptively respond to emotionally or physiologically challenging events. Through complex interactions with metabolic, sensory, and cognitive systems, the stress response effectively adjusts the motivational priorities of an individual in order to return the system to homeostasis (for a review, see Charmandari, Tsigos, & Chrousos, 2005). The stress response system is comprised of two distinct subsystems: the slow-acting corticotrophin system and the rapid locus-coeruleus-norepinephrine (LC-NE) system. The LC-NE system projects to a variety of limbic regions, including the amygdala and hippocampus, as well as regions within the prefrontal cortex, and the associated response involves the activation of the autonomic nervous system and subsequent release of the catecholamine norepinephrine. The corticotrophin system is primarily associated with the initiation of a cascade of physiological events that results in the secretion of the glucocorticoid cortisol. Importantly, stress can drastically alter decision making, and a large body of literature suggests that these behavioural alterations result, at least in part, from functional changes within the mesocorticolimbic system.

The stress response system and the mesocorticolimbic system interact extensively during physiologically arousing events. Both the LC-NE system and the corticotrophin system project to various sub regions within the amygdala, and interactions between these two systems are thought to underlie stress-induced enhancement of contextual fear conditioning and memory consolidation, and more generally, facilitate activation to contextually salient aspects of the environment (Roozendaal, McEwen & Chattarji, 2009). In particular, glucocorticoid receptors are widely distributed throughout the striatum (Härfstrand, et al., 1986), and studies have shown that glucocorticoid administration within the striatum increases synaptic plasticity by strengthening glutamatergic synaptic inputs into the striatum as well as strengthening excitatory inputs into the ventral tegmental area (Campioni, Xu, & McGehee, 2009; Saal et al., 2003). Numerous rodent models have also suggested that increases in corticosterone, the rodent analogue of cortisol, enhances the activity of dopaminergic neurons within the striatum via interactions with striatal glucocorticoid receptors (Piazza & Le Moal, 1996). Thus, a

large emphasis has been placed on understanding the specific contributions of individual differences in glucocorticoid function to individual differences in self-regulation.

1.2.1 Behavioural Associations

There is considerable agreement within the literature that stress influences decision-making assessed using a wide variety of tasks. Within the domain of feedback learning, the dominant account posits that stress enhances learning from positive feedback and disrupts learning from negative feedback. To assess the influence of stress on learning, participants are typically exposed to an acute stressor prior to task completion. Commonly used laboratory stressors include the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993) and the cold pressor method (Lovallo, 1975). In the Trier Social Stress Test, participants are given a very small amount of time to prepare for a stressful social situation, such as a public speech or an interview, and are then required to engage in the social situation. The cold pressor method requires participants to submerge their hand in uncomfortably cold water for an extended period of time. Both methods have been associated with reliable increases in circulating glucocorticoids.

Results from two independent studies employing both the Trier Social Stress Test (Petzold, Plessow, Goschke, & Kirschbaum, 2010) and a combined Trier Social Stress Test and cold pressor method (Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013) support the enhancement of positive feedback learning and the inhibition of negative feedback learning using similar probabilistic learning task . Importantly, in both studies, the effectiveness of the tasks was verified by cortisol measurement. The probabilistic learning task in these studies required participants to learn probabilistic associations between paired stimuli and outcomes in order to maximize correct selections. Within each pair of stimuli, one stimulus was associated with correct feedback more frequently than the alternative. Probabilities also varied between stimuli pairs, such that it was easier to establish which stimuli was correct in some pairs than others. Following acquisition, participants completed a test phase wherein the most frequently correct stimulus was paired with all other stimuli, and the least frequently correct stimulus was paired with all other stimuli. Participants were asked to select the best stimulus in each pair, but were not given feedback. The test phase serves as a measure of sensitivity to positive and negative

feedback; the extent to which participants select the stimulus that was associated with correct feedback most frequently over stimuli that were correct only slightly less frequently is used as an indication of sensitivity to positive feedback, and the extent to which participants avoid selected the least frequently rewarded stimulus over other stimuli that are rewarded only slightly less frequently is an index of sensitivity to negative feedback. Following the Trier Social Stress Test, participants showed lower avoidance of the least optimal stimulus during the test phase than controls; no influence was observed on propensity to select the most optimal stimulus. Following the combined Trier Social Stress Test and cold pressor method, participants selected the optimal stimulus more frequently in the test phase than controls; however, no influence was observed on sensitivity to negative feedback. Taken together, these results support the idea that acute stress both enhances sensitivity to positive feedback and reduces sensitivity to negative feedback, and may explain a large body of evidence suggesting that stress increases risk of drug abuse and relapse (for a review, see Sinha, 2001).

There is; however, conflicting evidence showing stress-induced reductions in reward sensitivity when participants completed the task under threat of electrical shock using the same probabilistic learning task (Berghorst, Bogdan, Frank, & Pizzagalli, 2013). The authors also reported a trend-level increase in sensitivity to negative feedback compared to controls, as well as a generalized increase in reaction time (RT) during the test phase. It was noted that the deviance from previous studies may have resulted from the fact that the threat of shock stress was salient throughout the duration of task completion, whereas in both of the previously discussed studies, the tasks were completed following the cessation of the stressor. Thus, behaviour may be influenced differently depending on the temporal characteristics of the stress induction procedure.

1.2.2 Functional Associations

The associations between stress and facilitated dopaminergic function within the mesocorticolimbic system identified in the animal literature have been confirmed in a human PET study, which found increased levels of synaptic dopamine release in the striatum following administration of a modified version of the Trier Social Stress Test (Wand et al., 2007). Additionally, Wand and colleagues found that the magnitude of the

stress response (measured via changes in circulating cortisol) was positively correlated with amphetamine-induced release of dopamine within the striatum, and that this effect was predictive of enhanced self-reported positive affective ratings to amphetamine. The identified stress-induced increase in striatal concentrations of dopamine were also observed in an independent PET study which induced stress by having participants complete a challenging arithmetic task throughout the collection of the imaging data (Pruessner et al., 2004). Collectively, these findings have lead to a hyperdopaminergic hypothesis of stress, wherein stress is hypothesized to enhance reward-related behaviours by increasing the sensitivity of the system to positive feedback. Furthermore, these findings converge with the previously discussed behavioural data suggesting increased sensitivity to positive feedback (Petzold et al., 2010) and decreased sensitivity to negative feedback (Lighthall, 2013) following administration of laboratory stressors.

Some functional neuroimaging procedures appear to support the hyperdopaminergic hypothesis of stress effects on decision-making; however, some evidence suggests reduced sensitivity of the striatum to rewards and potentially enhanced sensitivity to negative outcomes. Lewis, Porcelli, and Delgado (2014) provided evidence for the hyperdopaminergic hypothesis using a passive partial reinforcement task administered in an MRI scanner. The authors employed a between subjects design, and induced stress prior to specific functional runs using a cold pressor task adapted for use with neuroimaging procedures. Participants learned to associate neutral cues with either high or low magnitude gains and losses, and BOLD response in the ventral striatum was measured at CS onset. They found that individuals in the stress group showed higher ventral striatum BOLD response to CS predicting high magnitude compared to low magnitude gains, an effect that was not observed in the no stress group. Furthermore, individuals showing higher levels of reactivity to the laboratory stressor showed a more substantial magnitude effect than those who were less reactive to the stressor, which addresses the need to consider individual differences in physiological arousal when assessing the influence of stress on task-related brain function.

In contrast to the results reported by Lewis, Porcelli, and Delgado (2014), using a monetary incentive delay task, Montoya and colleagues (2014) found stress-related

global down-regulation of the basolateral amygdala and ventral striatum during anticipation of both appetitive and aversive outcomes. The authors pharmacologically manipulated circulating cortisol by oral administration of cortisol using a counterbalanced within-subjects design. The authors proposed that stress leads to hypoactivation of the mesocorticolimbic system. They also posited that these results might explain stress-induced reward-seeking behaviours, as individuals seek rewards to compensate for a hypoactive reward network. These particular results; however, were not supported by a similar study employing the same task using a different stressor. Kumar and colleagues (2014) used a negative evaluative feedback paradigm to induce stress while participants completed a modified version of the monetary incentive delay task. It is important to note that in this modified version, there was no loss condition; participants could either gain money or miss gaining money, but never lost money. Within this particular study, the influence of stress on both anticipation and feedback were assessed independently to see whether stress differentially influenced the function of the mesocorticolimbic system during different phases of learning. Interestingly, the authors reported opposing influences of stress on function within the ventral striatum and basolateral amygdala throughout the different phases. During anticipation, there was a trend towards increased BOLD response in both the ventral striatum and the basolateral amygdala when the cue predicted the possibility of gaining money in stressed versus non-stressed individuals. During feedback, however, there was a trend towards reduced BOLD response in these regions when participants received positive feedback in stressed versus non-stressed individuals. The authors suggest that stress may enhance the incentive value of anticipated outcomes, but may also reduce the hedonic value of rewards upon receipt.

1.3 Stress and the fMRI Environment

Few studies have directly assessed whether the neuroimaging environment itself may be perceived as stressful for some individuals. Two existing studies suggest that the scanning environment may elicit a stress response in adolescents (Eatough et al., 2009) and scanner naïve adults (Tessner et al., 2006). To assess the influence of previous exposure to the MRI environment on stress in adults, Tessner and colleagues measured

state and trait anxiety prior to scanning, and compared pre- and post-scan cortisol levels between scanner naïve and scanner experienced individuals. While there were no reported differences in anxiety prior to the scan, cortisol values were found to increase from pre-scan to post-scan in scanner naïve individuals; whereas the opposite trend was observed in scanner experienced individuals. Pertinently, Eatough and colleagues found a similar increase in circulating cortisol from pre-scan to post-scan in adolescents, even though participants completed a mock session immediately prior to completing of the MRI. Interestingly, values obtained prior to the mock session were similar to post-scan values. Furthermore, investigations have revealed that cortisol levels may increase in response to anticipation of a perceived stress (Kestler & Lewis, 2008). Not surprisingly, Preuß, Schoofs, Scholtz, and Wolf (2015) found that cortisol concentrations were elevated from baseline in University students immediately prior to the completion of both final examinations and oral presentations. Subsequently, in the present study, cortisol concentrations were measured immediately prior to the MRI as an index of an anticipatory stress.

1.4 Developmental Considerations

The majority of evidence reviewed thus far has been derived from studies in adults. Cross-sectional studies suggest that the development of self-regulation persists well into adulthood, and that this protracted development is likely the result of earlier maturation of subcortical systems and later maturation of top-down cognitive control systems (Galvan et al., 2006). With respect to feedback-related striatal activity, Galvan and colleagues (2006) found an inverted U-shaped trajectory between childhood and early adulthood. While the response of the ventral striatum to rewards was exaggerated in adolescents, responses observed in children closely resembled responses observed in adults. They also found that the activity of the orbitofrontal cortex was more distributed and less organized in both children and adolescents, and more focal in adults. These results have been independently verified in a similar cross-sectional study using a gambling task, which also found that risk-taking during low-reward gambles decreased as a function of age (Van Leijenjorst et al., 2010).

Importantly, children and adults may be similarly influenced by motivational and incentive information, and both appear to differ from adolescents (for a review, see Somerville & Casey, 2010). To date, no cross-sectional studies have directly assessed age-related changes in basolateral amygdala-ventral striatum associations, or how those associations may be influenced by physiological arousal. It is possible, however, that children may show more robust ventral striatum and basolateral amygdala feedback-related activity than adults due to protracted development of higher-order cortical networks. More generally, studies show that children may show a relatively reduced capacity to represent probabilistic associations compared to adults (Van Dujvenvoorde et al., 2013). Furthermore, using event related potential (ERP) measurement, Hämmerer and colleagues (2011) found age related decreases in the magnitude of the feedback related negativity (a component that is thought to reflect the relative valence of a particular outcome) measured using a probabilistic learning task. They also found that behaviourally, children tended to be more sensitive to losses than to gains, and more frequently changed their stimulus selection following a negative outcome than older age groups.

1.5 Purpose and Hypotheses

The lack of evidence related to the role of the basolateral amygdala in instrumental learning, particularly during feedback processing, points to a gap in our understanding of individual differences in striatal function, especially in light of the strong associations reported in an large body of animal literature. Physiological arousal may also play an important role in eliciting motivational shifts observed in these regions during feedback processing, and the scanning environment itself may be sufficient to induce a stress response in some individuals. Furthermore, these relationships have not been directly assessed in pre-adolescent populations, and associated individual differences within this age group may be predictive of particular developmental trajectories for self-regulation. Thus, the first aim of the present investigation was to determine whether the basolateral amygdala was involved in feedback processing during instrumental learning, and whether individual differences in basolateral amygdala activity to positive and negative feedback were associated with concomitant variability in ventral striatum activity. The second aim

of the present investigation was to determine whether observed individual differences in feedback-related basolateral amygdala and ventral striatum response were associated with individual differences in anticipatory elevations in physiological arousal elicited by the experimental environment measured via cortisol.

In order to assess these relationships, feedback-related changes in BOLD activity within the ventral striatum and basolateral amygdala were interrogated using a modified probabilistic learning task (Pessiglione et al., 2006) in a sample of typically developing children between the ages of 9 and 11 years. In this particular version of the probabilistic learning task, three separate pairs of stimuli were presented in each functional run; one pair was associated with the possibility of gaining points, one with the possibility of losing points, and one was associated with a neutral outcome. The distribution of valenced outcomes into separate stimulus pairs is thought to reduce competition between representation of gains and losses on any given trial, and allows for more accurate disambiguation of the independent functional correlates of positive and negative feedback. Additionally, the relatively large difference between outcome probabilities in each stimulus pair increases the rate at which stimulus-outcome associations are learned and requires fewer trials per functional run, which is beneficial in neuroimaging contexts. Possible anticipatory elevations in circulating cortisol were assessed by comparing cortisol values measured immediately prior to the MRI scan to a neutral baseline that was collected at-home prior to completion of the MRI.

The following hypotheses were assessed in the present study:

1. The basolateral amygdala responds similarly to positive and negative feedback, whereas activity in the ventral striatum increases in response to positive feedback and is suppressed in response to negative feedback.

2. Increased basolateral amygdala responses to positive and negative feedback is associated with increased corresponding bivalent ventral striatum responses, ipsilaterally.

3. Increased basolateral amygdala and ventral striatum responses to positive and negative feedback are positively associated with behavioural measures of sensitivity to rewards and losses, respectively.

4. Individual differences in anticipatory physiological arousal are associated with individual differences in basolateral amygdala and ventral striatum activity during both negative and positive feedback processing; specifically, increased circulating cortisol is negatively associated with feedback-related activity in the basolateral amygdala and ventral striatum.

5. Increased anticipatory physiological arousal is associated with enhanced sensitivity to rewards and reduced sensitivity to losses measured at the behavioural level.

Chapter 2

2 Methods

2.1 Participants

Thirty-one children (15 males) between the ages of 9- and 11-years old (M = 10.51; SD = 0.91) were recruited from Western University's developmental psychology research participant pool. Prospective participants were excluded if they had a diagnosis of ADD/ADHD or if they were currently taking medication for ADD/ADHD symptoms. Behavioural data was available for all 31 participants. Ten participants were excluded from analyses of neuroimaging data for excessive motion (greater than 3mm rotation or translation), and subsequently only 21 participants were included in analyses involving neuroimaging data, as well as analyses relating neuroimaging and behavioural data. Additionally, 10 participants were not included in analyses of the cortisol data; eight participants failed to provide baseline samples or had not had samples analyzed prior to completion of the present study, the measured cortisol concentrations for one participant were contaminated and could not be accurately assayed, and one participant was identified as an outlier using stem-and-leaf plots. Subsequently, 21 participants were included in analyses relating cortisol and behavioural data. In total, 14 participants had both useable neuroimaging data and usable cortisol data and were included in analyses focused on identifying associations between stress and task-related BOLD response. Parents of participants provided informed consent consistent with the policies of the Human Subjects Research Ethics Board at Western University (see **Appendix A**), and participants were compensated with gift cards for their participation in both the training session and the MRI session.

The participants described above reflect participants who successfully completed both the training and MRI portion of the study. Approximately 25% of children who completed the training session did not participate in the MRI portion for a variety of reasons. For example, some participants were unable to find a suitable time to return for the MRI, some participants failed to attend their scheduled MRI, and others were not interested in

completing the MRI for personal reasons (anxious, medical concerns, concerns about the safety of the MRI). Furthermore, two participants terminated the MRI prior to completion and did not wish to continue with the protocol, and were excluded from all analyses.

2.2 Experimental Procedure

All participants attended an initial mock scanning session prior to the MRI session to acclimate them to the scanning environment. Prior to participation in the training session, informed consent was obtained from participants' guardians and assent was obtained from participants themselves. Participants were then asked if they would like to feel what it is like to be inside a real scanner, and were invited to enter the mock scanner to practice staying as still as possible. While inside the mock scanner, participants listened to noises that mimicked the sounds that the real MRI scanner makes. After listening to the noises, participants watched a movie clip for approximately 5 min while attempting to stay as still as possible. The mock scanning session allowed for the identification of children who were uncomfortable with the scanning environment and gave participants the opportunity to make an informed decision about participation in the actual MRI procedure. At the end of the training session, participants who consented to participate in the MRI procedure were provided with materials for collection of an at-home baseline salivary cortisol sample, as well as instructions related to the collection protocol (see Appendix A). All participants received compensation for the initial visit.

Upon arrival to the MRI session, participants completed practice runs of the probabilistic selection task (PST). Immediately prior to entering the MRI, an additional salivary cortisol sample was collected. Participants were told that they could win up to $10 cash based on their performance on the probabilistic learning task in order to increase the incentive to respond as accurately as possible. Participants completed three functional runs of the probabilistic learning task in the scanner, following which an anatomical image was acquired. During the collection of the anatomical scan, participants watched videos of their choice. Two diffusion tensor images were also collected after the anatomical scan for future projects interested in structural connectivity. All stimuli were projected onto the centre of a 15cm high by 20cm wide display mounted outside of the magnet using a Windows PC running E-Prime 2.0 software (Psychology Software Tools,

Pittsburgh, PA). Participants were able to view the screen through a mirror placed above the head coil and 25cm from the display, which subtends approximately 43.6° of the visual angle. The duration of the scanning session was approximately 45 min. All participants received compensation for their time, and importantly, all participants were told they performed well on the probabilistic learning task and received the full $10 cash.

2.3 Cortisol Collection and Measurement

2.3.1 Collection

Passive saliva was collected for cortisol analysis on two separate occasions. All samples included in the present analyses were collected between 2:00 p.m. and 8:30 p.m. A baseline sample (baseline cortisol) was collected at home at the same time of day as the scheduled MRI, and a second sample (pre-MRI cortisol) was collected immediately before participants entered the MRI scanner. Participants were given detailed instructions regarding at the end of the training session. Briefly, participants were asked not to eat or drink anything but pure water and to avoid physical exertion for an hour before collection. For detailed instructions, see **Appendix B**. Saliva was collected by unstimulated passive drool into untreated sterile polystyrene tubes (16 x 100 mm). Participants were asked to store the baseline cortisol sample in a freezer (with no freeze-thaw cycle) immediately following collection until their scheduled MRI session, and were instructed to transport samples from home to the session in pre-conditioned TheraPak^{TM} cooler bags that were provided to them. The bags are guaranteed to maintain a frozen state for up to 4 hrs at ambient temperature. Samples collected at the scan were placed inside the coolers for the duration of the experimental protocol, which was typically 45 min. Following the MRI, both baseline cortisol and pre-MRI cortisol were immediately placed in a -20°C freezer with no freeze-thaw cycles, where samples were stored until analysis.

2.3.2 Measurement

Salivary cortisol was assayed by direct radioimmunoassay using an ImmuChemTM Coated Tube Cortisol 125I RIA kit (MP Biomedicals LLC, Orangeburg, NY). The kit uses a 125I label, and was modified for use with saliva. A 200 uL aliquot was used with

an extended incubation (22 hrs at RT). The standards were diluted 1:20. All samples were assayed in duplicate. Concentrations were expressed in nanomoles per liter (nmol/L). The sensitivity of the assay was 0.15 nmol/L and the intra-assay coefficient of variation was < 5%.

Shapiro-Wilk tests revealed that measured baseline cortisol and pre-MRI cortisol were not normally distributed within the sample, $S\text{-}W(22) = 0.83$, $p = .001$ and $S\text{-}W(22) = 0.82$, $p = .001$, respectively. Furthermore, outliers were identified using stem-and-leaf plots, and one participant was identified as an outlier and excluded from subsequent analyses. Obtained values for both baseline cortisol and pre-MRI cortisol were normalized by log-transformation for use in statistical analyses.

2.4 Probabilistic Learning Task

The probabilistic learning task was a modified version of the task described by Pessiglione et al. (2006). All stimuli were pictures of random objects or symbols presented on a black background. For each run, three different stimulus pairs were presented at random, and different stimuli were used in each run. For win pairs (AB), selection of the optimal stimulus (A) resulted in winning 10 points on 80% of trials (win), and returned 0 points (miss) on 20% of trials, whereas the paired stimulus (B) resulted in a win on only 20% of trials and a miss on 80% of trials. For loss pairs (CD), the optimal stimulus (C) returned 0 points on 80% of trials (avoid) and resulted in losing 10 points (loss) on 20% of trials, whereas the paired stimulus (D) resulted in a loss on 80% of trials and an avoid on 20% of trials. For neutral pairs, both stimuli (EF) returned 0 points on 100% of presentations. Paired stimuli were presented on either side of a central fixation cross, with random assignment of each stimulus within a pair to either the left or right side to avoid the influence of place preference. Subjective accuracy (%) and RT (ms) measures were computed for each participant. Separate values were computed for each run, as well as for each trial type (win, loss). Average subjective accuracy was computed using the following equation: $A = \frac{R_o}{R_T} \times 100$, where R_o is the number of optimal responses (A or C) and R_T is the total number of responses.

Participants completed three event-related functional runs, with 650 volumes collected in each run. Each run lasted for approximately 7 min, and typically consisted of 44 trials with the following distribution of stimulus pairs: 4 neutral, 20 win, and 20 loss. In order to desynchronize the timing of events with respect to acquisition and enhance variability in the signal time course, each trial was preceded with a variable intertrial interval (ITI), which consisted of a fixation cross on a black background and was presented for between 1000-5000 ms. Following the ITI, stimuli pairs were presented for 3000 ms, during which time participants used a button-press to select either the stimulus on the right or the stimulus on the left side of the screen. Following stimulus presentation, a feedback screen displayed either "+10", "-10", or "0" for 1000 ms, reflecting the outcome of their selection. If participants failed to select a stimulus, the message "too slow" was displayed on the feedback screen. The next ITI was initiated following feedback. A cumulative score was displayed at the bottom of the screen (centered) so that participants could keep track of their progress. See Figure 1 for a schematic representation of a trial sequence. Following the functional runs, anatomical scans were collected while participants watched a movie clip of their choice.

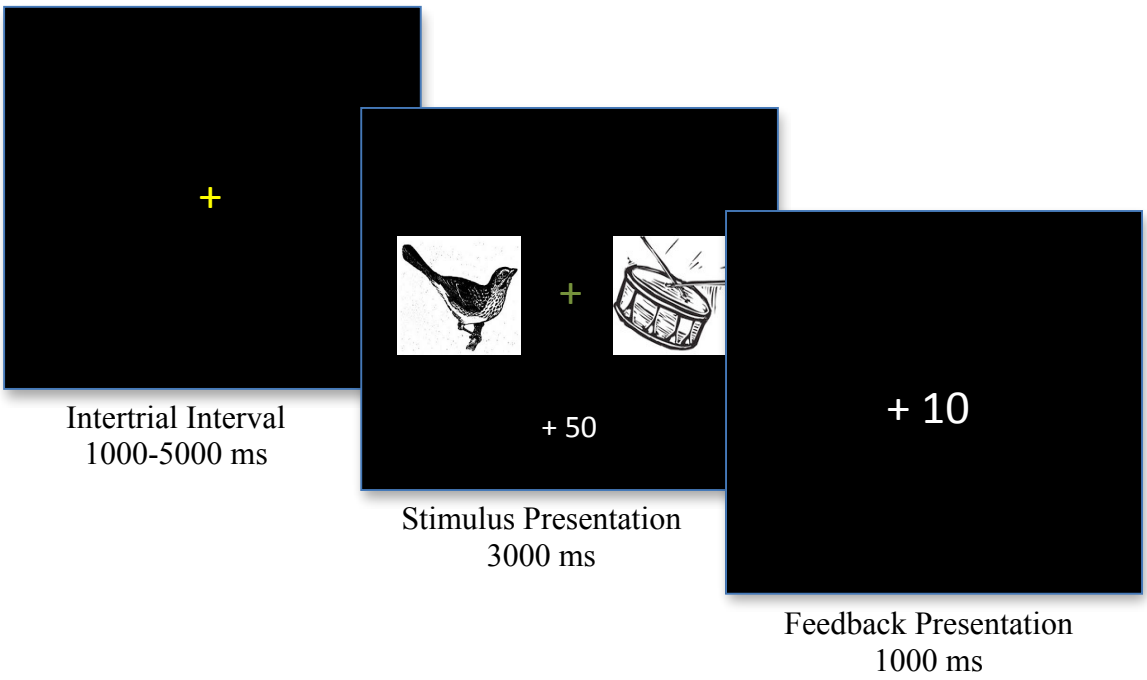

Figure 1: Schematic illustration of trial sequence.

2.5 fMRI Data Acquisition

All functional and structural images were acquired using a 3-Tesla Siemens Magnetom Prisma scanner, using a Siemens Prisma 32-channel head coil. T2*-weighted functional scans were acquired using an echo-planar imaging (EPI) pulse sequence. Slices were collected using an ascending, interleaved slice acquisition order (TR = 686 ms, TE = 30 ms, FOV = 192 x 192 mm, flip angle = 54°, resolution = 3 x 3 x 3 mm, 64 x 64 matrix). Thirty-two slices were collected per volume. A high-resolution T1 weighted anatomical scan was also obtained for each participant using a 3D MPRAGE pulse sequence (192 slices, resolution = 1 x 1 x 1 mm, 256 x 256 matrix).

2.6 fMRI Data Preprocessing

All functional images were preprocessed and analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). All acquired images were corrected for slice scan acquisition timing using cubic spline interpolation. Functional volumes were aligned to the first volume of the run to correct for motion both within and between runs for each participant. Volumes were then coregistered with structural T1 images. Coregistered volumes were normalized to Montreal Neuroimaging Institute space, and then spatially smoothed using an 8mm full-width at half-maximum isotropic Gaussian kernel.

2.7 fMRI Analysis

2.7.1 Whole Brain Analysis

In order to determine whether the task reliably engaged regions relevant for feedback learning in children, an initial whole brain analyses was conducted. A random-effects general linear model analysis was conducted on data acquired during completed functional runs. Separate regressors were modeled for positive feedback (wins) and negative feedback (losses). Event-related predictors were modeled at feedback onset for each run, and the resulting onset vectors were convolved with a canonical two gammas model of the hemodynamic response function. Six motion regressors (translation: x, y, z; rotation: pitch, yaw, roll) were also included in the general linear model as variables of

no interest. Regions showing greater activation to rewarding feedback were identified by contrasting estimates of the beta coefficients of win and loss predictors.

2.7.2 Region of Interest Analysis

Region of interest (ROI) analyses were conducted to independently characterize basolateral amygdala and ventral striatum activity to positive and negative feedback, as well as to test hypotheses related to individual differences in response profiles. For the bi-lateral basolateral amygdala, spherical ROIs (r = 5mm) were created in MarsBar with the centres set as the coordinates corresponding to the centres of mass reported in the SPM8 AnatomyToolbox (Amunts et al., 2005) which are as follows: left (x = -23, y = -6, z = -19); right (x = 25, y = -5, z = 19). The bi-lateral ventral striatum ROIs were defined functionally at the group level using the peak coordinates derived from the contrast of wins > losses. Parameter estimates in the form of T-statistics were extracted for each subject from regressors modeling wins and losses (independently) using MarsBar. Importantly, estimates were not extracted from contrasts of conditions; rather, estimates for each voxel within an ROI reflected a difference between task-related and baseline BOLD response (baseline estimate reflects the average signal within a given voxel measured across the entire duration of the run). Additionally, parameter estimates reflected the average effect size across all voxels within a particular ROI, and not peak signal change. All further statistical analyses were performed using SPSS.

At the group level, one-sample t-tests were conducted to determine whether the average effect size for each ventral striatum and basolateral amygdala ROI was reliably different from zero, and to identify the valence of responses to positive and negative feedback. In order to assess whether there were reliable differences between BOLD profiles as a function of trial type or Separate 2(trial type: win, loss) x 2(hemisphere: left, right) repeated measures analyses of variance (ANOVAs) were then computed to assess whether there were reliable differences between BOLD profiles as a function of trial type or hemisphere.

2.8 Individual Differences Analyses

2.8.1 Independent Group Differences

The first analysis of individual differences aimed to test whether individual differences in basolateral amygdala BOLD response were associated with concurrent differences in the ventral striatum. Participants were first identified as either high or low responders in terms of basolateral amygdala BOLD response to positive and negative feedback for each ROI (left and right hemispheres separately) by way of median split. Independent-samples t-tests were conducted to assess whether high responders showed higher average ventral striatum activity to feedback than low responders. Importantly, to further reduce the number of comparisons, only ipsilateral associations were tested, in accordance with evidence suggesting primarily ipsilateral communication between these regions (Ambroggi et al., 2008). Results were not corrected for multiple comparisons.

2.8.2 Correlational Analyses

Three series of bi-variate correlations were conducted in order to assess the following: the relationship between task-related BOLD response and behaviour; the relationship between circulating cortisol and behaviour; the relationship between circulating cortisol and BOLD response. For the first series, parameter estimates for bi-lateral ROIs estimating BOLD response to both positive and negative feedback were correlated with measures of subjective accuracy and RT. Next, baseline corrected cortisol measures were correlated with subjective accuracy and RT to determine whether there was an associated increase in accuracy during win trials and decrease in accuracy during loss trials. Finally, cortisol measures were correlated with parameter estimates for both the basolateral amygdala and ventral striatum ROIs associated with positive and negative feedback processing to determine whether there was an observed positive relationship between cortisol and the magnitude of the BOLD response to positive feedback and a negative relationship between cortisol and BOLD response to negative feedback. Results were not corrected for multiple comparisons.

Chapter 3

3 Results

3.1 Cortisol Analysis

There were no gender differences (10 males, 12 females) in baseline cortisol [(males: M = 0.38, SD = 0.11; females: M = 0.41, SD = 0.35), $t(20) = 0.36$, $p = .7$] or in pre-MRI cortisol [(males: M = 0.38, SD = 0.35; females: M = 0.36, SD = 0.31), $t(20) = 0.15$, $p = .9$]. There were also no correlations between age and either baseline cortisol, $r(22) = -.17$, $p = .4$, or pre-MRI cortisol, $r(22) = 0.010$, $p = 1.0$. A paired-samples t-test was then performed to determine whether there was a reliable difference between baseline cortisol (M = 0.39, SD = 0.32) and pre-MRI cortisol (M = 0.43, SD = 0.31). There was no reliable difference between the two measures, $t(22) = -0.46$, $p = .7$.

Difference scores were calculated for each participant (pre-MRI cortisol – baseline cortisol) to better visualize the relationship between the two variables. While some participants had reduced pre-MRI cortisol when compared with baseline cortisol, other participants showed an increase. In order to determine whether this outcome was driven primarily by variability in baseline cortisol or variability in pre-MRI cortisol, median splits were performed on baseline cortisol (MED = 0.30) and pre-MRI cortisol (MED = 0.43) and participants were identified as either high pre-MRI cortisol (H_{MRI}, ≥ 0.43) or low pre-MRI cortisol (L_{MRI}, < 0.43) and as either high baseline cortisol (H_B, ≥ 0.30) or low baseline cortisol (L_B, < 0.30). A 2 x 2 ANOVA was conducted with pre-MRI cortisol group (H_{MRI}, L_{MRI}) and baseline cortisol group (H_B, L_B) as between subjects factors and the difference score as the independent variable. There was a significant main effect of pre-MRI cortisol group, such that difference scores were significantly higher in the H_{MRI} group (N = 12; M = 0.27, SD = 0.28) than in the L_{MRI} group (N = 10; M = -0.20, SD = 0.28), $F(1,18) = 14.63$, $p = .001$. There was also a significant main effect of baseline cortisol; difference scores were significantly lower in the H_B group (N = 11; M = -0.18, SD = 0.30) than in the L_B group (N = 11; M = 0.25, SD = 0.28), $F(1,18) = 12.25$, $p = .002$. There was no interaction between baseline cortisol and pre-MRI cortisol, $F(1,18) =$

0.002, $p = 1.0$. Thus, participants with higher baseline cortisol and lower pre-MRI cortisol tended to have lower (negatively valenced) difference scores, and participants with lower baseline cortisol and higher pre-MRI cortisol tended to have higher (positively valenced) difference scores. Importantly, the difference scores were driven not only by variability in baseline cortisol but also by variability in pre-MRI cortisol. Although there was no observed group-level difference between pre-MRI cortisol and baseline cortisol, subsequent analyses sought to determine whether variability in pre-MRI cortisol influenced behavioural and neural correlates of feedback processing in the probabilistic learning task.

3.2 Behavioural Results

3.2.1 Group-Level Performance

As this particular task has not been implemented in a sample of this age group previously, initial analyses sought to confirm that participants were engaged in the task and were able to adequately understand instructions and perform the task to the best of their abilities. To qualitative assess task validity, group learning curves were calculated for win trials and loss trials. For win trials, the proportion of participants selecting the optimal stimulus (rewarded 80% of the time) was calculated for each trial in each run, and an average value was calculated for each trial across all runs. For loss trials, the proportion of participants selecting the suboptimal stimulus (punished 80% of the time) was calculated. See Figure 2 for a visualization of the group learning curves. These curves show that during the start of the task, the distribution of selections is random, whereas at the end of the task, more than 80% of participants successfully select the optimal stimulus and avoid selecting the suboptimal stimulus.

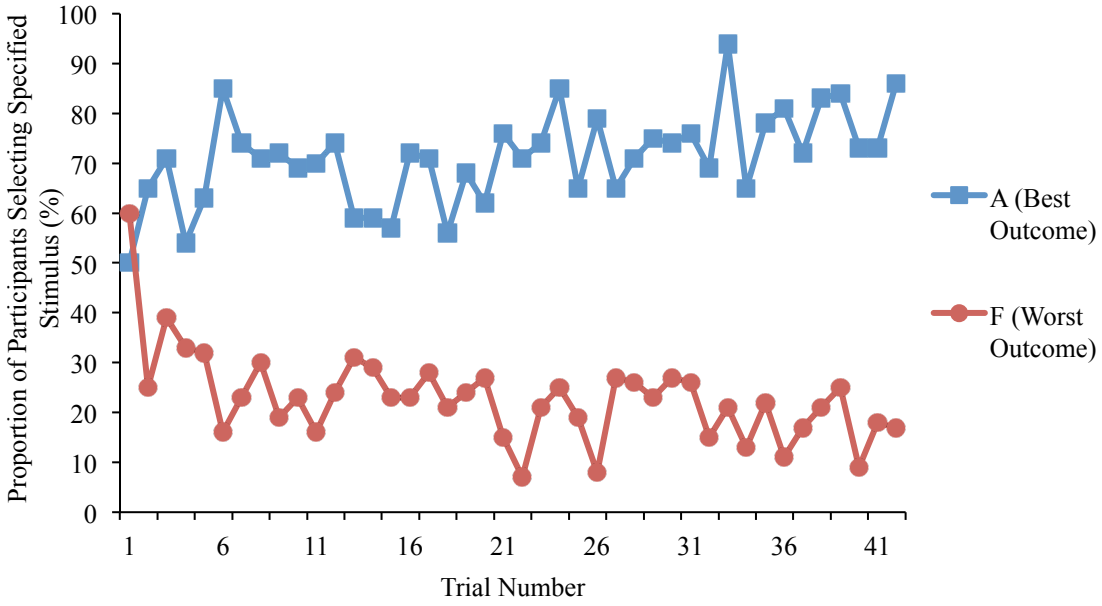

Figure 2: Learning curves representing proportion of participants who selected the optimal stimulus during win trials (blue) and selected the suboptimal stimulus during loss trials (red) as a function of time

3.2.2 Subjective Accuracy

There were no gender differences in subjective accuracy on win trials (males: $M = 70.30$, $SD = 17.65$; females: $M = 70.76$, $SD = 18.92$), $t(29) = -0.081$, $p = .9$, or loss trials (males: $M = 72.52$, $SD = 15.58$; females: $M = 71.29$, $SD = 12.95$), $t(29) = 0.24$, $p = .8$. There was also no correlation between age and average accuracy on win trials, $r(31) = .26$, $p = .2$, or on loss trials, $r(31) = .11$, $p = .6$. A 3 x 2 repeated measures ANOVA was conducted in order to determine whether subjective accuracy differed as a function of time (run 1, run 2, run 3) or feedback type (positive, negative). Four subjects were excluded from this analysis, as they did not have behavioural data for all three runs. There was no main effect of either trial type, $F(1,23) = 0.17$, $p = .7$, or time, $F(2,22) = 0.76$, $p = .5$, and no interaction between trial type and time, $F(2,22) = 0.21$, $p = .8$. See Table 1 for descriptive statistics.

Table 1: Means and standard deviations for average subjective accuracy (%) and reaction time (ms) as a function of trial type and time

Feedback	Run	Subjective Accuracy		Reaction Time	
		M	*SD*	*M*	*SD*
Win	1	66.92	28.41	1190.26	200.86
	2	72.32	30.19	1192.06	169.43
	3	71.99	28.81	1122.04	169.93
Loss	1	69.14	18.47	1201.14	206.27
	2	70.65	19.54	1223.49	190.84
	3	76.20	21.53	1249.52	144.60

3.2.3 Reaction Time

There were no gender differences in RT (ms) on win trials (males: $M = 1143.00$, $SD = 174.10$; females: $M = 1175.33$, $SD = 119.04$), $t(29) = -0.61$, $p = .5$, or loss Trials (males: $M = 1200.22$, $SD = 168.48$; females: $M = 1236.05$, $SD = 121.67$), $t(29) = -0.68$, $p = .5$. There was also no correlation between age and RT for win trials, $r(31) = -.026$, $p = .9$, or for loss trials, $r(31) = -.11$, $p = .6$. In order to test for the potential influence of circulating cortisol on RT, a similar 2 x 3 repeated measures ANOVA was conducted with RT as the independent variable (see Table 1 for descriptive statistics). There was a significant main effect of trial type, $F(1,23) = 5.49$, $p = .03$. Tukey's LSD post-hoc pairwise comparisons revealed that individuals responded faster to stimuli that were predictive of potential gains ($M = 1168.12$; $SD = 124.85$) than they did to stimuli predicting potential losses ($M = 1224.71$, $SD = 150.50$). There was no main effect of time, $F(2,22) = 0.25$, $p = .8$, and no interaction between trial type and time, $F(2,22) = 2.55$, $p = .09$.

3.3 Neuroimaging Results

3.3.1 Whole Brain Analysis

As the probabilistic learning task in the present study was adopted from the task used by Pessiglione et al., (2006), which has only been employed in adult populations, the first analyses aimed to determine whether the task reliably engaged regions that have been commonly cited as being involved in feedback processing. All participants who met motion criteria (< 3mm) were included in whole brain analyses. Regions with greater activation during reward processing were identified from a contrast of rewarding feedback greater than negative feedback (wins > losses), and regions with greater activation during loss processing were identified from a contrast of negative feedback greater than rewarding feedback (losses > wins). A significance level of $p < .005$ (uncorrected) was used to identify significant clusters. Anatomical identification of peak coordinates was carried out using the Anatomy Toolbox. For wins > losses, a significant cluster was identified in the ventral striatum. Three significant clusters were identified in the loss > wins contrast, including the bi-lateral insula and dorsal anterior cingulate cortex. See Table 2 for a list of peak values and coordinates and Figure 3 for visualization of a) significant cluster for wins > losses and b) significant clusters for losses > wins.

Table 2: Brain regions more activated during wins > losses and losses > wins

Contrast	Region	Hemisphere	Cluster Size (mm^3)	*T*	MNI
Wins > Losses	VS *	L	1453	4.49	-6, 8, -4
Losses > Wins	Insula**	R	2759	8.16	44, 30, -8
	dACC	R	1887	6.09	8, 22, 40
	Insula**	L	1143	5.70	-36, 28, 10

Note: MNI coordinates are for the peak voxel identified within each cluster

* this cluster also included the right VS and right ventromedial prefrontal cortex

** these were large cluster that also included inferior frontal gyri

ventral striatum = VS; dorsal anterior cingulate cortex = dACC

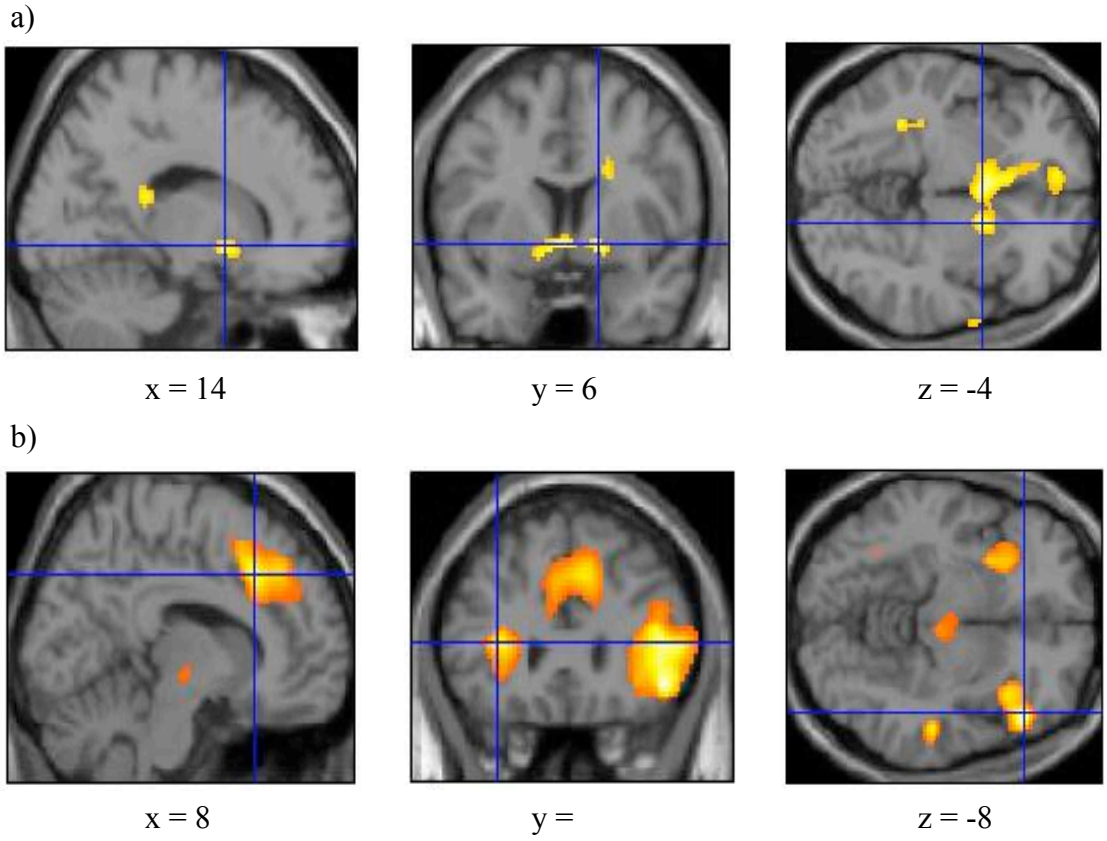

Figure 3: Visualization of significant clusters for contrasts of a) wins > losses, coordinates for the right ventral striatum and b) losses > wins, coordinates for the dorsal anterior cingulate cortex, left insula, and right insula, respectively, $p < .005$ (uncorrected)

3.3.2 Region of Interest Analysis: Ventral Striatum and Basolateral Amygdala BOLD Response to Positive and Negative Feedback

The aim of the group-level ROI analysis was to determine the independent response profiles of the ventral striatum and basolateral amygdala to positive and negative feedback. The bi-lateral basolateral amygdala ROIs were identified using the method described previously. The bi-lateral ventral striatum ROIs were defined functionally at the group level using the peak coordinates derived from the contrast of wins > losses.

The cluster containing the right and left ventral striatum was imported into MarsBar, and was then convolved with spherical ROIs (r = 5mm) with centres corresponding to the peak t-values reported for each hemisphere in Figure 3b and Table 2, respectively. This method ensured that areas within the clusters that fell outside of the ventral striatum were not included in subsequent ROI analyses. For follow-up control analyses, ROIs were also defined for the bi-lateral dorsal anterior cingulate cortex and bi-lateral insula clusters identified at the group level using the same procedure. As a significant cluster was identified only in the right dorsal anterior cingulate cortex, a symmetrical ROI was created for the left dorsal anterior cingulate cortex. T-statistics were extracted from each ROI for each participant and were used in subsequent group-level and individual subjects analyses. There were no gender differences in average BOLD response in the basolateral amygdala or ventral striatum (averaged across left and right ROIs) for either win trials or loss trials (for descriptive and inferential statistics see Table 3). There were also no correlations between average BOLD response in the basolateral amygdala or ventral striatum and age (for inferential statistics see Table 3).

Table 3: Descriptive and inferential statistics for the independent-samples t-test assessing gender differences in effect size (T), as well as inferential statistics from the correlation between age and effect size.

ROI (Feedback)	*M*(*SD*)		Gender Difference (t-test)			Correlation with Age		
	Males	Females	*t*	df	*p*	*r*	df	*p*
BLA (Win)	0.71 (2.00)	0.34 (1.89)	0.43	19	.7	.38	21	.09
BLA (Loss)	0.0017 (1.17)	-0.34 (1.74)	-0.52	19	.6	-.21	21	.4
VS (Win)	0.92 (1.17)	1.09 (1.91)	-0.24	19	.8	.011	21	1.0
VS (Loss)	-0.20 (2.14)	-1.06 (1.60)	1.05	19	.3	-.012	21	1.0

ventral striatum = VS; basolateral amygdala = BLA; region of interest = ROI

In order to assess the particular response profiles of each of the ROIs to positive and negative feedback independently, average trial-specific group-level T-statistics for each ROI were subject to one-sample t-tests against the null hypothesis of no difference. The average effect size for both the left basolateral amygdala and right basolateral amygdala was not significant for either wins [left: $t(20) = 1.57$, $p = .1$; right: $t =(20) = 0.76$, $p = .4$)] or losses [left: $t(20) = -0.45$, $p = .7$; right: $t(20) = -0.68$, $p = .5$]. The average effect size for the right ventral striatum, but not the left ventral striatum was significantly greater than zero during win trials [left: $t(20) = 1.81$, $p = .09$; right: $t(20) = 3.47$, $p = .002$] and the average BOLD response for the left ventral striatum, $t(20) = -2.57$, $p = .02$, but not the right ventral striatum, $t(20) = -0.75$, $p = .5$, was significantly less than zero during loss trials [left: $t(20) = -2.57$, $p = .02$; right: $t(20) = -0.75$, $p = .5$]. See Figure 4 for descriptive data.

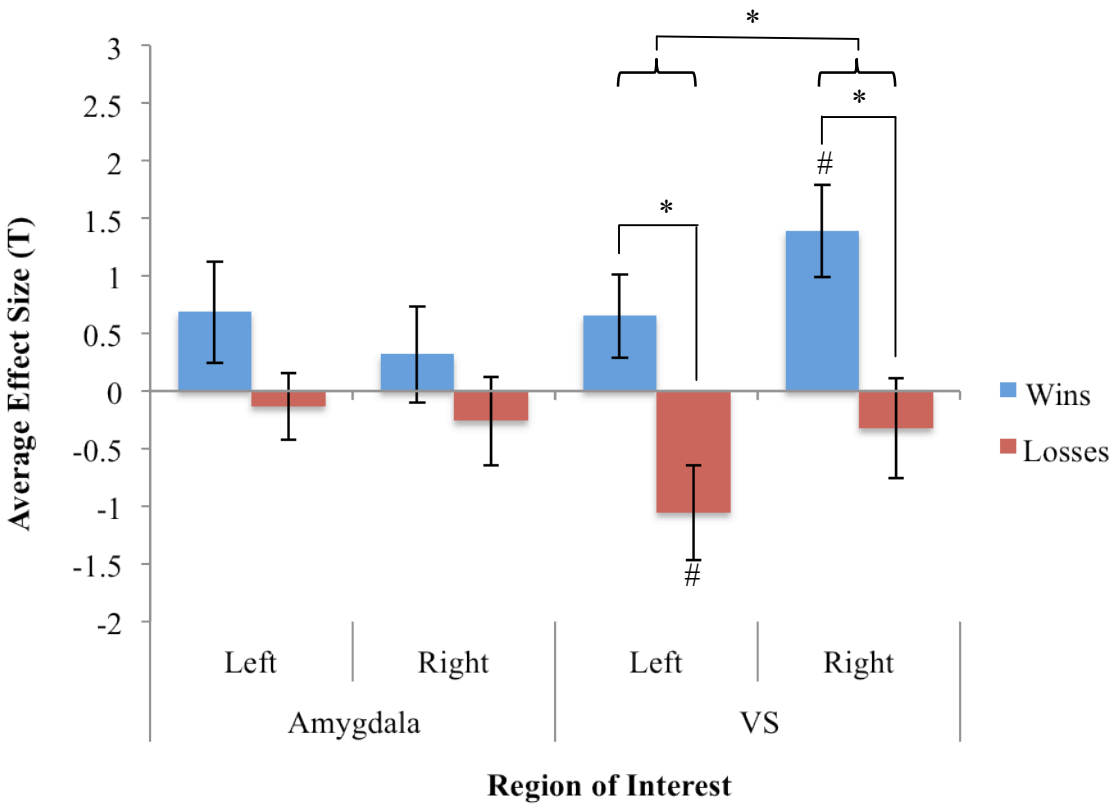

Figure 4: BOLD response in bi-lateral BLA and VS ROIs during receipt of positive feedback (wins) and negative feedback (losses), error bars represent standard error of the mean.

 # denotes average effect size different from zero, $p < .05$

** denotes significant difference in BOLD response between factors, $p < .05$*

A follow-up analysis was conducted to determine whether BOLD profiles in the basolateral amygdala or ventral striatum reliably differed as a function of feedback type (wins, losses), or hemisphere (left, right) using two independent 2 x 2 repeated measures ANOVAs. For the basolateral amygdala, there was a trend-level main effect of trial type. Post-hoc Tykey's LSD pairwise comparisons revealed that average basolateral amygdala BOLD response (averaged across the left and right hemispheres) was marginally greater in response to wins ($M = 1.00$, $SD = 1.53$) than losses ($M = 0.23$, $SD = 1.77$). There was

no main effect of hemisphere and there was no interaction between feedback type and hemisphere (see Table 4 for ANOVA results). For the ventral striatum, there was a significant main effect of feedback type, as well as a significant main effect of hemisphere (see Table 4). Post-hoc Tukey's LSD pairwise comparisons revealed that the average BOLD response (averaged over left ventral striatum and right ventral striatum) was significantly greater in response to wins (M = 1.02, SD = 1.60) than losses (M = -0.69, SD = 1.85), $p < .001$. Furthermore, the average BOLD response (averaged over wins and losses) was significantly greater in the right ventral striatum (M = 0.53, SD = 1.65) than in the left ventral striatum (M = -0.20, SD = 1.56), $p = .004$.

Table 4: Results of 2 x 2 repeated measures ANOVA assessing the influence of feedback type (Win, Loss) and hemisphere (Left, Right) on BOLD response in the BLA and ventral striatum

	BLA				VS			
Source	*df*	*F*	η^2	*p*	*df*	*F*	η^2	*p*
(A) Feedback	1(20)	2.58	.11	.08	1(20)	22.41	.53	< .001
(B) Hemisphere	1(20)	3.07	.13	.1	1(20)	10.63	.35	.004
A x B	1(20)	0.86	.04	.4	1(20)	0.00	.00	.1

Note**:** Between groups *df* are reported outside of parentheses and within groups *df* are reported within parentheses

ventral striatum = VS; basolateral amygdala = BLA

3.4 Individual Differences Analyses

3.4.1 Associations Between Basolateral Amygdala and Ventral Striatum

The first purpose of the individual differences analyses was to establish whether there was a relationship between individual differences in BOLD responses in the basolateral amygdala and BOLD responses in the ventral striatum to negative and positive feedback. A series of planned comparisons were conducted between ipsilateral basolateral amygdala and ventral striatum ROIs as a function of feedback type. Individuals with high and low parameter estimates in the left and right basolateral amygdala for both win trials and loss trials were identified by median split [win: left (*MED* = 0.65), right (*MED* = 0.23); loss: left (*MED* = 0.12), right (*MED* = 0.01)]. Independent samples t-tests were then conducted to determine whether group differences in ipsilateral ventral striatum BOLD response existed between individuals with high and low basolateral amygdala responses to positive and negative feedback. For win trials, high responders had significantly higher average ipsilateral ventral striatum BOLD responses than low responders regardless of hemisphere [left: $t(19) = 2.91$, $p = .009$; right: $t(19) = 2.18$, $p = .04$]. For loss trials, the same pattern emerged; high responders had significantly higher average ipsilateral ventral striatum BOLD responses [left: $t(19) = 2.32$, $p = .03$; right: $t(19) = 2.38$, $p = .03$] than low responders. See Figure 4 a) for descriptive statistics. Thus, increased basolateral amygdala activity was associated with increased ipsilateral ventral striatum activity, regardless of feedback type or hemisphere.

To assess whether the observed relationships between basolateral amygdala and ventral striatum activity was unique, a follow-up analysis was conducted to assess whether similar group differences between high responders and low responders were apparent in BOLD responses of the insula or dorsal anterior cingulate cortex. Identical independent samples t-tests were conducted between ipsilateral basolateral amygdala and insula as well as basolateral amygdala and dorsal anterior cingulate cortex ROIs as a function of feedback type. There were no group differences in ipsilateral dorsal anterior cingulate cortex BOLD responses between high responders and low responders during the processing of either positive [left: $t(19) = 0.062$, $p = .9$; right: $t(19) = -0.045$, $p = .1$] or

negative [left: $t(19) = 0.53$, $p = .6$; right: $t(19) = -0.70$, $p = .5$] feedback. Similarly, no group differences in ipsilateral insula responses between high responders and low responders during the processing of either positive [left: $t(19) = 0.11$, $p = .9$; right: $t(19) = 0.041$, $p = .1$] or negative [left: $t(19) = 1.13$, $p = .3$; right: $t(19) = 0.87$, $p = .4$] feedback. See Figure 5 for a visualization of the relationship between basolateral amygdala activity and: b) dorsal anterior cingulate cortex activity, c) insula activity.

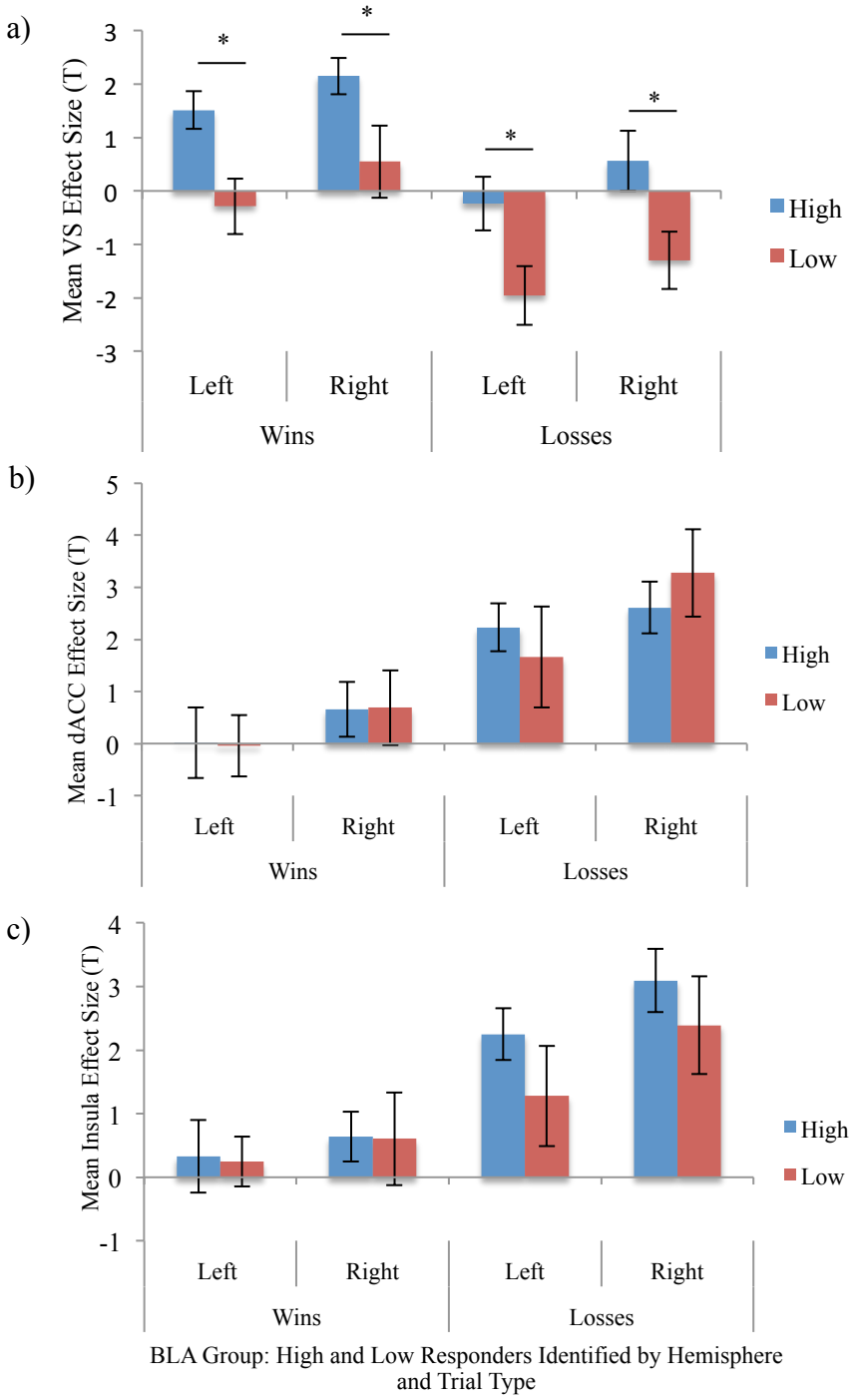

Figure 5: Relationship between individual differences in bi-lateral BLA BOLD responses and individual differences in ipsilateral a) ventral striatum b) dorsal anterior cingulate cortex, and c) insula BOLD responses during positive and negative feedback processing, error bars represent standard error of the mean

** denotes p < .05; basolateral amygdala = BLA*

3.4.2 Behavioural Associations with BOLD Response in Ventral Striatum and Basolateral Amygdala

This analysis aimed to identify whether individual differences in BOLD response in the basolateral amygdala and ventral striatum ROIs were associated with individual differences in either subjective accuracy or RT measures. As there were no effects of either trial type or time on subjective accuracy, total average subjective accuracy, averaged across win trials and loss trials and over all runs, was used in subsequent analyses. Furthermore, as there was a main effect of trial type on average RT, average RTs during presentation of win pairs and loss pairs (across runs) were included separately. Bi-variate correlations were performed between the aforementioned behavioural variables and the parameter estimates extracted from bi-lateral ventral striatum and basolateral amygdala ROIs for win trials and loss trials. Results were not corrected for multiple comparisons. There were no correlations between RT to either positive or negative stimuli and BOLD responses to wins or losses in either the ventral striatum or basolateral amygdala, bi-laterally (see Table 5). There were, however, positive correlations between BOLD responses to positive feedback in the bi-lateral basolateral amygdala and the right ventral striatum and average subjective accuracy (see Table 5).

Table 5: Correlations between individual differences in BOLD response of bi-lateral BLA and VS ROIs to positive and negative feedback and subjective accuracy and RT during win and loss trials

Behavioural Measure		BLA							
		Positive				Negative			
		Left		Right		Left		Right	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Accuracy	(Total)	.45	.04	.44	.05	-.030	.9	-.11	.6
RT	(Win)	-.016	.9	-.078	.7	.25	.3	.078	.7
	(Loss)	.24	.3	.16	.5	.30	.2	.25	.2
Behavioural Measure		VS							
		Positive				Negative			
		Left		Right		Left		Right	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Accuracy	(Total)	.095	.7	.43	.03	.21	.4	.18	.4
RT	(Win)	-.13	.6	-.20	.4	.072	.8	.39	.08
	(Loss)	.29	.2	-.052	.8	.27	.2	.27	.3

Note**:** $N = 21$ for all correlations

ventral striatum = VS; basolateral amygdala = BLA; reaction time = RT; region of interest = ROI

3.4.3 Associations with Individual Differences in Cortisol

Bi-variate correlations were conducted between pre-MRI cortisol and average subjective accuracy and RT to determine whether there was a direct association with behaviour. As a priori hypotheses predicted that increased cortisol would be associated with enhanced performance during win trials and reduced performance during loss trials, average subjective accuracy for both trial types were assessed independently. Reaction time measures averaged across runs for each trial type were also included. There were no significant correlations between pre-MRI cortisol and average RT to positively (r = -.24, p = .4) or negatively (r = -.40, p = .2) valenced stimuli pairs, and no correlations between pre-MRI cortisol and average subjective accuracy during win trials (r = -.36, p = .2) or loss trials (r = -.37, p = .2).

Subsequent correlations were conducted between pre-MRI cortisol and bi-lateral basolateral amygdala and left ventral striatum parameter estimates to assess the hypothesis that cortisol would be negatively correlated with feedback-related activity in these regions. A significant negative correlation between pre-MRI cortisol and left basolateral amygdala activity and a marginal negative correlation with right basolateral amygdala activity during win trials was observed. No other correlations with pre-MRI cortisol were observed. Results were not corrected for multiple comparisons. See Table 6 for results of the correlation analyses, and see Figure 6 for a visualization of the correlations between pre-MRI cortisol and BOLD response in the bi-lateral basolateral amygdala during win trials.

Table 6: Results of correlation analyses between cortisol and BOLD response in the bi-lateral ventral striatum and BLA (T) to positive and negative feedback

ROI	Positive				Negative			
	Left		Right		Left		Right	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
BLA	-.60	.02	-.50	.06	-.26	.4	-.20	.5
VS	-.20	.5	-.38	.2	.11	.7	-.12	.7

Note: $N = 14$ for all correlations
ventral striatum = VS; basolateral amygdala = BLA; region of interest = ROI

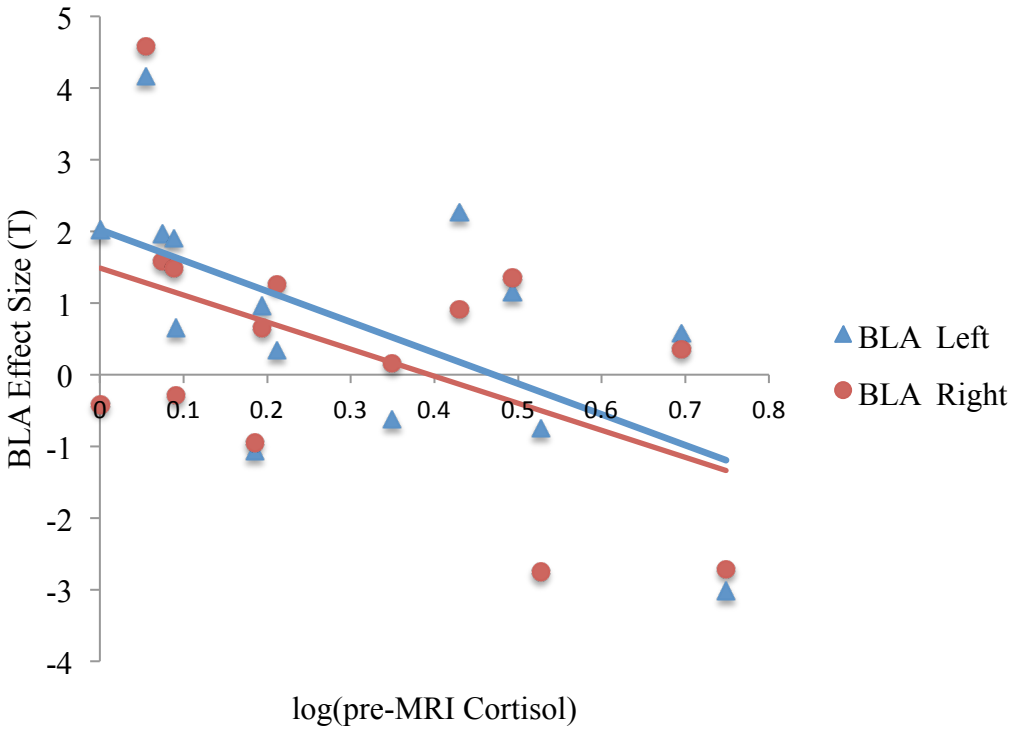

Figure 6: Correlation between individual differences in salivary cortisol measured prior to the MRI and BOLD response to positive feedback in the bi-lateral basolateral amygdala (BLA).

Chapter 4

4 Discussion

There is presently a gap in our understanding of the relationship between the basolateral amygdala and the ventral striatum during feedback processing in instrumental learning tasks, particularly in the pre-adolescent stage of development. Animal models overwhelmingly suggest that the basolateral amygdala is critical for feedback-guided learning, and that the basolateral amygdala directly influences striatal responses during both anticipatory and feedback phases of learning. The basolateral amygdala is thought to relay general information about the overall motivational state of the individual, or 'state incentive' to the ventral striatum in order to adaptively guide behaviour in a contextually appropriate manner. The basolateral amygdala may also be especially sensitive to changes in physiological and psychological arousal through interactions with the stress response system, and likely uses arousal-related information to dynamically adjust representations of state incentive. The ventral striatum may also be directly influenced by changes in physiological arousal through independent interactions with the stress response system. Furthermore, the neuroimaging environment itself may serve as an arousing context, and individual differences in the extent to which the MRI protocol is perceived as stressful may influence the functional and behavioural correlates of feedback processing, especially in children and scanner naïve individuals.

In the present study, participants between the ages of 9- and 11- years old completed a probabilistic learning task (Pessiglione et al., 2006) in an MRI scanner, during which they were required to learn probabilistic associations between ambiguous stimuli and either positive, negative, or neutral outcomes. Circulating levels of cortisol were measured immediately prior to participation in the imaging protocol as an index of anticipatory stress, and results were compared with a baseline sample that was collected at home on a different day. Whole brain and region of interest analyses were conducted at the group level to assess task-related BOLD response in both the basolateral amygdala and ventral striatum. Individual differences analyses were then conducted to assess the relationships between basolateral amygdala and ventral striatum during feedback processing, as well as

to determine whether individual differences in anticipatory stress were associated with individual differences in task-related activity within these ROIs.

4.1 Task-Related Behaviour

Behavioural analyses revealed that participants responded faster, on average, when responding to stimuli that were associated with potential gains than they did to stimuli that were associated with potential losses, which is consistent with the RT bias that was observed in the original implementation of this task in adults (Pessiglione et al., 2006). This RT bias is thought to reflect trial-related differences in the recruitment of cognitive resources. For example, evaluation of the group contrasts reported in the present study found that only the ventral striatum was identified as showing a relatively greater response to rewards than losses; however, the dorsal anterior cingulate cortex and bilateral anterior insula were identified as showing greater responses during losses than rewards. These data suggest that negative feedback processing may require a more diffuse network of brain regions than positive feedback processing, which likely explains the commonly observed RT bias.

On average, participants were able to successfully learn the contingencies as the task progressed. During the initial phase of the task, the proportion of participants selecting the optimal stimulus and avoiding the suboptimal stimulus was approximately equal, whereas near the end of the task, most participants were selecting the optimal stimulus and avoiding the suboptimal stimulus. Similar acquisition data has been reported from related learning tasks employed in pre-adolescent children (van den Bos, Güroğlu, van den Bulk, Rombouts, & Crone, 2009). Additionally, on average, participants were equally effective at learning which stimulus was optimal in positive feedback pairs and negative feedback pairs, which was reflected by no observed differences in subjective accuracy between conditions. While at face value these results may seem to conflict with observations of enhanced sensitivity to negative feedback reported by Hämmerer and colleagues (2011), the measures used to assess feedback related performance in the present study are not equivalent. Specifically, the authors measured feedback sensitivity as the extent to which participants adjusted subsequent stimulus selections as a function of either positive or negative feedback. Children were observed to switch their selection

following receipt of negative feedback (lose-shift) more frequently than they continued to select a rewarded stimulus (win-stay). In the present study, subjective accuracy merely reflected the extent to which they selected the optimal stimulus over the course of the run, and the number of stimulus presentations was selected to optimize performance on the task and ensure that participants were able to effectively learn the contingencies. Thus, the lack of observed difference in the present study may simply confirm that participants were given adequate time to learn the contingencies in both conditions.

4.2 Task-Related Changes in BOLD Response

A preliminary whole brain analyses was conducted to ensure that the task reliably engaged brain regions that have been associated with probabilistic learning in other similar tasks. Results indicated that the bi-lateral ventral striatum was more active during the processing of positive feedback than negative feedback, and that the dorsal anterior cingulate cortex and bi-lateral anterior insula were more active during the processing of negative feedback than positive feedback. These results are consistent with those reported by Pessiglione and colleagues (2006) in the original implementation of this probabilistic learning task in an adult population. Regions of interest were subsequently created for the bi-lateral ventral striatum and basolateral amygdala, and estimates of task-related changes in BOLD response were extracted for regressors specific to positive feedback onset and negative feedback onset independently. Subsequent analyses were aimed at identifying the particular dynamics of reward-related and loss-related changes in ventral striatum and basolateral amygdala BOLD responses.

4.3 Amygdala-Striatal Interactions During Feedback Processing

4.3.1 Bivalent Response of the Ventral Striatum to Rewards and Losses

As hypothesized, the ventral striatum responded in a bivalent fashion to positive and negative feedback. In particular, the BOLD response in the right ventral striatum was significantly higher during reward receipt than during baseline, and the BOLD response in the left ventral striatum was significantly lower than baseline during receipt of a loss.

This particular functional pattern is consistent with results of prior studies assessing striatal response to positive and negative feedback (Delgado et al., 2000). In light of these findings, it is likely that the increased striatal response to wins versus losses observed in the whole brain analysis was a function of not only increased activity during positive feedback processing but also reduced activity during negative feedback processing. These results also seem to suggest lateralization of response to positive and negative feedback, although care should be taken when inferring functional lateralization from these results. Specifically, the whole brain analysis contrast from which the ventral striatum ROIs were extracted identified one large cluster showing a significantly higher BOLD response during wins than losses. Both the left ventral striatum and the right ventral striatum were located within this cluster, likely as a consequence of the close spatial proximity of these regions. Due to the diffuse nature of the hemodynamic response, it is not possible to conclude that values obtained from one ROI are not contaminated by changes in the hemodynamic profile of the adjacent ROI.

4.3.2 Basolateral Amygdala Does Not Show Task-Related Changes in BOLD

At the group level, there were no observed task-related changes in BOLD response within the basolateral amygdala in either win or loss conditions. These results may suggest that the basolateral amygdala serves a more general-purpose function during feedback processing than the ventral striatum, and supports incentive value models of the basolateral amygdala. Specifically, incentive value models posit that changes in basolateral amygdala activity reflect changes in subjective perceptions of motivational or affective significance, as opposed to the valence of a particular outcome (Morrison & Salzman, 2010). While a variety of factors, such as the valence or magnitude of a particular outcome may contribute to perceived incentive value, a variety of other factors, such as the physiological state of the individual or competing environmental inputs also likely contribute to perceived incentive value.

In order to assess reward and loss related responses independently, parameter estimates in the present study reflect a contrast between task-related BOLD estimates and an intrinsic baseline, and it is important to consider the nature of this baseline when interpreting the

resulting parameter estimates. For any given voxel in the data matrix, the intrinsic baseline represents the average change in BOLD response within that voxel measured across the entire duration of a given functional run. This may be particularly problematic for estimation of task-related changes in the basolateral amygdala, as the basolateral amygdala likely responds to various aspects of the task, as well as external factors such as changes in physiological arousal. For example, using single-unit electrode recording in the basolateral amygdala, Belova, Paton, and Salzman (2008) found that in primates, the amygdala represented not only the positive and negative value of both conditioned and primary reinforcers, but also the fixation cross that predicted the subsequent presentation of conditioned reinforcers. The basolateral amygdala may respond more generally to a variety of stimuli during task completion, and the resulting signal time course was likely quite noisy. This noise may have resulted in an inflated intrinsic baseline, which could have contributed to the lack of observed task-related activity.

It is also possible that the lack of an observed basolateral amygdala response to feedback in this task reflected both the relatively easy probabilities as well as the stability of feedback magnitude over time. The temporal characteristics of the ventral striatum response during feedback learning, for example, suggest that as stimuli become increasingly predictable, the peak striatal response may shift to stimulus onset and instead become a largely predictive cue. Although the temporal dynamics of the basolateral amygdala response during feedback learning have not been as extensively studied as those of the ventral striatum, there is some evidence for complementary temporal changes in the magnitude of the basolateral amygdala response in this context (Boll et al., 2013). Using computational modeling, Boll and colleagues found that the temporal dynamics of the basolateral amygdala response during a probabilistic reversal-learning task (PRL) were reliably predicted by a cue's associability. They defined associability as the effectiveness with which a cue is determined to be associated with a particular outcome, and is thought to decrease with increasing predictability. Importantly, activity within the basolateral amygdala was negatively correlated with associability, which suggests that the basolateral amygdala may represent, at least in part, the predictability of the stimulus-outcome associations. As outcome predictions become more reliable, the basolateral amygdala response may increase. In consideration of these findings, it is also possible

that the temporal dynamics of the basolateral amygdala BOLD response contributed to the observed lack of task-related activity in the present study.

4.3.3 Associations Between Basolateral Amygdala and Ventral Striatum During Feedback Processing

The importance of the basolateral amygdala for feedback-guided learning has been well established in animal models (Ambroggi et al., 2008; Proemba & Gabriel, 1999; Wellman, Gale, & Malkova, 2010). It was thus hypothesized that the magnitude of the BOLD response in the basolateral amygdala would be positively associated with the magnitude of the BOLD response in ipsilateral ventral striatum ROIs. Furthermore, as the basolateral amygdala has been found to facilitate learning in both appetitive and aversive contexts (Gottfried, O'Doherty & Dolan, 2002), it was hypothesized that this positive relationship would be observed during both positive and negative feedback processing. In concurrence with these predictions, individuals who had higher feedback related activity in the basolateral amygdala showed higher feedback-related ipsilateral ventral striatum activity than individuals with lower basolateral amygdala activity. This effect was observed bi-laterally in both feedback conditions. Furthermore, follow-up analyses confirmed that this relationship was unique, and that the positive association observed between the basolateral amygdala and the ventral striatum did not extend to other regions showing task-related activity at the group level, including the dorsal anterior cingulate cortex and insula.

Taken together, these results suggest that the activity of the basolateral amygdala is closely related to the activity of the ventral striatum during feedback processing. While it appears that increased basolateral amygdala activity may facilitate ventral striatum activity during reward processing, it is difficult to determine whether the nature of the basolateral amygdala – ventral striatum association during negative feedback processing facilitated or hindered the sensitivity of the system to negative feedback. Specifically, results of the present study confirmed a bivalent relationship between ventral striatum activity and feedback type. The nature of the ventral striatum response to positive feedback is well established in the literature, and there is substantial evidence that the magnitude of the positively valenced ventral striatum response correlates positively with

the magnitude and the unexpectedness of the appetitive outcome (Pessiglione, 2006; van Dujvenvoorde et al., 2014). In light of this evidence, basolateral amygdala activity seemed to facilitate ventral striatum sensitivity to positive feedback. While less intensively investigated, it is likely that the negatively valenced ventral striatum responses to negative feedback functions in a similar manner, with higher magnitude suppressions in ventral striatum response predicting qualitatively larger or more unexpected aversive outcomes (Büchel et al., 2011). In this context, increased basolateral amygdala activity during negative feedback processing may be associated with reduced ventral striatum sensitivity to negative feedback.

Determining whether engagement of the basolateral amygdala hindered ventral striatum sensitivity to negative feedback requires a more thorough understanding of the task-related dynamics of the basolateral amygdala response. For example, while there is evidence that basolateral amygdala responds similarly to reward-predictive cues and loss-predictive cues during classical conditioning (Gottfried, O'Doherty & Dolan, 2002), investigations in human neuroimaging studies have not yet distinguished the functional characteristics of the basolateral amygdala during feedback processing in an instrumental learning task. It is possible that the basolateral amygdala, like the ventral striatum, also responds bivalently to feedback. In the present study, no significant differences were observed in the BOLD responses of the basolateral amygdala ROIs during positive or negative feedback processing. As previously mentioned, the lack of task-related changes in the basolateral amygdala BOLD response does not necessarily mean that the basolateral amygdala was not actively engaged during feedback processing. Furthermore, There was a visible trend in the data that suggested a potential bivalent response to positive and negative feedback within the basolateral amygdala. Although this interpretation should be considered with caution, within this framework basolateral amygdala activity could be considered a facilitator of the ventral striatum response to negative feedback as opposed to an inhibitor.

4.4 Individual Differences in Basolateral Amygdala and Ventral Striatum Response to Positive Feedback Predict Average Subjective Accuracy

It was originally hypothesized that enhanced basolateral amygdala-ventral striatum activity during feedback processing would be positively correlated with individual differences in subjective accuracy in corresponding feedback conditions. It is important to note that the condition-specific subjective accuracy values obtained from the present study do not wholly correspond with measures of reward and loss sensitivity typically reported from the test phase of the pedagogical probabilistic learning task (Frank et al., 2009). Importantly, although the potential outcomes associated with win pairs and loss pairs in the present task were initially either inherently positive or inherently negative (reflecting appetitive and aversive outcomes), successful acquisition of contingencies in both trial types reflected the capacity to select the optimal stimulus within the pair. Subsequently, both trials likely elicited both positive and negative prediction errors that reflected outcomes that were either better or worse than expected, respectively. This interpretation is supported by the observation that subjects performed equally well in the positive and negative feedback conditions. There were still substantial individual differences in overall subjective accuracy, which likely reflect variability in the capacity of the individuals to learn from both positive and negative prediction errors. It was not possible, however, to disambiguate the contributions of individual differences in positive and negative prediction error processing to overall performance using the derived subjective accuracy measures.

Interestingly, correlational analyses revealed a positive correlation between overall subjective accuracy and individual differences in bi-lateral basolateral amygdala and right ventral striatum responses to positive feedback, but not negative feedback. This finding suggests that individuals performing better on the task may have assigned a higher incentive value to rewards and subsequently had a higher propensity towards selecting the optimal stimulus, regardless of whether the optimal stimulus was framed in terms of the possibility of either winning or losing points. In consideration of the task design, it is possible that individuals who assigned a higher incentive value to rewards also assigned

higher incentive value to the optimal stimulus in loss pairs, even though it did not predict a 'reward' per se. For example, Pessiglione and colleagues (2006) found that the magnitude of the striatal response to misses (successfully avoiding a negative outcome) was just as robust as the striatal response to wins. There were no correlations between overall subjective accuracy and ventral striatum-basolateral amygdala responses to negative feedback, which suggests that in this task, successful performance may have been more contingent upon the sensitivity of the basolateral amygdala and ventral striatum to the incentive value of the preferred outcomes. That is not to say that sensitivity to negative feedback did not contribute to overall performance, but that individual differences sensitivity to negative feedback may have been influenced by other factors, such as related activity within the dorsal anterior cingulate cortex and insula.

4.5 Individual Differences in Cortisol are Associated with Differences in Basolateral Amygdala BOLD Response to Positive Feedback

Analyses revealed that, at the group level, salivary cortisol measures taken immediately prior to the MRI were not reliably different from baseline samples collected at home at the same time of day. There was, however, variability within the cortisol measure obtained prior to the MRI, and interestingly, there was a negative correlation between pre-MRI cortisol measures and basolateral amygdala BOLD responses to positive feedback. These results concur with the findings reported by Kumar and colleagues (2014), and support the theory that stress may lead to reduced sensitivity of the basolateral amygdala to rewards during the feedback phase of instrumental learning. Specifically stress may have reduced the hedonic value associated with rewards in the present study. The relationship between stress and basolateral amygdala activity observed in the present investigation was more robust than the trend reported by Kumar et al., which may relate to developmental changes in top-down modulation of activity within the basolateral amygdala by structures such as the medial prefrontal cortex (Galvan et al., 2006; McLaughline, Hill, & Gorzalka,, 2014). Surprisingly, no associations between stress and basolateral amygdala activity were observed during negative feedback processing, although the trend of the relationship was negative as well. In the present

study, physiological arousal may have thus been associated specifically with reduced hedonic valuation of positive feedback, without influencing the valuation of negative feedback.

Individual differences in cortisol were not associated directly with reduced ventral striatum activity to positive or negative feedback. It is possible that the level of physiological arousal observed in this naturalistic context was not sufficient to directly influence striatal function. Another possibility; however, is that cortisol itself may not be directly responsible for some of the observed stress-induced alterations in striatal function reported in other studies. For example, Imperato, Puglisi-Allegra, Casolini, and Angelucci (1991) found that exogenous administration of corticosterone in rats, even in extremely large dosages, did not result in changes in dopamine release in the nucleus accumbens. Furthermore, adrenalectomy did not prevent the release of dopamine in the nucleus accumbens in response to restraint stress. Additional research suggests that stress induced effects on dopaminergic function in the nucleus accumbens may be facilitated by interactions between the prefrontal cortex and the autonomic nervous system (NicNiocaill & Gratton, 2007). Studies assessing group differences in striatal activity between stress-exposed and non-exposed individuals may be more likely to observe stress-related changes in the dopaminergically mediated ventral striatum function as individuals in the stress groups typically show both higher corticotrophin system and autonomic nervous system engagement than those in the control groups. The present study; however, only measured individual differences in cortisol, which may not have been reflective of individual differences in autonomic nervous system activity.

Another possible explanation for these observations is the contribution of additional factors of individual variability to the relationship between stress and striatal function, such as constitutional differences that arise from naturally occurring genetic variants. For example, genetic variation within the mineralocorticoid receptor, which is involved in the regulation of the stress response, has been found to predict the extent to which exposure to an acute stressor impaired learning from rewarding outcomes (Bogdan, Perlis, Fagerness, & Pizzagalli, 2010). Other research has suggested that the magnitude of stress-induced impairments in reward-related learning may also be modulated by

polymorphic variation within the serotonin-transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene (Nikolova, Bogdan, & Pizzagalli, 2011). While this overview of potential genetic variants that may modulate the sensitivity of the mesocorticolimbic system to stress is far from exhaustive, it highlights the importance of understanding that stress does not influence all individuals in the same manner; some individual may be more sensitive to stress, whereas others may be more resilient. As the present study did not take other potential modulatory factors into account, it is possible that associations between individual differences in cortisol and ventral striatum activity were not identifiable because of lack of consideration of these factors.

4.6 Limitations and Future Directions

There are several limitations to the method that was employed to extract parameter estimates for the ROIs within the present study that should be considered. For example, whole-brain analyses typically compare parameter estimates associated with measures of interest versus control measures. The resulting estimates reflect the difference in the magnitude of parameter values between the two measures. In the present study, the neutral condition was not a suitable control, as out of a total of 44 stimulus pair presentations in a given run, only four neutral pair presentations were observed. With so few presentations, it was not possible for participants to learn that it did not matter which stimulus they chose, and participants were likely still actively trying to determine which stimulus was the optimal stimulus. Thus, the neutral condition was not suitable for use as a control trial for analysis of the imaging data. Further investigations should aim to more clearly identify which aspects of feedback learning engage the basolateral amygdala and ventral striatum using an adequate control condition, as well consider temporal changes in activity that may occur within these regions during acquisition.

Additional limitations should be noted when considering associations with the cortisol measures employed. Specifically, in the present study, no reliable difference was observed between baseline and pre-MRI cortisol values. Although at first glance this result could be taken to suggest that children are not particularly affected by the experimental context, several limitations should be noted. First of all, only one baseline sample was collected per participant. Participants were instructed to avoid engaging in

behaviours known to elicit a stress response prior to collection, but it is impossible to know whether all instructions were followed during the at-home collection. Furthermore, due to the inherently reactive nature of the stress response system, even small perturbations, such as a fight with a sibling or playing an exceptionally arousing video game could lead to elevated active cortisol. It would have been beneficial to collect numerous baseline samples, and get an average for each participant as opposed to relying on only one measure. In addition, although there is evidence that anticipation of a stressor is sufficient to elicit changes in active cortisol, it is possible that the peak in active cortisol could have occurred at different times for different participants, and may not have occurred prior to the commencement of the actual MRI. Thus, it is not possible based on the present data to conclude whether the scanning environment was sufficient to induce a reliable stress response in this group of participants or not. Future implementations of this study should also aim to obtain multiple measures of cortisol at various time points throughout the MRI to gain a better idea of the temporal changes in cortisol that may occur within each participant.

It should also be noted that the sample of participants in the present study might have been biased. As previously discussed, following the mock scanning session, some participants decided not to participate in the MRI because of nervousness or anxiety. Additionally, a small number of participants elected to end the MRI session prior to task completion due to distress. Subsequently, the participants who successfully completed the study may disproportionately represent individuals who are less sensitive to potentially stressful environments, which may have reduced the observed variability in cortisol measures. The data presented herein were also derived from a relatively small sample and should be interpreted with caution, especially in consideration of the fact that results were not corrected for multiple comparisons. These results require validation in a larger sample. Furthermore, the present study only assessed individual differences in cortisol, although individual differences in autonomic nervous system function may have also contributed to individual differences observed in measures of self-regulation. It would be interesting in future studies to include synonymous measures of autonomic nervous system function, such as galvanic skin conductance and heart rate, to disambiguate

functional and behavioural associations with differences in corticotrophin activity and autonomic nervous system activity.

Despite the noted limitations, the present study found that individual differences in active cortisol measured prior to task completion was associated with reduced basolateral amygdala activity in response to positive feedback. Activity of the basolateral amygdala to positive feedback was, in turn, associated with the magnitude of ipsilateral ventral striatum activity to positive feedback as well as overall subjective performance on the probabilistic learning task. The initial intention was to determine whether the MRI environment elicited a stress response itself among participants within the age group. The data that was obtained was not sufficient to adequately address this question. What was apparent; however, was that regardless of the cause, individual differences in active cortisol measured prior to the MRI might have influenced the neural and behavioural measures of feedback learning reported herein, although it is not possible to know the direction of this relationship for certain due to the correlational nature of the study.

There are a variety of factors that may have contributed to the observed individual differences. For example, while participants typically completed the MRI between 4:00p.m. and 8:30p.m., a time when the baseline value of cortisol is relatively stable, baseline cortisol levels do fluctuate throughout the day according to a diurnal rhythm. Thus, time of day may have contributed to the individual differences observed among participants. Other factors that may influence the observed variability in cortisol include genetic differences as well as differences in the quality of the early environment. In terms of genetic influences, a variety of genetic variants, including variants within the 5-HTTLPR region of the serotonin transporter gene described previously, have been associated with individual differences in the level of reactivity of the corticotrophin system to acute stress (Miller, Wanker, Stalder, Kirschbaum, & Alexander, 2013). Furthermore, exposure to prenatal stress, as well as exposure to unstable and/or physically and psychologically harmful early environments has been shown to have long-term consequences on the function of the stress response system (for a review, see Lovallo, 2012). Future research should aim to identify to what extent individual differences in measures of the corticotrophin and autonomic nervous systems are

influenced by relevant proximal factors (such as time of day, hunger, level of anxiety), genetic factors, as well as early experiences. It was also not possible in the present study to disambiguate the extent to which the observed associations with individual differences in cortisol were the result of dynamic changes in cortisol (state-level influences) or of inherent differences that are associated with a more reactive phenotype (trait-level influences). Thus, an independent assessment of stress reactivity outside of the scanner would be beneficial.

Chapter 5

5 Summary and Conclusions

Individual differences in the capacity to dynamically and adaptively adjust behaviours to maximize positive outcomes and avoid aversive outcomes measured in childhood have been found to predict future propensity towards maladaptive behaviours as well as physiological and psychological well being in adolescence and adulthood. A large body of research has surfaced that is devoted to characterizing the nature of these individual differences by assessing the functional dynamics of the mesocorticolimbic system. Changes in physiological and psychological levels of arousal have been shown to drastically alter both the behavioural and functional correlates of feedback learning in both animal models and human imaging studies. Many of these studies have focused specifically on direct associations between changes in the glucocorticoid cortisol and task-related ventral striatum function; however, the basolateral amygdala may be particularly sensitive to changes in cortisol, and may either facilitate or inhibit task-related activity within the ventral striatum. Few neuroimaging studies have directly assessed the interactions between basolateral amygdala and ventral striatum activity during instrumental learning tasks, and fewer still have assessed these interactions in children. The first aim of the present study was to characterize the response profiles of the ventral striatum and basolateral amygdala during the processing of positive and negative feedback in a sample of typically developing children, and to determine whether individual differences in activity within the basolateral amygdala were associated with concomitant profiles of ventral striatum activity. The second aim of the study was to determine whether individual differences in cortisol measured prior to the completion of the task in the MRI scanner predicted the observed feedback-related activity within these regions of interest.

In the present study, the probabilistic learning task robustly recruited commonly cited regions involved in instrumental learning, including the bi-lateral ventral striatum, anterior insula, and the dorsal anterior cingulate cortex. Subsequent ROI analyses revealed a bivalent feedback-related response in the ventral striatum, with increased

BOLD response in the right ventral striatum observed during processing of positive feedback and a relatively reduced BOLD response in the left ventral striatum during processing of negative feedback. Although there was no observed task-related change in BOLD response in the basolateral amygdala, individual differences in feedback-related activity within this region were associated with variability in observed ipsilateral ventral striatum activity to both positive and negative feedback. During the receipt of positive feedback, increased basolateral amygdala activity was associated with increased activity within the ventral striatum bi-laterally. During the receipt of negative feedback, higher basolateral amygdala activity was associated with a blunted reduction in the ventral striatum response bi-laterally. Follow-up analyses revealed that the associations between the basolateral amygdala and ventral striatum were unique, and increased basolateral amygdala activity was not associated with similar increases in other task-relevant regions including such as the bi-lateral dorsal anterior cingulate cortex and insula. Moreover, increased engagement of the bi-lateral basolateral amygdala as well as the right ventral striatum during positive feedback processing was positively correlated with overall subjective accuracy measured across both win trials and loss trials. Taken together, these results suggest that the basolateral amygdala is likely an important facilitator of feedback-guided learning in children, and may directly influence the capacity of the system to learn from probabilistic associations by adjusting the incentive value of particular outcomes.

Overall, the data from the present study was not sufficient to determine whether the MRI environment itself elicited a reliable stress response in this sample of participants. There was, however, a large amount of variability in active cortisol measured immediately prior to task completion. While individual differences analyses did not observe direct associations with behaviour or feedback-related activity within the ventral striatum, there were negative correlations observed between individual differences in cortisol estimates and positive feedback-related activity within the bi-lateral basolateral amygdala. These results suggest that individuals with higher levels of active cortisol may have associated rewards with reduced incentive value during task completion.

Despite the limitations addressed previously, at a minimum, these results have important methodological implications for researchers concerned with individual differences in

self-regulation. Individual differences in active cortisol may influence, either directly or indirectly, the functional and behavioural correlates of self-regulation. Thus, cortisol measures should be included, at least as a control, when assessing constructs that may be influenced by changes in stress hormones. Furthermore, the current findings highlight the need for a more nuanced understanding of the relationship between the basolateral amygdala and the ventral striatum during instrumental learning, particularly when assessing the influences of factors that may alter the physiological or psychological state of the individual.

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Appendix A: HSREB Approval

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Prof. J Bruce Morton
Department & Institution: Social Science\Psychology,Western University

HSREB File Number: 102387
Study Title: Genetic and Environmental Contributions to Differences in Self-Regulation Early in Development (REB# 18839)
Sponsor:

HSREB Amendment Approval Date: October 23, 2014
HSREB Expiry Date:

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Letter of Information & Consent		2014/10/09
Revised Western University Protocol		2014/10/09
Advertisement	Recruitment Poster	2014/10/09

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Amendment Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix B: Instructions Provided to Participants for Salivary Cortisol Collection

Saliva Collection for Cortisol

IMPORTANT: This sample should be collected before the day of your MRI session at the exact same time of day that your appointment is scheduled. For example, if your MRI is scheduled for Tuesday April 2nd at 6:00 p.m., you would collect the sample any day before April 2nd at 6:00 p.m. according to the guidelines provided below.

1. Keep your test tubes sterile and free from dust before use. For example, store them with the caps on or keep them inside a clean plastic bag.

2. In preparation for sample collection, it is important to follow these guidelines:

    a. Do **not** eat food, drink beverages other than plain water, smoke, chew gum, or brush your teeth for 60 minutes before saliva collection. **Note:** coffee and tea are *not* plain water, nor are flavored water beverages.
    b. Remove any substances from lips (i.e., lip gloss, lotions, etc.) before collection.
    c. Avoid vigorous physical activity for 1 hour before saliva collection.
    d. Avoid sample collection within 60 minutes after a major meal.

3. Rinse your mouth with water to remove any loose food debris that may be present. Wait 5 minutes before beginning collection. Do **not** consume any water or other substances after the initial rinse or before collection of entire sample has been completed.

4. To collect the sample:

    a. Sit or stand during collection (lying down reduces saliva flow).
    b. Tilt your head slightly forward (i.e., tilt chin downward) and allow the saliva to freely accumulate under your tongue near the front of your mouth. Do not try to force the saliva, just let it accumulate gently and naturally.
    c. When a large amount of saliva has accumulated, place the collection tube against your lower lip and expel the accumulated saliva into the tube. Repeat as needed until you have reached the line indicated on the collection tube.
    d. If excessive bubbles are present, you may need to provide additional saliva to ensure that enough saliva is present once the bubbles have dissipated.
    e. Do not poke fingers, Kleenex, or anything else into the tubes.
    f. Cap the test tube immediately to prevent airborne contaminants from getting into the saliva. Press firmly to be sure the cap is securely in place.
    g. A sticky note will have been provided in your package. Please make note of the date and time of collection.

5. Once the sample is securely capped, samples should **immediately** be placed in an upright position in a freezer (freezers used for storage should **not** be the frost-free type as they go through freeze-thaw cycles). It is important that tubes are **not** kept out at room temperature for longer than 1 hour and that the saliva does not come into contact with the cap.

6. Samples should be transported to the lab for the second portion of the study in the coolers provided. It is important that you condition the gel packs (place them in the freezer) well before transportation. Ensure that you place both gel packs provided in the cooler with the sample. The container will keep the sample frozen for a maximum of 4 hours. It is important that samples are returned in a frozen state; therefore, we ask that you try to minimize the amount of time required for transport from your freezer to the lab.

Curriculum Vitae

Name	Haley Fallowfield
Post-Secondary Education and Degrees	University of Western Ontario London, Ontario, Canada 2008 – 2013 B.Sc.
Honours and Awards	Dean's Honor List 2013 Award of Excellence: Teaching Assistant 2014-2015 Canadian Psychological Association (CPA) Award of Academic Excellence 2012-2013
Related Work Experience	Teaching Assistant The University of Western Ontario 2013-2015