

## ABSTRACT

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NEURAL CORRELATES OF APPROACH  
AND AVOIDANCE LEARNING IN  
BEHAVIORAL INHIBITION

Sarah M. Helfinstein, Ph.D., 2011

Directed By:

Professor Nathan A. Fox, Human Development

Behavioral inhibition is a temperamental trait characterized in infancy and early childhood by a tendency to withdraw from novel or familiar stimuli. Recent neuroimaging research indicates that BI individuals have atypical neural responses to information regarding reward and punishment in the striatum and amygdala—regions of the brain that receive information about salient stimuli and use it to guide motivated behavior. Activation to rewarding and punishing stimuli in these regions follows a “prediction error” pattern. My research examines whether behaviorally inhibited young adults display atypical prediction error responses, and whether these responses are specific to rewarding or aversive events. Prediction error signals are theorized to be critical for approach and avoidance learning, and a second study examined probabilistic approach and avoidance learning in the same sample, examining differences in approach and avoidance learning between behaviorally

inhibited and non-inhibited individuals, and the relation between learning and neural prediction error signals to reward and punishment.

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BEHAVIORAL INHIBITION

By

Sarah M. Helfinstein

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Advisory Committee:  
Professor Nathan A. Fox, Chair  
Professor Donald J. Bolger  
Dr. Monique Ernst  
Dr. Daniel S. Pine  
Professor Thomas S. Wallsten

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## Chapter 1: Overview

Behavioral inhibition is a temperamental trait characterized in infancy and early childhood by a tendency to withdraw from novel or unfamiliar stimuli (Kagan, et al., 1984; Fox, et al., 2004). This temperament is known to increase the risk for the development of psychopathology in adolescents and young adults (Chronis-Tuscano, et al., 2009). A great deal of research has aimed to explore both the neural and the psychological correlates of behavioral inhibition. Recent neuroimaging studies (Guyer, et al., 2006; Bar-Haim, et al., 2009; Helfinstein, et al., 2011) have focused particularly on the role of the striatum—a region of the brain that receives information about salient stimuli and uses it to guide motivated behavior—in the development of behavioral inhibition.

These studies indicate that behaviorally inhibited individuals show greater striatal activation than behaviorally non-inhibited individuals to cues that indicate their action could lead to a gain or a loss (Guyer, et al., 2006; Bar-Haim, et al., 2009). Further, behaviorally inhibited individuals show greater activation to salient negative feedback, but no enhanced activation to positive feedback (Helfinstein, et al., 2011), suggesting that the enhanced striatal activation seen in behaviorally inhibited individuals may be specific to salient negative information. Thus, one aim of the present study is to further clarify the role of valence in heightened striatal response in behaviorally individuals.

Several neuroimaging studies have shown that striatal activation to salient stimuli follows a “prediction error” pattern (e.g., Pagnoni, et al., 2002; O’Doherty, et al., 2003; Seymour, et al., 2004; Abler, et al., 2006; Cohen, et al., 2010). Prediction

errors are discrepancies between the previously expected value of the environment and its current value, as adjusted to reflect current environmental cues (Schultz, 2000), and these prediction errors are reflected in the firing of dopaminergic neurons that densely innervate the ventral parts of the striatum (Schultz, et al., 1997; Mogenson, et al., 1980). However, it is not known if the enhanced striatal activation seen in behaviorally inhibited individuals is the result of an enhanced prediction error response, either generally or specifically to salient aversive events. Thus, another aim of the present study is to test whether BI individuals show greater prediction errors to unexpected salient events, either rewarding or punishing. This was tested in two ways: By examining striatal activation to salient stimuli that differ in prediction error in a neuroimaging study, and by modeling subject prediction error based on their behavioral choices in a paradigm where subjects learn from punishment and reward.

It has been hypothesized that prediction errors play a key role in goal-shifting (Schultz, et al., 1997), alerting an individual to the presence of a salient stimulus in the environment so that action can be directed towards the stimulus. Rodent work indicates that dopaminergic interactions with the shell of the nucleus accumbens, a brain region located in the ventral striatum, are critical for certain types of goal-directed behavior: injecting a GABA agonist into the rostral part of the nucleus accumbens shell causes rats to engage in appetitive feeding behavior, while injecting the caudal part of the accumbens shell elicits defensive escape behaviors (Reynolds & Berridge, 2002; 2008), but these effects are abolished if dopaminergic signaling is blocked (Faure, et al., 2009). This suggests a possible mechanism through which the functional striatal differences seen in behaviorally inhibited individuals could

contribute to the behaviorally inhibited phenotype: a larger striatal activation to aversive events could lead to greater avoidance behavior.

An avoidant coping style, where individuals withdraw from threat and from cues that have previously been associated with threat, is considered a core feature of behavioral inhibition (Perez-Edgar & Fox, 2005), and a greater tendency to withdraw or approach has long been considered a differentiator between individuals of different temperaments (Jung, 1921; Schneirla, 1959; 1965). However, behaviorally inhibited individuals' avoidance tendencies have never been measured in a strictly controlled paradigm where they must learn to avoid stimuli that are probabilistically punished. The present study examines approach and avoidance learning in behaviorally inhibited and non-inhibited individuals using such a paradigm, and further, examines the relationship between approach and avoidance learning and prediction errors to rewarding and aversive stimuli.

Thus, the present study aims to achieve two overarching goals. First, it aims to further characterize the enhanced striatal activation seen in behaviorally inhibited individuals, testing whether it is valence-specific and whether it is related to the dopaminergic prediction errors the striatum receives. Second, it aims to examine a possible influence that this functional difference could have on the behavioral patterns of behaviorally inhibited individuals, by examining whether behaviorally inhibited individuals differ from their peers in approach and avoidance learning, and whether this behavior is correlated with prediction errors to reward and punishment.

## Chapter 2: Background

The goal of this chapter is to describe the extant evidence supporting relations between behavioral inhibition, increased avoidance behavior, and enhanced striatal activation to punishment. First, the temperamental trait of behavioral inhibition will be described, with a particular emphasis on the role of avoidance in behavioral inhibition, and a broader discussion of the role of approach and avoidance motivation as a driver of temperament and personality will be provided. Second, the chapter will review the current understanding of the neural and physiological correlates of behavioral inhibition, with a particular focus on the extant data indicating the striatal system as an area of functional difference for behaviorally inhibited individuals. Third, the role of the striatal system in responding to salient information will be reviewed, including a discussion of dopaminergic prediction errors and their relation to striatal functional activation. Evidence for the role of the striatal system in approach and avoidance behavior and individual differences in personality will also be provided.

### **2.1 Behavioral inhibition and approach and avoidance**

#### **2.1a What is behavioral inhibition?**

Behavioral inhibition is a temperamental trait first defined by Kagan and colleagues in 1984 (Garcia-Coll, Kagan, & Reznick, 1984), used to describe children showing a tendency to withdraw from unfamiliarity and threat. These individuals have the tendency to display enhanced anxiety, attention bias to threat, and an

avoidant coping style (Perez-Edgar & Fox, 2005). Infants selected for negative reactivity, thought to be a precursor for later behavioral inhibition, show a greater tendency to avoid fear-eliciting stimuli in a standardized laboratory protocol (Hane, et al., 2008). Behavioral inhibition is present from early in life, and remains moderately stable across childhood and adolescence (Degnan & Fox, 2007; Kagan, et al., 1988; Fox, et al., 2001). This temperamental trait is a risk factor for the development of anxiety disorders later in life. According to one study (Schwartz, et al., 2003), 15% of young adults who are characterized as behaviorally inhibited in early childhood will be diagnosed with social anxiety disorder. Another study (Chronis-Tuscano, et al., 2009) found that individuals who showed early stable behavioral inhibition were 3.8 times more likely to be diagnosed with social anxiety disorder by the time they were adolescents than children who did not. It remains unclear if there are particular aspects of the behaviorally inhibited profile that exacerbate this risk.

### **2.1b Behavioral inhibition and avoidance**

A core feature of the behaviorally inhibited profile is what is often described as an “avoidant coping style” (e.g., Perez-Edgar & Fox, 2005). This refers to the tendency to rapidly withdraw from threat when detected, and to avoid what triggered the threat, both at that time and in the future. Indeed, in the “risk room” paradigm (Kagan, Reznick, & Gibbons, 1989) that is typically used to assess behavioral inhibition, behavioral inhibition is largely measured by the tendency of the child to avoid a series of unfamiliar and somewhat frightening toys and experiences, such as jumping onto a mattress from the top of a short set of stairs, or interacting with a

robotic dinosaur. Behavioral inhibition is also measured in older children by their tendency to withdraw during interactions with unfamiliar peers (Fox, et al., 2005). These children are more likely to engage in “reticent” behavior in unfamiliar social settings, consisting of watching peers without playing with them, and remaining unoccupied (Coplan, et al., 1994). Thus, when a child is characterized as behaviorally inhibited, they are known, by virtue of the way the construct is assessed, to have a tendency to systematically withdraw in certain situations where cues are present that indicate potential threat.

### **2.1c Approach and avoidance motivation**

Approach and avoidance motivation have been observed as a core temperamental feature from long before the construct of behavioral inhibition appeared in the psychological literature. In 1921, Jung noted that the principle difference between extroverts and introverts was their tendency to either approach or avoid social stimuli. Schneirla (1959) theorized that a commonality across all organisms was the presence of approach (A-type) mechanisms and withdrawal (W-type) mechanisms, and, further (Schneirla, 1959; 1965), that an individual organism’s tendency to engage in either A-type or W-type processes was a key differentiator between different individual organisms within a species. Individual differences in approach and avoidance tendencies have been observed in monkeys (Suomi, 1983), rats (Garcia-Sevilla, 1984), birds (Verbeek et al., 1994), and fish (Wilson, et al., 1993). The abundance of evidence for individual differences in approach and avoidance across many species suggests that this behavior must be driven in part by a

neural mechanism shared across many species, but it remains unclear precisely what anatomical or functional differences distinguish between approach-oriented and avoidance-oriented organisms within any species, including humans.

## **2.2 Neural and physiological underpinnings of behavioral inhibition**

There is, however, a growing body of research examining the neural and physiological correlates of behavioral inhibition. Behaviorally inhibited individuals differ physiologically from their non-inhibited peers in many ways, including higher baseline cortisol levels (Kagan, Reznick, & Snidman, 1987; Schmidt, et al., 1997; Schmidt, et al., 1999), increased heart rate and decreased beat-to-beat variability (Marshall & Stevenson-Hinde, 1998), a greater potentiated startle response to threat (Schmidt & Fox, 1998), and greater right frontal electroencephalogram (EEG) asymmetry (Fox, et al., 2001). Neuroimaging studies (Schwartz, et al., 2003; Perez-Edgar, et al., 2007) have also shown that under certain circumstances BI individuals show greater functional activation of the amygdala, a brain region that responds to threat (LeDoux, 1996), than their non-inhibited peers. Finally, the most recent line of research examining the neural correlates of behavioral inhibition, and the one most relevant for the present study, has focused on the striatum. This research will be discussed in depth below.

### **2.2a Abnormal striatal activation in behavioral inhibition**

The striatum is a sub-cortical structure that responds to salient cues and events (Knutson & Cooper, 2005). Three recent findings (Guyer, et al., 2006; Bar-Haim, et

al., 2009; Helfinstein, et al., 2011) have shown that BI individuals display heightened functional activation of this brain region under certain circumstances. In Guyer, et al. (2006), BI adolescents performed a monetary incentive delay task where they were presented with cues at the beginning of each trial indicating the amount of money that they could or avoid losing if they responded quickly enough to the target. The findings revealed that the BI subjects showed greater striatal activation to the cues indicating large potential gain or loss than the non-BI adolescents. In Bar-Haim, et al. (2009), a different group of BI and non-BI adolescents performed a reward contingency task where subjects saw two types of cues. One cue indicated subjects had to make a simple motor response to receive money; the other indicated that subjects had to choose between two options, and if they made the correct choice, they would receive money. The data indicated that BI subjects again showed greater striatal activation to the cues than their peers, but only to the cues that indicated subjects had to make a choice. BI and BN subjects responded equally to the cues that indicated a certain monetary gain.

As will be discussed in greater depth below, the striatum responds both to salient rewarding events and salient aversive events (Knutson, et al., 2000; Knutson, et al, 2003; Pagnoni, et al., 2002; O'Doherty, et al, 2003; Seymour, et al, 2007). To determine whether the heightened striatal activation seen was specific to either rewarding or aversive events, an additional analysis was performed on the Bar-Haim, et al. (2009) data, examining striatal response to the feedback subjects received on the contingent trials. The findings revealed (Helfinstein, et al., 2011) that BI subjects showed heightened striatal activation to negative feedback, indicating they had made



the incorrect choice, but not to positive feedback indicating that their choice was correct. Thus, this finding suggests that BI individuals show heightened striatal activation specifically to salient negative information.

### **2.3 The striatum and ventral tegmental area**

To better understand and interpret these findings, it's helpful to discuss the role of the striatum in greater depth. The striatum is a sub-cortical brain structure consisting of three subregions: the nucleus accumbens, the caudate nucleus, and the putamen. The nucleus accumbens and the caudate nucleus, sometimes referred to together as the ventral striatum, respond to salient stimuli, such as reward, punishment and novelty. They are densely innervated by dopaminergic projections from the ventral tegmental area, as well as inputs from the hippocampus, amygdala, and ventromedial prefrontal cortex, and project along a pathway that ultimately initiates motor movement via the dorsal striatum and sends information to the prefrontal cortex, which is involved in higher cognitive processes and goal-setting behavior (Mogenson, et al., 1980). Based on its connectivity, the striatum has often been thought of as a region important for processing rewarding and aversive information in the environment and using it to influence goal-directed behavior. The dopaminergic projections to the ventral striatum from the ventral tegmental area have been studied extensively (see Schultz, 2000 for a review), and their role will be discussed below.

### **2.3a The dopaminergic prediction error response**

Dopaminergic tegmental neurons show short, phasic bursting responses to rewards (Schultz, 1986; Romo & Schultz, 1990), punishment (Sorg & Kalivas, 1991; Young, Joseph, & Gray, 1993), novelty (Ljungberg, Apicella, & Schultz, 1992; Horvitz, 2000), or to stimuli that predict reward or punishment (Schultz & Romo, 1990; Young, Joseph, & Gray, 1993). However, this dopaminergic signal seems to be tuned specifically to surprising or unexpected salient events. Thus, a cue that predicts a reward elicits a dopaminergic bursting response, but the fully predicted reward itself does not (Ljungberg, Apicella, & Schultz, 1992; Mirenowicz & Schultz, 1994). Moreover, cues that partially predict reward will elicit a burst that is proportional with their predictive ability (Hollerman & Schultz, 1998)—the greater the likelihood, the larger the burst. A salient event that does *not* occur after a cue that has always been paired with it in the past elicits a depression in dopaminergic firing (Ljungberg, Apicella, & Schultz, 1992; Mirenowicz & Schultz, 1994). This pattern of firing led Schultz and colleagues (1997) to describe this pattern of dopaminergic firing as a ‘prediction error’: it indicates a difference between your previous predictions of the environment and your updated predictions, based on the event that has most recently occurred.

### **2.3b Prediction error response in fMRI**

Because the ventral striatum is the primary downstream target of these dopaminergic prediction error signals, it is thought that functional MRI responses to salient events in the striatum are linked to prediction error responses. Indeed, numerous fMRI studies (e.g., Pagnoni, et al., 2002; O’Doherty, et al., 2003;

Seymour, et al., 2004; Abler, et al., 2006; Murray, et al., 2007; Cohen, et al., 2010) have shown that striatal activation to salient cues and outcomes follows a prediction error pattern. Importantly, these prediction error patterns have been seen both to appetitive cues, such as money (e.g., Abler, et al., 2006; Cohen, et al., 2010; Seymour, et al., 2007), and to aversive cues, such as the loss of money (Seymour, et al., 2007 ) and pain (Seymour, et al., 2004).

### **2.3c The role of the striatum in approach and avoidance behavior**

It has been theorized that prediction errors serve a critical role in shifting from one goal-directed behavior to another. This is consistent with recent animal research indicating there is a role for the striatum in certain goal-directed behavior, and that this role is mediated by dopaminergic input. Reynolds & Berridge (2002; 2008) have found that in rats, injecting a GABA agonist into the rostral part of the shell of the nucleus accumbens—a part of the ventral striatum that is densely innervated by dopamine neurons from the VTA—elicits appetitive feeding behavior, whereas injecting the caudal part of the accumbens shell elicits defensive treading behavior. Rostral injections also elicited greater positive hedonic response to food and greater conditioned place preference, while caudal injections elicited negative aversive reactions to tastes and conditioned place avoidance. Further, these appetitive and aversive responses are dopamine-dependent; when dopamine antagonists are applied to the accumbens, the effect is obliterated (Faure, et al., 2009).

## **2.4 Individual differences in dopamine and individual differences in approach and avoidance behavior**

However, just because dopaminergic prediction errors mediate approach and avoidance behaviors does not necessarily mean that there is meaningful individual variability in this system. Is there evidence that individual variability in dopaminergic response result in individual differences in approach and avoidance?

A handful of studies to date have examined this question. Abler and colleagues (2006) measured prediction error response to probabilistic reward cues and outcomes in an imaging task. They found striatal responses increased to probabilistic cues and outcomes as the prediction error increased. Moreover, the amplitude of this prediction error response was correlated with two approach-oriented personality traits: thrill- and adventure-seeking and exploratory excitability. A second study (Krebs, et al., 2008) has shown a correlation between prediction error response to reward and the trait of reward dependence. Prediction errors are also seen to novel stimuli, and two studies (Krebs, et al., 2008; Wittman, et al., 2008) have found that prediction-error modulated striatal response to novelty correlates with the personality trait of novelty-seeking. Thus, it appears that individual differences in prediction error response to reward and novelty are related to individual differences in approach-oriented and novelty-oriented personality traits, respectively. Group differences in prediction error response to reward have also been seen in psychotic populations (Murray, et al., 2004) and adolescents (Cohen, et al., 2010). To date, no one has examined individual differences in prediction error response to punishment.

Finally, one study to date has directly manipulated dopamine levels in an effort to measure its effect on approach and avoidance behavior. This study used a

probabilistic learning paradigm in which subjects are presented with pairs of stimuli, each with different probabilities of being correct, and over time learn to select the more frequently correct stimuli. This can be accomplished in one of two ways: by learning to choose the stimuli that are usually correct, or by learning to avoid the stimuli that are usually incorrect. One can assess which of these strategies the subject employed in a test block, where the most frequently correct and most frequently incorrect stimulus, which were previously presented as a pair, are now presented separately from each other paired with different stimuli. Subjects who learned to choose the correct stimulus will perform well on the test trials with that stimulus, while those who learned to avoid the incorrect stimulus will perform well on the test trials with that stimulus. In 2004, Frank and colleagues had a group of Parkinson's patients, who have chronically low levels of dopamine, perform this task while off medication, and while on L-Dopa, a chemical precursor of dopamine that is rapidly converted after crossing the blood-brain barrier. Findings revealed that while on L-Dopa, subjects performed better on the choose-correct test trials, while off L-Dopa they performed better on the avoid-incorrect trials, indicating that the increased dopamine levels increased their tendency to learn to approach correct stimuli.

## **2.5 Summary**

The aim of this chapter has been to review what is currently known about three areas that are relevant to the present study. The research to be conducted hypothesizes that there is a relation between the temperamental trait of behavioral

inhibition, prediction errors to reward and punishment, and approach and avoidance behavior.

Thus, this chapter first provided a basic overview of the temperamental trait of behavioral inhibition, focusing particularly on the role of avoidance behavior as a core feature of the behaviorally inhibited profile. A broader discussion of approach and avoidance motivation as a core component of personality was also included.

It then discussed current knowledge of the physiological and neural correlates of behavioral inhibition, with an emphasis on the recent research suggesting that behaviorally inhibited and non-inhibited individuals display functional differences in activation of the striatum to certain salient stimuli.

Third, a detailed background on the ventral tegmental area and the striatum and their role in processing salient stimuli was provided. The concept of the dopaminergic prediction error was introduced, and evidence that striatal BOLD responses to reward and punishment can reflect these prediction errors was provided. Evidence from rodent research indicating a role for the striatum in approach and avoidance behavior was provided.

Finally, an overview was provided of the current research that directly supports the hypothesis that individual differences in prediction errors to particular types of salient stimuli are reflected both in personality traits related to those stimuli, and to approach and avoidance behavior itself.

These findings lay the groundwork for the present study: an examination of a) prediction-error responses to reward and punishment in behavioral inhibition, measured both through striatal BOLD response and through choice behavior; b)

approach and avoidance behavior in behavioral inhibition, as measured through choice behavior in response to learning from reward and punishment; and c) the relation between prediction errors and approach and avoidance behavior in these individuals.

## Chapter 3: Methods

The proposed studies examined, within a sample of young adults characterized in childhood with behavioral inhibition, both differences in neural response to unpredicted indicators of reward and punishment, and differences in feedback related learning. Specifically, Study #1 measured differences between behaviorally inhibited (BI) and behaviorally non-inhibited (BN) individuals in their prediction-error (PE) modulated striatal BOLD response to cues indicating unpredicted reward and punishment. Study #2 measured differences between BI and BN individuals in their ability to learn to approach rewarding stimuli and avoid punishing stimuli in a probabilistic learning task. Finally, the relation between striatal PE response to reward and punishment in study #1 and feedback-related learning in study #2 was examined.

### **3.1 Participants**

Participants were 42 young adults (21 female) characterized in infancy and early childhood on their level of behavioral inhibition. These subjects were drawn from among 155 subjects recruited and selected when they were four months of age based on their reactivity to unfamiliar stimuli (Fox, et al., 2001; Calkins, et al., 1996). At 9 months, 14 months, 24 months, 4 years, and 7 years, subjects participated in behavioral and questionnaire assessments examining their developing temperament. From this sample, a total of 22 BI subjects (12 male) and 20 BN subjects (9 male) participated in the imaging and behavioral experiments.



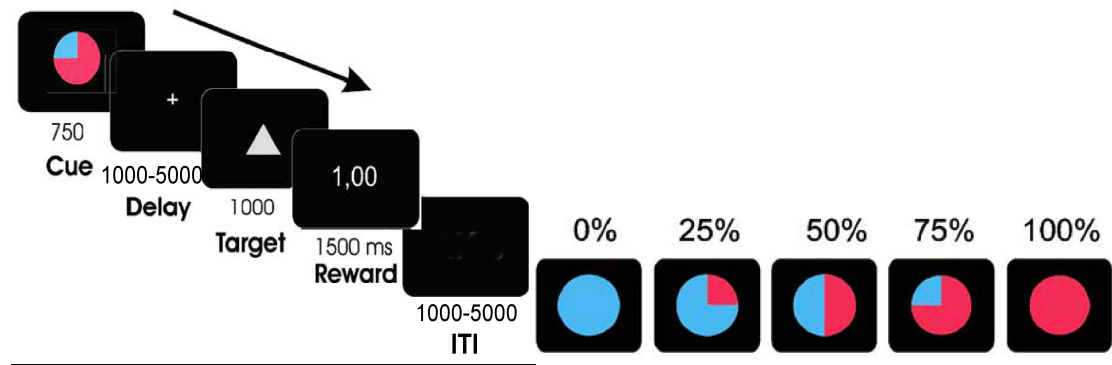
### **3.1a Participant selection**

To create a composite measure of stable behavioral inhibition, scale scores of laboratory observations and maternal reports of behavior at four time points (14 months, 24 months, 4 years, and 7 years) were used. Laboratory observations employed Kagan's protocol (Calkins, et al., 1996; Kagan, et al., 1988) at 14 and 24 months, presenting the children with novel and unfamiliar objects and people. At ages 4 and 7, children's reticent behavior with unfamiliar peers was noted using the Play Observation Scale (Rubin, 1989). Maternal ratings of social fear were collected at 14 and 24 months with the Toddler Behavior Assessment Questionnaire (TBAQ) (Goldsmith, 1996). Mothers rated shyness at ages 4 and 7 with the Colorado Child Temperament Inventory (CCTI) (Rowe & Plomin, 1977). Each of the individual behavioral and maternal report scores were standardized and then averaged to create a single score of behavioral inhibition. Subjects in the top 50% of the sample were considered eligible for participation in the BI group, and those in the bottom 50% were considered eligible for participation in the BN group of the study. Subjects were selected from these groups based on eligibility to scan and willingness and availability to participate. All subjects were assessed for psychopathology using the Structured Clinical Interview for DSM-IV (SCID) (First & Spitzer, 1995), a semi-structured interview designed for making the major DSM-IV Axis I diagnoses. Six subjects in our sample (3 BI and 3 BN) had current Axis I diagnoses: three (2 BN and 1 BI) were diagnosed with specific phobias, one (BI) with social phobia, one (BN) with generalized anxiety disorder and bulimia, and one (BI) with an anxiety disorder, not otherwise specified.

### 3.2 Study #1 - Imaging Task

#### 3.2a Experimental paradigm (modified from Abler, et al., 2006)

Figure 1. Behavioral experimental paradigm



The experimental paradigm was an incentive task in which the probability of receiving a reward or escaping a punishment and the size of the potential reward or punishment varies from trial to trial. Each session consisted of two blocks, counterbalanced, one with reward incentives and one with punishments, of 80 trials apiece (5 – 13 seconds per trial; 16 trials per trial type per block). Trials began with a cue indicating the probability of receiving a reward (or escaping a punishment) if target response is correct. After a delay, subjects saw a target to which they had to respond by button press (left button for triangle, right button for square). Feedback followed the targets providing the subjects with reward, punishment, or nothing, in accordance with that trial's cue probability. Rewards were a pleasant sound (the sound of a windchime) and receipt of \$0.50; punishments were an aversive sound (a combined 1000 Hz tone and white noise) and loss of \$0.50. Subjects begin the experiment with a bank of \$20, and left the experiment with an average of \$17.56. Sounds were selected from a group of 12 sounds rated by a different group of 18 subjects on a 7-point likert scale for pleasantness. The windchime received the most

positive rating (mean: 5.30, s.d.: 1.56), and the white noise and tone received the most negative rating (mean: 1.45, s.d.: 0.69). Immediately prior to scanning, contingencies between cue symbols and outcomes were explained to the subjects and subjects performed a 5-minute practice session of the task.

### **3.2b Neuroimaging data collection**

While performing the prediction error incentive task, subjects' hemodynamic responses were recorded in a GE 3T scanner acquiring images with 36 contiguous 3.0 mm axial slices parallel to the AC/PC line and using an echo-planar single shot gradient echo T2\* weighting (TR=2300 ms; TE=23 ms; FOV=240 mm; 96 x 96 matrix; 2.5 x 2.5 x 3.0 mm voxel). Immediately prior to the task, high-resolution T1-weighted volumetric scans using a magnetization prepared gradient echo sequence (MP-RAGE) (124 1.2 mm axial slices; FOV=220 mm, NEX = 1, TR = 7.8 ms, TE = 3.0 ms; matrix = 256 x 256; TI = 725 ms) were acquired for each subject.

### **3.2c Neuroimaging data analysis**

#### *fMRI Analysis*

Functional imaging data were analyzed using AFNI software (available at <http://afni.nimh.nih.gov/afni>). Movement was mitigated by registering the images to one volume and concatenating all runs into one data set. Individual subjects' data were smoothed with a 6-mm full-width at half-maximum isotropic Gaussian filter. Trials in which the subject did not respond in the time allotted or responded incorrectly were excluded from analysis. Two subjects were excluded for incorrect

responses on greater than 20% of trials. The remaining subjects' average number of incorrect responses was 10.56 (s.d.: 8.58), for an average of 6.6% of trials excluded.

Each trial was modeled using two impulse regressors, one at cue and one at feedback. To allow for optimal analysis of prediction error activation, each subjects' data was regressed using two different models: a standard model and an amplitude-modulated regression model. In the standard model, a separate regressor was used for each type of cue and feedback, for a total of 5 cue regressors and 8 feedback regressors in each block. Six motion parameters and two regressors modeling baseline and linear trends were also included as regressors of no interest, as well as regressors for cues and feedbacks on trials where subjects did not respond or responded incorrectly. Regression coefficients were calculated at the level of the individual subject and included in a random-effects analysis of variance.

In the amplitude-modulated regression, regressors for motion, baseline and linear trends and regressors for cues and feedback on incorrect trials were again included as regressors of no interest. Only two regressors of interest were included in each block: one for all cues, and one for all feedback. These regressors were weighted differently for each event based on the amount of prediction error it was expected to elicit. Prediction error calculated as the difference between actual outcome and predicted outcome. On feedback trials, actual outcome was coded as 1 for receipt of the salient outcome (reward in the reward block and punishment in the punishment block) and 0 for non-receipt, and predicted outcome was coded as the probability of the salient outcome indicated by the cue on that trial. On cue trials, the predicted cue value was 0.5, the mean value of all cue trials, and the actual value was the

probability of the salient outcome indicated by the cue. See table 1 for mappings of cues and feedback to weightings.

*Table 1. Prediction error weightings of events*

Event	Prediction Error
<i>Cues</i>	
0% cue	-0.5
25% cue	-0.25
50% cue	0
75% cue	+0.25
100% cue	+0.5
<i>Feedback</i>	
75% cue, non-receipt	-0.75
50% cue, non-receipt	-0.5
25% cue, non-receipt	-0.25
0% cue, non-receipt	0
100% cue, receipt	0
75% cue, receipt	+0.25
50% cue, receipt	+0.5
25% cue, receipt	+0.75

To examine overall prediction error in the brain, two contrasts were made between the amplitude-modulated reward regressors and amplitude-modulated punishment regressors: one for cues and one for feedback. For each contrast, clusters were identified that are significant at a voxel threshold of  $p < .005$ , cluster threshold of  $p < .05$ , both across the whole brain, and within five regions of interest. These regions were the amygdala, which sends projections to and receives projections from the VTA, and has been theorized to play a key role in behavioral inhibition; the anterior cingulate cortex, which receives dopaminergic projections from the ventral tegmental area and plays a key role in error-processing; and the three sub-regions of the striatum: the nucleus accumbens; the caudate; and the putamen.

Second, regression coefficients in the standard model for each cue and feedback type were extracted from each subject for our five anatomical regions of interest: the nucleus accumbens, caudate, putamen, amygdala, and anterior cingulate cortex. Talairach anatomical boundaries provided by AFNI were used to define voxels that fell within each region of interest after spatial normalization (Talairach and Tournoux, 1988). The contrast values generated from each ROI from each subject were entered into repeated measures ANOVAs. One ANOVA was conducted for cues and one for feedback, each with group (BI, BN) as a between-subjects factor, and valence (reward block, punishment block), region (nucleus accumbens, caudate, putamen, amygdala), and prediction error level (-0.5, -0.25, 0, +0.25, +0.5 for cue; -0.75, -0.5, -0.25, 0, +0.25, +0.5, +0.75 for feedback) as within-subject factors. Interactions between group, valence and prediction error level were the effects of primary interest. It is hypothesized that in the nucleus accumbens, a group by valence by prediction error level interaction will occur, such that BI subjects show a greater effect of prediction error than BN subjects in the punishment block.

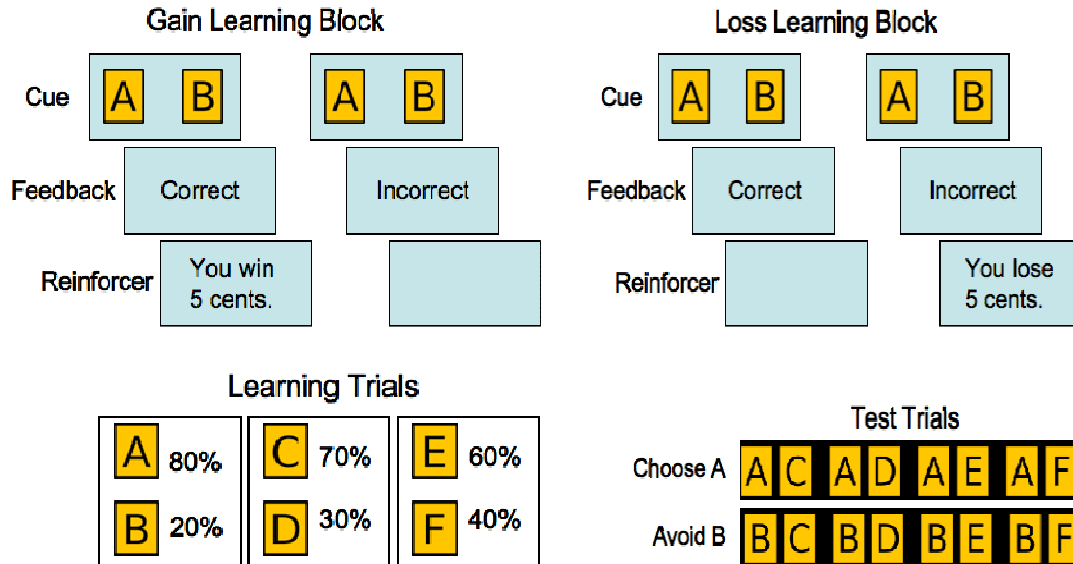
### **3.3 Study #2 – Behavioral Task**

#### **3.3b Behavioral data analysis (modified from Frank, Seeberger, O'Reilly, 2004)**

The probabilistic learning paradigm assesses an individual's ability to learn to choose a positively reinforced stimulus and to avoid a punished stimulus. In the present version of the paradigm, learning via positive reinforcement and learning via punishment were tested in separate blocks, so that each type of learning could be assessed independently of the other. The entire task was composed of four blocks: a

reward learning block, a reward test block, a punishment learning block, and a punishment test block.

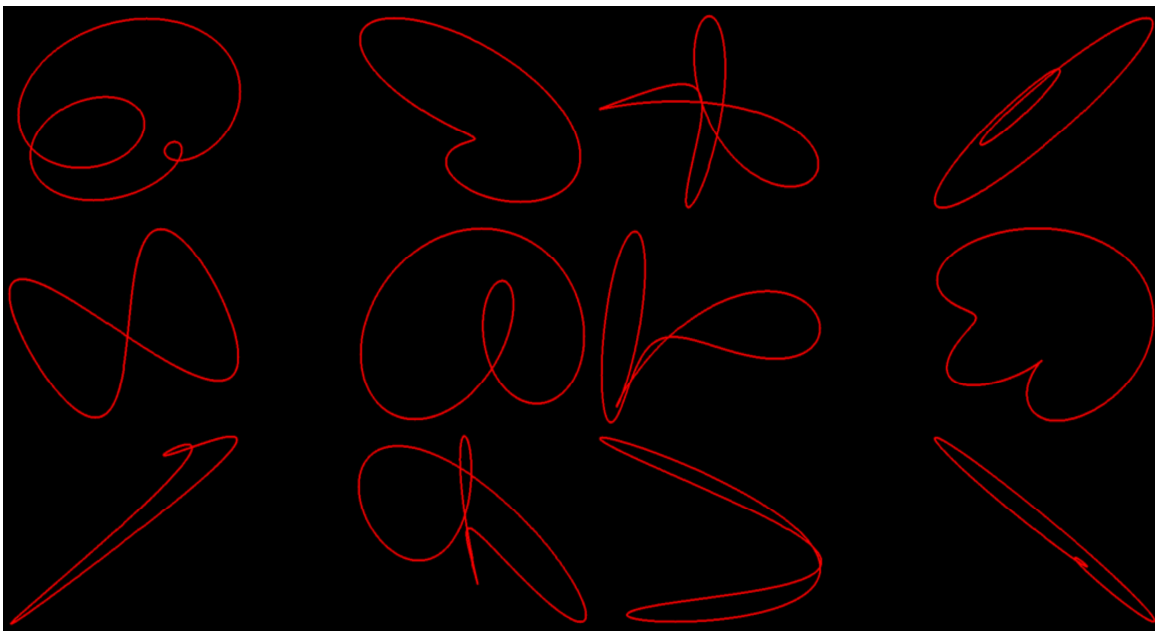
Figure 2. Behavioral Experimental Paradigm



In the learning blocks, on each trial participants were presented with one of three different pairs of stimuli (AB, CD, and EF) and asked to select one of the two stimuli from the pair by button press. After selection, participants received feedback as to whether the stimulus they chose was correct or incorrect. This feedback was probabilistic, with each stimulus having a different probability of being correct. In A-B pairs, A is correct 80% of the time and B is correct only 20% of the time. C-D pairs have reinforcement rates of 70%-30%, and E-F pairs of 60%-40%. Over the course of training, subjects were expected to learn to choose A, C, and E more frequently than B, D, and F. Subjects can learn these reinforcement contingencies in one of two ways: they can either learn that the correct stimulus is usually correct, and select it whenever they see it, or they can learn that the incorrect stimulus is usually incorrect, and avoid it whenever they see it. Which of these strategies the subject used was

assessed during a test block administered after the learning block. In the test block, subjects see stimuli A through F presented in new combinations. On half the trials, “choose-A trials,” the stimulus that was most frequently correct during learning was paired with one of the stimuli C-F. On the other half, “avoid-B trials,” the stimulus that was most frequently incorrect was paired with one of the stimuli C-F. Subjects who learn from positive feedback will consistently choose A on A trials, while those subjects who learn from negative feedback will consistently avoid B on B trials. Subjects received no feedback during the test block.

*Figure 3. Stimuli used in behavioral paradigm*



To assess learning from reward separately from learning from punishment, the present study had both a ‘reward’ learning block and a ‘punishment’ learning block, each with a novel set of six stimuli. In the reward learning block, subjects saw a screen indicating that they had earned a monetary reward for their performance on correct trials after seeing the correct feedback screen. Incorrect trials were not be reinforced. In the punishment learning block, subjects were instead punished on



incorrect trials, seeing a screen indicating they had lost money after receiving feedback that their selection was incorrect. Correct trials were not reinforced. The reward learning and punishment learning blocks were counterbalanced across subjects, and subjects were paid the total amount of money they had earned at the end of the two blocks.

### **3.3b Behavioral data analysis**

#### *Temporal Difference Learning*

To characterize each subject's learning behavior, a temporal difference learning model was fitted to their observed choices. For each pair of stimuli A and B, the model calculated an expected value  $Q_A$  and  $Q_B$ , which was determined based on each subject's individual choices and feedback. On each trial, the expected value of the chosen stimulus was updated according to the rule

$$Q_A(t+1) = Q_A(t) + [\alpha_{Pos} * \delta(t)]_+ + [\alpha_{Neg} * \delta(t)]_-.$$

The outcome prediction error,  $\delta(t)$ , is the difference between the actual and the expected outcome:

$$\delta(t) = R(t) - Q_A(t).$$

$R(t)$  is set at 1, -1, and 0, for reward, punishment, and neutral outcomes, respectively.  $\alpha_{Pos}$  and  $\alpha_{Neg}$  are learning rate parameters that reflects the extent to which the subject adjusts the previously calculated expected value based on new learning on correct trials ( $\delta_+$ ) and incorrect trials ( $\delta_-$ ), respectively. These learning rates estimate the

effect of each positive or negative outcome on the updated expected value of the stimulus.

Given the expected values for the two stimuli presented, the probability of a given choice was estimated using the softmax rule as:

$$P_A(t) = \exp[Q_A(t)/\beta] / \{ \exp[Q_A(t)/\beta] + \exp[Q_B(t)/\beta] \},$$

where  $\beta$  is a temperature parameter that reflects the subject's preference for exploration vs. exploitation.

Separately for the reward learning block and the punishment learning block,  $\alpha_{Pos}$ ,  $\alpha_{Neg}$ , and  $\beta$  was determined for each subject using maximum likelihood estimation so as to maximize the probability of the actual choice behavior seen.

### *Behavioral Analysis*

Two primary behavioral dependent variables of interest were examined: subject performance during the test blocks, and subject learning rates, as modeled by  $\alpha$ . For each subject, accuracy rate was calculated for choose-A trials (where accuracy was defined as selecting A) and for avoid-B trials (where accuracy was defined as selecting the stimulus that is not B) separately for the reward test block and the punishment test block. These accuracy rates were examined in a 2 x 2 trial type (choose A vs. avoid B) by block (reward block vs. punishment block) repeated measures analysis of variance. It was hypothesized that a significant interaction would emerge: In the reward learning block, accuracy rates would be higher on choose-A trials than avoid-B trials, while in the punishment learning block, accuracy rates would be higher on avoid-B trials than choose-A trials.

Second, to examine the hypothesis that behaviorally inhibited individuals are uniquely well-equipped to use punishing information to learn to avoid aversive stimuli, accuracy rates would be examined in a 2 x 2 x 2 between-subjects trial type by block repeated measures analysis of variance. A three-way interaction was hypothesized to emerge, indicating that individuals in the behaviorally inhibited group show greater accuracy in the avoid-B punishment trials, an enhanced accuracy effect that would be specific to that condition.

Third, to examine the hypothesis that behaviorally inhibited individuals show patterns of behavior that are consistent with enhanced prediction errors to punishment, learning rates ( $\alpha$ ) were examined in a 2 x 2 between-subjects repeated measures analysis of variance. An interaction was hypothesized to emerge indicating that BI individuals show greater learning rates than BN individuals in the punishment block, but not the reward block.

Fourth, data from study #1 and study #2 were combined to test the hypothesis that there is a relation between individual differences in striatal prediction error activation to reward and punishment and individual differences in approach and avoidance learning. Each subject's reward block choose-A accuracy and punishment block avoid-B accuracy scores were correlated with their BOLD activation to the 100% high reward cue in the reward cue cluster and their BOLD activation to the 100% high punishment cue in the punishment cue cluster. It was hypothesized that the reward cue activation to choose-A accuracy and the punishment cue activation to avoid-B accuracy correlations will be significant, but not vice versa.

## Chapter 4: Results

Overall, findings revealed a different pattern of results than were hypothesized. First, study #1 revealed that in the nucleus accumbens BOLD response followed a valence-encoding pattern of activation rather than a salience-encoding pattern: in the punishment block, subjects showed increased nucleus accumbens activation to cues and feedback that indicated a lower likelihood of punishment than was expected. Second, study #1 indicated that in both punishment and reward blocks BN and BI individuals encode prediction error differently in the amygdala. Specifically, BI individuals show increased BOLD activation to more unexpectedly good news whereas BN individuals show increased activation to more unexpectedly bad news. This pattern of response is also seen, although to a lesser extent, in the caudate. The behavioral data in study #2 found no differences between BI and BN individuals in their ability to learn to approach rewarding stimuli or avoid punishing stimuli. Finally, no relations were found between nucleus accumbens PE response to reward and punishment in study #1 and feedback-related learning in study #2.

### **4.1 Participants**

A total of 22 BI subjects (12 male) and 20 BN subjects (9 male) participated in both the imaging and behavioral experiments. All subjects were 18-21 years old (mean: 19.18 years, s.d.: 1.39 years). Of these participants, 3 BN subjects (1 male) and 7 BI subjects (5 male) were excluded from the imaging data analyses: 4 were run on an earlier version of the task before a change in task design; 3 were excluded due to experimenter error; 2 were excluded for responding correctly to the target stimulus on

fewer than 80% of the trials; and 1 subject participated in the behavioral task, but could not be scheduled to participate in the imaging task. Altogether, this left 15 BI subjects (7 male) and 17 BN subjects (8 male) with usable data for study #1. For study #2, one male BI subject was excluded due to experimenter error and one female BN subject was excluded due to subject non-compliance, leaving a total of 21 BI subjects (11 male) and 19 BN subjects (9 male) with usable data. 15 BI subjects (7 male) and 16 BN subjects (8 male) had usable data for both study #1 and study #2, who were used for the brain-behavior correlational analyses.

## **4.2 Study #1 - Imaging task**

### **4.2a Behavioral findings**

#### *Stimuli Preferences*

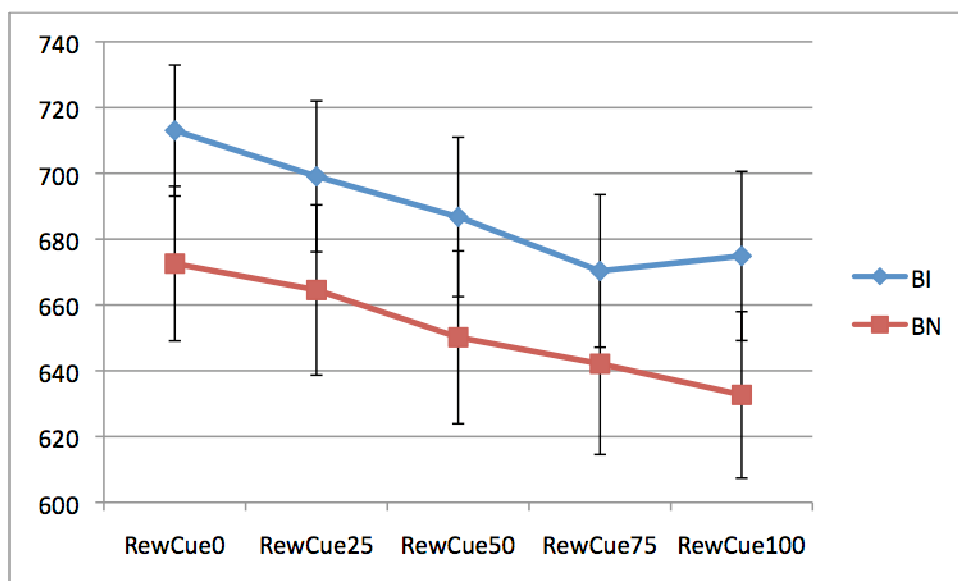
A group x sound-type ANOVA revealed a main effect for sound ( $F(2,27)=6.211, p=.004$ ). Post-hoc tests found that, consistent with the intentions of the design, subjects found the aversive white noise sound more unpleasant than the neutral pump noise ( $t(1,29)=2.417, p=.022$ ) and the rewarding ding noise ( $t(1,29)=3.192, p=.003$ ). No effect of group or group x sound interaction was seen ( $ps > .1$ ).

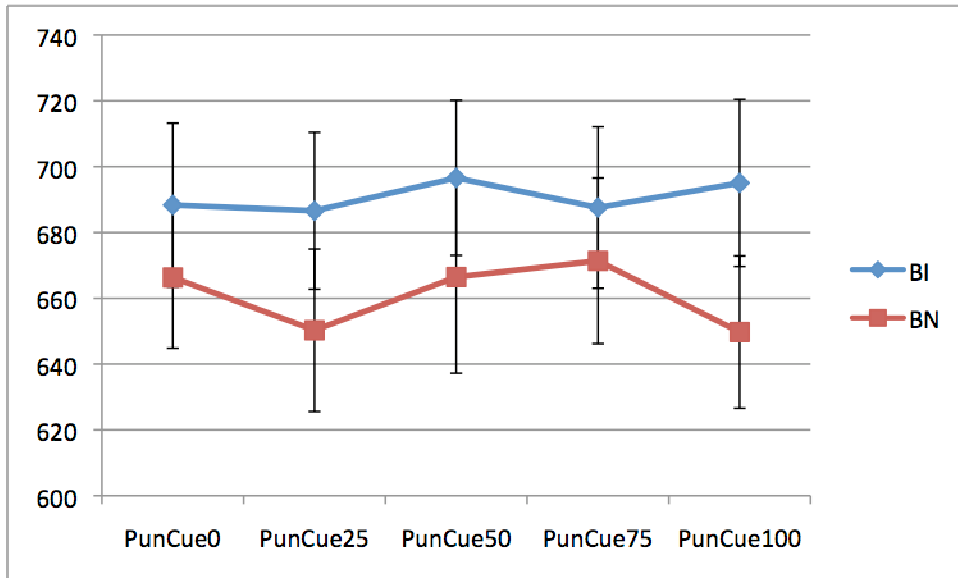
A group by stimulus type ANOVA revealed a main effect of stimulus type ( $F(3,28)=24.799, p<.0005$ ), but no effect of group or group x stimulus type interaction ( $ps > .1$ ). Post-hoc t-tests indicated that subjects preferred cues indicating certain reward (mean=6.31, s.d.=3.76) over cues indicating certain escape from punishment (mean=4.22, s.d.=4.4), which was preferred over cues indicating certain non-reward (mean=-2.34, s.d.=5.02) or certain punishment (mean=-2.44, s.d.=5.79).

### Reaction Times

Subjects showed a significant effect of cue prediction error on reaction time ( $F=7.049$ ,  $p<.001$ ), with a significant block by prediction error interaction ( $F=10.796$ ,  $p<.001$ ). In the reward block, subjects showed a linear effect of prediction error on reaction time, with cues indicating higher probabilities of reward eliciting speedier reaction times ( $F=14.617$ ,  $p<.001$ ), but no such effect was seen in the punishment block ( $p>.2$ ) (see figure 3). An interaction of prediction error and BI status also emerged ( $F=2.706$ ,  $p=.05$ ). Post-hoc tests revealed that BN subjects showed a significant linear effect of prediction error level on reaction time, with decreasing reaction times as prediction error level increased ( $F=5.340$ ,  $p<.01$ ). BI subjects did not show a significant linear effect of prediction error level ( $F=2.503$ ,  $p=.103$ ). No other main effects or interactions were significant.

Figure 4. Cue reaction times by cue type and BI status





#### 4.2b Overall prediction error modulated activation in the brain

To determine the brain regions that follow a prediction error pattern of activation, the contrasts between amplitude-modulated regressors for reward cues and punishment cues, and between reward feedback and punishment feedback, were examined. These contrasts highlight the brain regions that responded most consistently to the prediction error of a stimulus. Negative values represent increased activation to more unexpectedly bad news, while positive values represent increased activation to more unexpectedly good news.

##### *Amplitude-modulated prediction error to cues*

Whole-brain analyses revealed significant prediction-error-modulated negative activation in the right lateral orbitofrontal cortex (OFC) and left lateral OFC, with increased BOLD activation to more undesirable cues. Significant prediction-





*Amplitude-modulated prediction error to feedback*

Whole-brain analyses revealed significant prediction-error-modulated negative activation in the medial prefrontal cortex/motor cortex, the cuneus, the right precentral gyrus, the right supramarginal gyrus, and two clusters in the right insula (one anterior and one posterior) (see table 2 and figure 4). The whole-brain analyses revealed no prediction-error-modulated positive action. Examination of the regions of interest revealed significant positive activation in the left nucleus accumbens (peak activation: 3.84).

*Table 3. Regions with significant whole-brain activation in the contrast of prediction-error-modulated activation to reward block feedback v. prediction-error-modulated activation to punishment block feedback*

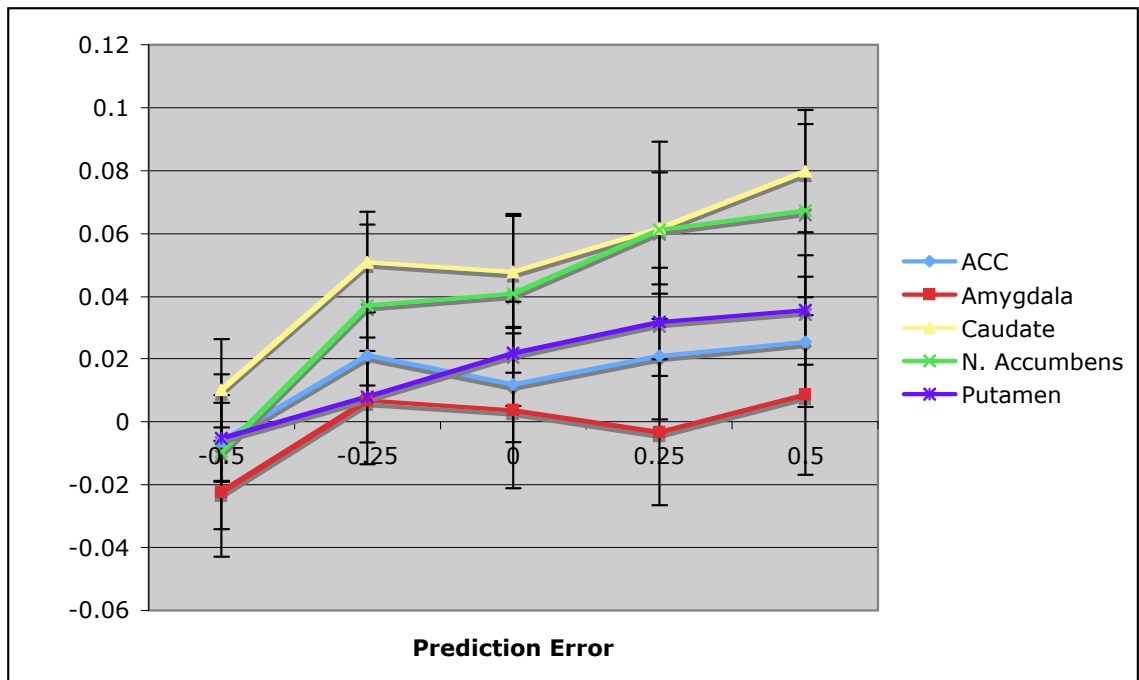
Region	Peak Activation	Coordinates	Cluster Size
mPFC/R. motor	-5.07	34, -29, 59	1482
Cuneus	-4.97	14, -76, 21	753
R. precentral gyrus	4.33	44, 24, 34	374
R. insula (anterior)	5.43	41, 14, 11	360
R. supramarginal gyrus	4.55	61, -41, 34	288
R. insula (posterior)	4.20	46, -24, 14	176

*Figure 6. Prediction-error-modulated activation to reward block feedback v. prediction-error-modulated activation to punishment block feedback, thresholded at  $p < .005$  (blue = activation to rewarding prediction error; red = activation to aversive prediction error)*



of the Valence main effect revealed that overall mean BOLD activation was greater to cues in the punishment block (mean activation = 0.046, S.E. = 0.017) than cues in the reward block (mean activation = 0.002, S.E. = 0.015). A post-hoc analysis of the Prediction Error Level main effect revealed that, as expected, activation to cues followed a linear pattern,  $F(1, 30) = 9.983, p < .005$ , with increased activation to more desirable cues. The lack of significant interactions revealed that this linear relation did not change as a function of Region, Valence, or Group, indicating that this pattern of increased activation to more unexpectedly good news was seen in both the reward and punishment block, across all ROIs, and equally for both BI and BN subjects.

Figure 7. Activation to cues by region

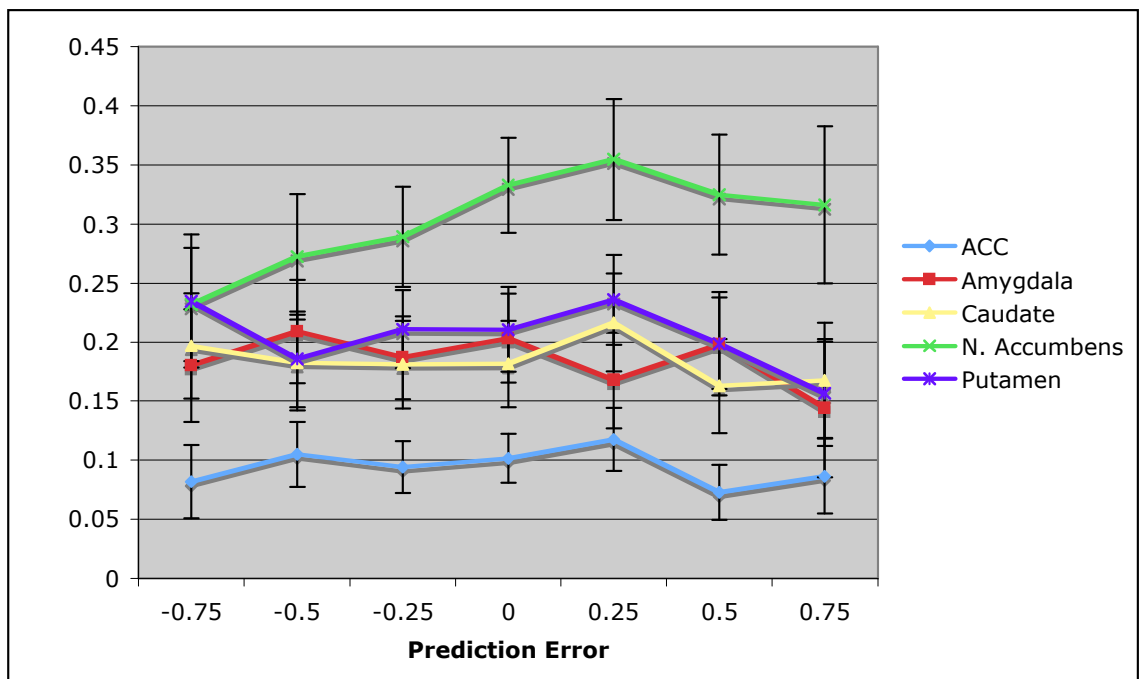


Prediction Error Activation to feedback in anatomical ROIs

BOLD activation to the feedback was subjected to a similar Region x Block x Valence x Group repeated measures ANOVA. Results revealed a main effect of Region,  $F(4, 27) = 8.947, p < .001$  which was qualified by a Region x Prediction Error Level interaction,  $F(24, 7) = 2.434, p < .01$ . This interaction was further qualified by a Region x Prediction Error Level x Group interaction,  $F(24, 7) = 1.868, p < .05$ . No other effects were significant.

Post-hoc analyses of the region main effect revealed that mean BOLD activation to feedback was greater in the nucleus accumbens (mean = 0.303; S.E. = 0.044) than all other regions (Amygdala (mean = 0.184, S.E. = 0.042;  $F(1,1)=7.981, p < .01$ ), Caudate (mean = 0.184, s.d. = .045;  $F(1,1)= 13.162, p = .001$ ), Putamen (mean = 0.205, s.d. = .045,  $F(1,1)=10.080, p < .005$ ), and ACC (mean = 0.094; s.d. = 0.026;  $F(1,1)=46.759, p < .0005$ )) and activation in the ACC was lower than activation in all other regions (see figure 6).

Figure 8. Activation to feedback by region

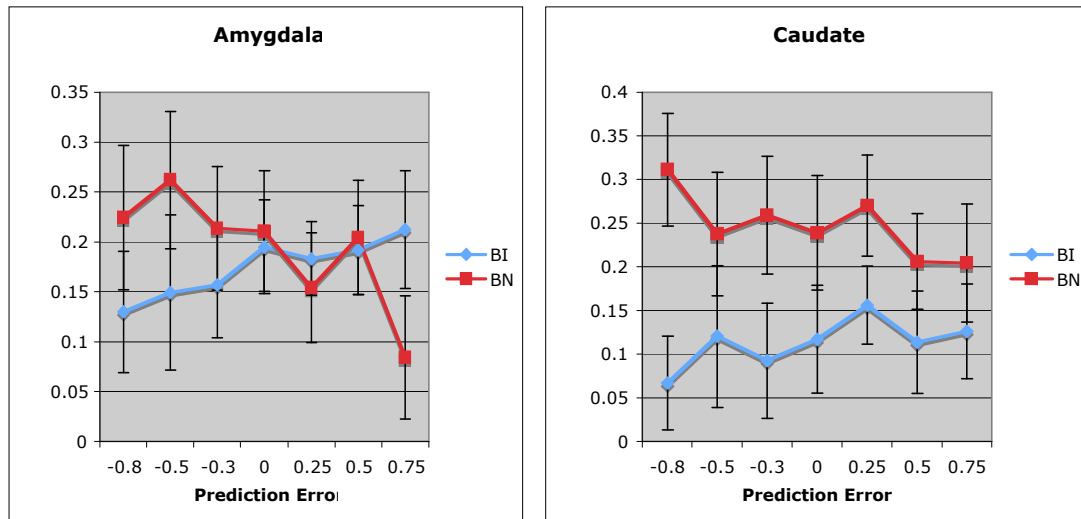


Post-hoc analyses of the region x prediction error level interaction revealed that there was a significant effect of prediction error level in the nucleus accumbens,  $F(6, 26) = 2.474, p < .05$ . No significant effect of prediction error level was seen in any of the other regions. Consistent with these findings, the effect of prediction error level in nucleus accumbens differed from the effect of prediction error level in all other regions when tested in individual region x prediction error level repeated measure ANOVAs, while the effects of prediction error level in all other regions do not differ from one another. The effect of prediction error level in the nucleus accumbens followed a linear pattern,  $F(1, 30) = 4.783, p < .05$ , with greater activation to more unexpectedly good news. As for cues, no interaction with valence was seen, indicating this pattern was present both in the reward and punishment blocks.

To explore the Region x Prediction Error Level x Group interaction, separate ANOVAs were conducted within each Region to examine the Prediction Error Level x Group interaction. Results revealed a significant linear prediction error level x group interaction in the amygdala,  $F(1, 30) = 4.495, p < .05$ , and a trend for such an effect in the caudate,  $F(1, 30) = 3.257, p = .081$ . No such interactions were seen in the nucleus accumbens, ACC, or putamen. The group x prediction error level effect in the amygdala was significantly greater than that in the nucleus accumbens,  $F(6, 26) = 3.622, p < .01$ ) and the anterior cingulate cortex,  $F(6, 26) = 3.293, p = .01$ ), and also significantly greater in the caudate than the anterior cingulate cortex,  $F(6, 26) = 2.881, p < .05$ ). The group by prediction error level by region interactions are driven by the fact that while BI show a pattern of increased prediction error activation as news gets better in all regions, BN show an effect of salience in the opposite direction

in both the amygdala and caudate, with increased activation to unexpectedly bad news and decreased activation to unexpectedly good news. These findings can be seen in figure 7.

Figure 9. BOLD activation to feedback by group



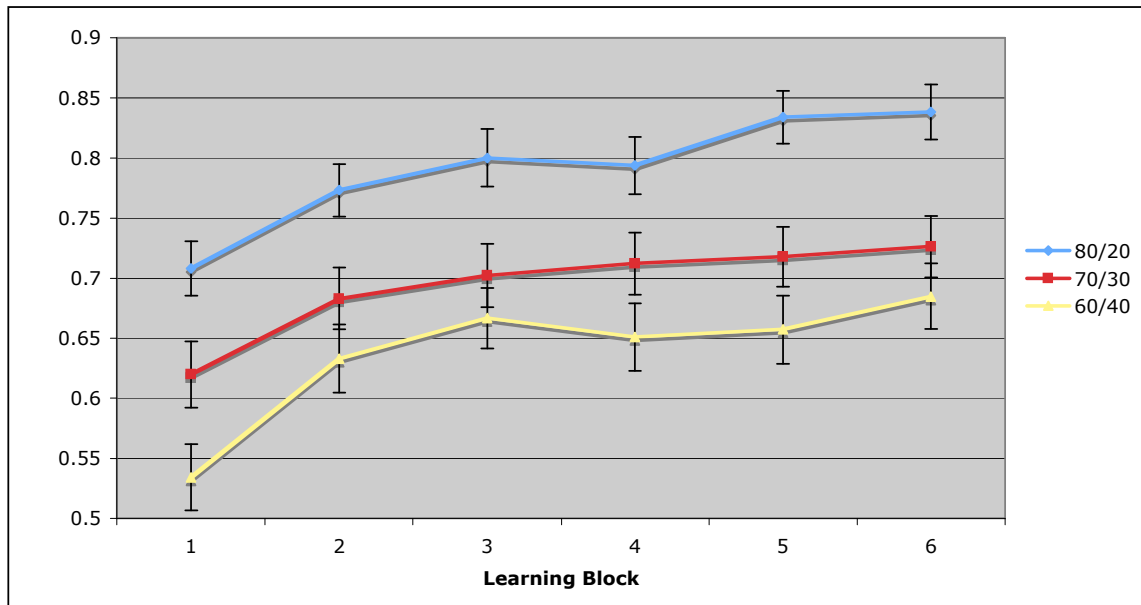
### 4.3 Study #2 – Behavioral task

#### 4.3a Overall learning effects

As a check to ensure participants were able to learn on the task, overall learning effects were examined. Accuracy data from the two learning blocks were subjected to a 2 x 6 x 3 Repeated Measures ANOVA with Block (reward block, punishment block), Time (1<sup>st</sup> 60 trials, 2<sup>nd</sup> 60 trials, 3<sup>rd</sup> 60 trials, 4<sup>th</sup> 60 trials, 5<sup>th</sup> 60 trials, 6<sup>th</sup> 60 trials), and Trial Type (80-20, 70-30, 60-40) as within subjects factors. As expected, subjects learned the task contingencies; there was a significant effect of Time,  $F(5, 35) = 14.076, p < .001$ , indicating that subjects' performance improved over time. There was also a significant effect of trial type,  $F(2, 38) = 15.067, p < .001$ , indicating that subjects chose the preferred stimulus more frequently on 80-20 trials than 70-30 trials,  $F(1, 39) = 12.696, p = .001$ , and more frequently on 70-30

trials than 60-40 trials,  $F(1, 39) = 8.164, p < .01$  (see figure 8). Subjects showed no main effect of block,  $F(1, 39) = .003, p > .05$ , indicating that, overall, they performed equally well in both the reward and punishment blocks, and no interaction effects were significant.

Figure 10. Subject learning in behavioral task



#### 4.3b Performance effects on test trials

To examine test trial performance, accuracy data from the two test blocks was subjected to a 2x2x2 Repeated measures ANOVA with Block (reward block, punishment block) and Trial Type (Choose 80 v. Avoid 20) as between subjects factors and Group (BI v. BN) as a within subjects factor. Contrary to the hypotheses, no significant main effects or interactions effects were present (all  $ps > .05$ ), indicating that BI and BN subjects performed equally well on both trial types in both blocks, and trial type performance did not vary by block.

### 4.3c Learning rates

To examine differences in learning rate, a reinforcement learning model was used to model positive learning rate ( $\alpha_{\text{pos}}$ ), negative learning rate ( $\alpha_{\text{neg}}$ ), and temperature ( $\beta$ ) separately for the reward block and punishment block for each subject. Learning rates were subjected to a 2 x 2 x 2 ANOVA with Block (reward block, punishment block) and Alpha Type (positive alpha, negative alpha) as within subjects factors and Group (BI, BN) as a between subjects factor. This ANOVA revealed a main effect of alpha type,  $F(1, 38) = 42.009, p < .0005$ , and a trend for an alpha type x group interaction,  $F(1, 38) = 3.095, p = .087$ . Post-hoc analyses indicated that the main effect of alpha type was due to larger alphas for positive feedback (mean = 0.272, standard error = 0.028) than for negative feedback (mean = 0.085, standard error = 0.022). The alpha type x group trend was due to non-inhibited subjects having relatively higher alphas for positive feedback (BN: mean = 0.312, standard error = 0.041; BI: mean = 0.231, standard error = 0.039) and behaviorally inhibited subjects having relatively higher alphas for negative feedback (BN: mean = .075, standard error = 0.032; BI: mean = 0.096, standard error = .030).

Temperatures were subjected to a 2 x 2 ANOVA with Block (reward block, punishment block) as a within subjects factor and Group as a between subjects factor. No significant main effects or interactions were present for temperatures. See table 3 for details.

Table 4. Learning rates and temperatures by temperament group

	Gain Block Pos	Gain Block	Loss Block	Loss Block	Gain Block	Loss Block
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	Alpha	Neg Alpha	Pos Alpha	Neg Alpha	Beta	Beta
BI	Mean: 0.23 s.e.: 0.04	Mean: 0.09 s.e.: 0.05	Mean: 0.24 s.e.: 0.06	Mean: 0.10 s.e.: 0.04	Mean: 0.28 s.d.: 0.05	Mean: 0.33 s.d.: 0.05
BN	Mean: 0.22 s.e.: 0.10	Mean: 0.10 s.e.: 0.05	Mean: 0.41 s.e.: 0.05	Mean: 0.05 s.e.: 0.04	Mean: 0.36 s.d.: 0.06	Mean: 0.34 s.d.: 0.05

#### 4.3d Relations between brain and behavior

Finally, to examine the relations between BOLD activation in the nucleus accumbens and test block performance, subjects' mean BOLD activation to the 100% Reward cue and the 100% Punishment cue was correlated with behavioral measures assessing approach of reward learning and avoidance of punishment learning: reward block choose 80% accuracy, and punishment block avoid 20% accuracy. No correlations were significant (all  $ps > .05$ , see table 4).

*Table 5. Correlations between neural activation and learning*

	Choose 80 Rew Block	Avoid 20 Pun Block
N. Accumbens Activation Rew	$r = .131$	$r = .023$
N. Accumbens Activation Pun	$r = .093$	$r = .149$

## Chapter 5: Discussion

The purpose of the current study was to investigate relations between the temperamental trait of behavioral inhibition, striatal and amygdalar prediction error responses to reward and punishment, and implicit learning from reward and punishment. Forty-four young adults categorized for their behavioral inhibition or non-inhibition in childhood participated in two tasks: one behavioral task measuring probabilistic learning to reward and punishment, and one imaging task measuring prediction-error-modulated BOLD response to cues and feedback providing information about rewards and punishment.

Overall, while some differences between inhibited and non-inhibited individuals were detected, the findings were largely inconsistent with the initial hypotheses regarding the role of prediction errors and approach and avoidance learning in differences in temperament between behaviorally inhibited and non-inhibited subjects. Specifically, inhibited and non-inhibited subjects did not differ in their ability to learn from reward or punishment—although there was a trend for inhibited subjects to adjust their expected values of stimuli more based on incorrect feedback and less based on correct feedback than did their non-inhibited peers. The groups also showed differences in their encoding of prediction error in the amygdala. In the striatum, a trend level effect was seen in caudate, specifically to feedback, indicating that behaviorally inhibited individuals tend to show greater activation in the caudate as positive prediction error increases, while non-inhibited individuals show greater activation in the caudate as negative prediction error of feedback increases. Furthermore, independent of behavioral inhibition, we found no evidence

supporting a relation between nucleus accumbens prediction error response, recorded in the scanner, and approach and avoidance learning outside of the scanner. In this discussion, we will take each of these domains in turn and discuss how best to understand these findings and how these findings relate to and extend our knowledge from previous research.

### **5.1 Approach and avoidance learning**

In terms of their general learning, the current sample responded in ways consistent with previous research. First, subjects showed an overall learning effect, with performance improving over time. Second, subjects' choice behavior for each pair roughly matched the reinforcement contingencies for that pair, with subjects choosing the 80% correct stimuli roughly 80% of the time, the 70% stimuli roughly 70% of the time, and so on. Both of these patterns are consistent with performance behavior in other studies using probabilistic paradigms (Frank, et al., 2004; Frank, et al., 2007; Cohen, et al., 2010). Moreover, the proportional matching behavior is seen across a wide range of tasks with both animals and humans (Herrnstein, 1974). Third, reinforcement models indicated that subjects showed a much stronger tendency to increase their expected value for a stimulus after receiving correct feedback than to decrease their expected value for a stimulus after receiving incorrect feedback, as reflected in the higher values of alpha-positive than alpha-negative. This, too, has been shown in other studies where learning rates for correct feedback and learning rates for incorrect feedback were modeled separately (Frank, et al., 2007; Doll, et al., 2011). Overall, these findings suggest that the probabilistic learning task, as designed,

elicited expected patterns of learning behavior and served as an effective measure of probabilistic learning.

The aspect of the task that differed from other probabilistic learning tasks was the presence of two blocks: one where correct responses were rewarded and incorrect responses were not reinforced; and another where correct responses were not reinforced, but incorrect responses were punished. Our hypothesis was that this difference between the two blocks would shift learning behavior. First, we expected that subjects would learn to approach more frequently correct stimuli better in the reward block and would learn to avoid more frequently incorrect stimuli better in the punishment block, because these stimuli would be more salient. Second, we expected that, due to these differences in salience, subjects would show increased learning rates to correct feedback in the reward block relative to the punishment block, while the opposite pattern would hold for learning rates to incorrect feedback. Neither of these hypotheses were borne out by the data: subjects performed similarly on choose-correct and avoid-incorrect test trials, and showed similar learning rates across the two blocks. These findings suggest that subjects didn't treat the reward block and punishment block as fundamentally different—they seemed to simply encode the best option available as positive, and the worst option available as negative. As will be discussed in the next section, the imaging data also appear to provide neural support for this interpretation.

More importantly, we saw very little in the way of predicted effects of group differences in learning to reward and punishment. Subjects showed no group differences in their overall choice behavior in the two blocks, or differences in their

tendencies to learn to approach good stimuli vs. avoid bad stimuli, or differences in their learning rates in the reward block vs. the punishment block. The only finding suggesting a difference between the two groups was an effect, at the level of a trend, indicating that non-inhibited subjects have higher learning rates for correct feedback, while inhibited subjects have higher learning rates for incorrect feedback.

How do we interpret these results, given the known tendency for behaviorally inhibited subjects to show enhanced avoidance behavior in ecologically valid settings? There are several possibilities that can be explored in future studies.

One possibility is that, as originally proposed by Kagan and colleagues (1984), behaviorally inhibited individuals specifically show heightened fear and avoidance of novel stimuli. When exposed to stimuli repeatedly, their avoidance learning is normal. In this task, subjects get substantial exposure, and equal exposure, to all stimuli, so differences in novelty avoidance wouldn't lead to group differences in the task.

Another possibility is that inhibited individuals' punishment learning is only sensitized to certain ecologically valid, prepared forms of stimuli, such as loud noises, snakes, social situations, etc. There is a large body of research suggesting that fear learning is more easily acquired to certain, evolutionarily relevant stimuli (for review, see Ohman, et al., 2001). Thus, it could be that while inhibited individuals would show heightened avoidance learning under these circumstances, they have no greater ability to learn to avoid arbitrary stimuli such as squiggles. One could test this hypothesis by using a different, more relevant, learning stimulus.

Conversely, inhibited individuals could be able to more easily learn to avoid a wide range of stimuli and situations, but only when paired with certain types of punishment, such as social punishment. Punishments like monetary loss and aversive noises are ineffective.

An additional possibility is that behaviorally inhibited individuals learn in the same ways as non-inhibited individuals, but have been exposed to different environments in early life, where they have been exposed to more aversive experiences or have learned to fear due to social learning from their parents. While this goes against the traditional temperament model of behavioral inhibition, which holds that temperamental tendencies are due to innate characteristics (Kagan, et al., 1984), behavioral inhibition in our sample was measured between 9 months and 7 years of age, with later assessments being weighted equally with earlier assessments. Thus, it is entirely possible that experiences in early childhood could affect the avoidance displayed by inhibited individuals in the lab, and there is substantial evidence that social, informational learning from parents and others can induce learned fear (Olsson & Phelps, 2007), anxiety (Muris, et al., 2001), and avoidance (Muris, et al., 2010).

Finally, it also remains a possibility that behaviorally inhibited individuals do in fact differ from their non-inhibited peers in their ability to learn from punishment under all circumstances, but that we were unable to detect that difference due to one of two limitations in our sample. The simplest possibility is that our sample was simply too small to detect the effect. However, given the extremely low F-statistics for the group contrasts on the behavioral measures (the F-stats were less than 0.4 for

all tests where group differences were hypothesized, indicating considerably more within-group variance than between-group variance), and the reasonable sample sizes, any effect that may exist could reasonably be assumed to have a fairly small effect size, and therefore is unlikely to be the primary cause of the differences in avoidance behavior seen between inhibited and non-inhibited individuals.

A failure to detect effects could also be due to other limitations of our sample. In particular, the behavioral inhibition status of the present sample was measured between the ages of 14 months and 7 years, while the subjects are now 18-21. While temperament displays moderate stability over time (Kagan, et al., 1984; Kagan, et al., 1988; Fox, et al., 2001), there is also some amount of instability, and these studies have focused only on stability throughout childhood—it is unknown the extent to which temperamental traits remain constant into adulthood. Thus, some of the non-inhibited children have presumably become more inhibited over time, and some of the inhibited children more non-inhibited, adding noise to our measure of temperament, which is already a challenging construct to assess with high reliability.

## **5.2 Neural prediction error responses**

### **5.2a General findings**

A number of interesting findings emerged from our examination of neural prediction error response. First, findings revealed a clear pattern of prediction-error activation in several regions that are functionally connected to the midbrain dopaminergic system. These activations were seen very robustly in the nucleus accumbens, the main recipient of dopaminergic projections from the VTA (Mogenson, et al., 1980), in both the cue and the feedback condition. In the cue

condition, prediction error modulated activation was also seen in the cingulate and the insula, both known to receive input from dopaminergic neurons and to encode error signals (Holroyd, et al., 2004; Preusschoff, et al., 2008), and in the midbrain itself, in the vicinity of the ventral tegmental area and substantia nigra. Finally, strong negative prediction-error activation—activation encoding the aversiveness of cues—was seen in both the left and right lateral orbitofrontal cortex. These regions are known to encode the value of aversive stimuli and to receive dopaminergic projections from the VTA (Rolls, 2004). In the feedback condition, strong activations were again seen in the insula and medial prefrontal cortex, with additional activations seen in the cuneus, precentral gyrus, and supramarginal gyrus. While these regions are not commonly associated with prediction error activations, dopaminergic projections do innervate regions throughout the cortex.

Most interestingly, the present data allowed us to address the controversy of whether prediction error activation encodes unexpectedly *rewarding* events, or unexpectedly *salient* events. Schultz' original characterizations of the dopaminergic signals described them as encoding reward (Schultz, et al., 1997), and a follow-up study specifically examining dopaminergic response to aversive events indicated that an unpleasant salient event elicited a dip in dopaminergic firing (Ungless, et al., 2004), further supporting the reward-encoding model. However, additional research indicating that under certain circumstances, dopaminergic neurons also showed bursting to aversive events (Sorg & Kalivas, 1991; Young, Joseph & Gray, 1993), and to stimuli that predict punishment (Young, Joseph & Gray, 1993). Recent studies (Matsumoto, et al., 2009; Wang & Tsien, 2011) identified two groups of



dopaminergic neurons within the VTA and SN: one that follows a reward-encoding model, responding to rewards with increased firing and punishments with decreased firing, and another that follows a salience-encoding model, responding to both rewarding and aversive events with bursts. It is also unclear whether prediction-error-modulated BOLD response follows a reward-encoding or salience-encoding pattern, with some studies showing increased BOLD activation in the nucleus accumbens (Levita, et al., 2009) or caudate (Seymour, et al., 2007) to aversive stimuli, while others show decreased activation (Pessiglione, et al., 2006).

Our data show an overwhelmingly clear pattern of reward-based prediction error encoding, with subjects showing decreased activation to more negative stimuli in both the reward block and the punishment block. Of note, the aversive sound paired with punishments—white noise overlaid on a high-pitched tone—has previously been shown to produce increased activation in the nucleus accumbens (Levita, et al., 2009), although not in a prediction error paradigm. The present study differed from other studies in which a strong salience-encoding prediction error pattern was seen in that both monetary losses and monetary gains were presented as stimuli in the task, albeit in different blocks, and both gains and losses were summed together to produce the total sum subjects received at the end of the task. Thus, even though reward trials (with gains) and punishment trials (with losses) were presented in separate blocks, subjects may have treated them as part of the same scale, leading the punishment trials to be coded as deactivations and reward trials as activations.

## 5.2b Individual differences

When examining differences between behaviorally inhibited and non-inhibited individuals in their BOLD response to cues and feedback that elicit prediction error activation, we see no group differences in responses to cues. However, in response to feedback, a group x salience x region interaction emerged. Post-hoc tests indicated that this was largely driven by a group x salience interaction in the amygdala. In this region, inhibited individuals showed a pattern of greater activation to more unexpectedly good feedback, whereas non-inhibited individuals showed a pattern of greater activation to more unexpectedly bad feedback. There was no significant effect of block, meaning that this pattern of encoding was seen both in the block where feedback was either reward or non-reward, and in the block where feedback was either punishment or non-punishment.

This interaction was not hypothesized, and requires understanding the role of the amygdala in the encoding of unexpected reward and punishment. The amygdala is closely linked to the dopaminergic prediction error system, both sending projections to and receiving projections from the VTA and SN. However, fMRI research has failed to reliably elicit prediction-error-patterned activation in the amygdala (Delgado, 2008; Li, et al., 2011), although more recent research has demonstrated that some amount of information about the reinforcement value of stimuli is being encoded in the amygdala, as well as many other locations (Vickery, et al., 2011).

There are two hypotheses present in the literature regarding the role of the amygdala in reinforcement learning. One is that the amygdala is responsible for gating the amount of attention paid to stimuli, essentially up- and down-regulating the learning rate based on how much the reward and punishment contingencies of stimuli

appear to be in flux. This trait, known as associability, is a feature of the Pearce-Hall model of learning (Pearce & Hall, 1980), and both animal (Holland & Gallagher, 1999; Roesch, et al., 2010) and human research (Li, et al., 2011) indicate that it is tracked by amygdalar response. However, while this appears to be an important role for the amygdala in many types of reinforcement learning, in the present study reinforcement contingencies do not change and they are explicitly told to the subject for each cue type; thus, associability should not play a prominent role in the current paradigm.

Another hypothesized role for the amygdala in reinforcement learning is shifting prediction error response from an unconditioned stimulus to the conditioned stimulus, essentially enabling associative learning (Hazy, et al., 2010). In order to do this, the amygdala needs to fire in a similar pattern as the VTA and the nucleus accumbens, and thus should follow a prediction error pattern.

Based on our data, it appears that behaviorally inhibited individuals are following a standard pattern of prediction error activation, but behaviorally non-inhibited individuals are not, instead showing the opposite pattern of findings. It is unclear what effect that would have on their prediction error learning.

A final important issue to address is how to reconcile the present findings with previous research on the role of the striatum in behavioral inhibition. Three previous studies (Guyer, et al., 2006; Bar-Haim, et al., 2009; Helfinstein, et al., 2011) have found group differences in the striatum between inhibited and non-inhibited individuals in reward processing studies. We hypothesized that what caused these patterns of activation was a difference in prediction error response between these

groups, and designed the present study to narrowly test this hypothesis. Other than a fairly weak trend for group differences in prediction error in the caudate, which was not in the same direction as the findings in previous studies, no group differences in prediction error in the striatum emerged, a stark contrast to the strong differences in activation seen in a monetary incentive delay task (Guye, et al., 2006), for example. This suggests that differences in simple prediction error response can be eliminated as a cause for the striatal group differences seen in other reward processing tasks. One likely possibility, consistent with both the present findings and our previous findings, is that behaviorally inhibited subjects show enhanced prediction error activation specifically in situations where receipt of rewards and punishments are contingent on their own actions. This is consistent, in particular, with the findings of Bar-Haim and colleagues (2009), which found that inhibited subjects showed enhanced activation in the caudate only on trials where reward was contingent on subjects making an appropriate response; on trials where subjects had to make a simple button press to receive a reward, no differences between the two groups emerged. In both Guye, et al. (2006) and Helfinstein, et al. (2011), group differences were found in situations where outcomes were contingent on subjects' performance. The present study was designed to specifically test the prediction error hypothesis, so no contingent actions were required to receive a reward or avoid a punishment; subjects only had to make simple button press responses on each trial. If contingent actions are the cause of behaviorally inhibited individuals' enhanced striatal prediction error responses in reward tasks, then one would expect no striatal differences in the present task. Other research has suggested that behavioral inhibited individuals show enhanced

sensitivity in circumstances where subjects have to use feedback to monitor their own behavior (McDermott, et al., 2009), and is consistent with our perception of behaviorally inhibited individuals as afraid to make mistakes. Thus, the heightened responses seen in the striatum on these tasks may not be a result of enhanced prediction errors, but rather due to enhanced attention in an effort to avoid mistakes. This hypothesis needs to be examined in more depth in future studies.

### **5.3 Final conclusions**

In sum, the findings presented here continue to raise as many questions as they answer. However, a few critical points can be taken away from the findings at large. First, the present findings strongly support the reward-encoding model of prediction error, and refute the valence-encoding model. Second, our behavioral results suggest that behaviorally inhibited and non-inhibited individuals do not differ from one another in either approach or avoidance learning in a simple probabilistic learning paradigm, although both groups are able to learn in these paradigms in the typical way. Third, the present findings indicate that behaviorally inhibited and non-inhibited individuals do not differ in their striatal prediction error responses to reward or punishment, although they do show differences in amygdalar prediction error responses to feedback. The lack of striatal group differences suggests that differences in prediction error amplitude cannot explain the striatal differences seen in previous studies, and suggests that behaviorally inhibited individuals may show enhanced striatal responses only on incentive tasks where outcomes are contingent on subject

behavior. Clearly, additional research is needed to more precisely understand exactly how these differences in striatal responding are linked to behavioral inhibition.

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