Approach Related Deficits and Reward Based Learning in Schizophrenia

BY

EMILY K. OLSEN
B.S., University of California, Davis, 2005

THESIS
Submitted as partial fulfillment of the requirements for the degree of Master of Arts in Psychology in the Graduate College of the University of Illinois at Chicago, 2012

Chicago, Illinois

Defense Committee:

Ellen Herbener, Chair and Advisor
Jamie Roitman
Stewart Shankman
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>A. Background</td>
<td>1</td>
</tr>
<tr>
<td>B. Purpose</td>
<td>6</td>
</tr>
<tr>
<td>II. METHODS</td>
<td>9</td>
</tr>
<tr>
<td>A. Participants</td>
<td>9</td>
</tr>
<tr>
<td>B. Assessments and Measures</td>
<td>9</td>
</tr>
<tr>
<td>C. Data Collection and Reduction</td>
<td>12</td>
</tr>
<tr>
<td>D. Statistical Analyses</td>
<td>13</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>15</td>
</tr>
<tr>
<td>A. Demographic Characteristics</td>
<td>15</td>
</tr>
<tr>
<td>B. Learning Phase</td>
<td>15</td>
</tr>
<tr>
<td>C. Relationship between Learning and Retention Performance</td>
<td>22</td>
</tr>
<tr>
<td>D. Clinical Correlates of Performance</td>
<td>27</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>32</td>
</tr>
<tr>
<td>A. Learning Phase Results</td>
<td>32</td>
</tr>
<tr>
<td>B. Retention Phase Results</td>
<td>33</td>
</tr>
<tr>
<td>C. Clinical Correlates</td>
<td>34</td>
</tr>
<tr>
<td>D. Implications for Wanting and Liking</td>
<td>36</td>
</tr>
<tr>
<td>E. Limitations</td>
<td>36</td>
</tr>
<tr>
<td>F. Future Directions</td>
<td>37</td>
</tr>
<tr>
<td>CITED LITERATURE</td>
<td>38</td>
</tr>
<tr>
<td>IRB APPROVAL</td>
<td>43</td>
</tr>
<tr>
<td>VITA</td>
<td>46</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS</td>
<td>17</td>
</tr>
<tr>
<td>II. INTERCORRELATIONS OF CLINICAL AND PERFORMANCE VARIABLES</td>
<td>29</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>DESCRIPTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Learning phase discrimination</td>
<td>18</td>
</tr>
<tr>
<td>2.</td>
<td>Learning phase bias</td>
<td>19</td>
</tr>
<tr>
<td>3.</td>
<td>Learning phase accuracy among healthy participants</td>
<td>20</td>
</tr>
<tr>
<td>4.</td>
<td>Learning phase accuracy among schizophrenia participants</td>
<td>21</td>
</tr>
<tr>
<td>5.</td>
<td>Comparison of response bias during the learning and retention phases</td>
<td>24</td>
</tr>
<tr>
<td>6.</td>
<td>Comparison of accuracy during the learning and retention phases</td>
<td>25</td>
</tr>
<tr>
<td>7.</td>
<td>Comparison of reaction time during the learning and retention phases</td>
<td>26</td>
</tr>
<tr>
<td>8.</td>
<td>Relationship between PANSS positive symptoms and improved response bias</td>
<td>30</td>
</tr>
<tr>
<td>9.</td>
<td>Relationship between HQLS quality of life and improved response bias</td>
<td>31</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
<td></td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition</td>
<td></td>
</tr>
<tr>
<td>GPe</td>
<td>External Globus Pallidus</td>
<td></td>
</tr>
<tr>
<td>GPI</td>
<td>Internal Globus Pallidus</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>Healthy Participants</td>
<td></td>
</tr>
<tr>
<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
<td></td>
</tr>
<tr>
<td>HQLS</td>
<td>Heinrich’s Quality of Life Scale</td>
<td></td>
</tr>
<tr>
<td>LTD</td>
<td>Long Term Depression</td>
<td></td>
</tr>
<tr>
<td>LTP</td>
<td>Long Term Potentiation</td>
<td></td>
</tr>
<tr>
<td>ms</td>
<td>Milliseconds</td>
<td></td>
</tr>
<tr>
<td>OFC</td>
<td>Orbital Prefrontal Cortex</td>
<td></td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>Reaction Time</td>
<td></td>
</tr>
<tr>
<td>SZ</td>
<td>Schizophrenia Participants</td>
<td></td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
<td></td>
</tr>
<tr>
<td>WRAT</td>
<td>Wide Range Achievement Test</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

The present study examined the relationship between associative reward learning and approach related deficits (i.e., anhedonia and goal-directed behavior) in 22 individuals with schizophrenia (SZ) and 25 healthy individuals (HC). Participants completed a signal detection task (Pizzagalli et al., 2005) designed to measure acquisition and retention of implicit reward contingencies.

SZ and HC demonstrated similar acquisition of reward contingencies during the learning phase, reflective of intact basal ganglia driven learning. SZ with higher indices of goal-directed behavior evidenced greater improvements in learning during this phase.

Both SZ and HC retained reward contingencies over a 24-hour period however, only HC flexibly adapted their behavior in the absence of continued reinforcement, which is believed to relate to orbital frontal cortex function. Results suggest that the capacity to learn from experience and to modulate behavior to receive rewards is directly related to successful pursuit of goal directed activities.
I. INTRODUCTION

A. **Background**

Negative symptom deficits have long been recognized as core defining features of schizophrenia due largely to the significant impact they have on the course and outcome of the illness (Herbener & Harrow, 2004). While psychotic symptoms (i.e., delusions, hallucinations) tend to be episodic and relatively responsive to medication, negative symptoms are thought to predate overt psychosis by several years (Cannon et al., 2002; Kwapis, 1998; Niendam, Jalbrzikowski, & Bearden, 2009), are considered difficult to treat, and may be familial in nature (Schurhoff et al., 2003). Of these symptoms, deficits in motivational drive and hedonic capacity are thought to play a crucial role in social engagement and functional outcome (Foussias & Remington, 2010; Horan, Kring, & Blanchard, 2006), making them critical targets for clinical intervention and translational research.

Efforts to understand the nature of hedonic and motivational deficits in schizophrenia have yielded promising albeit inconsistent results as assessment and operational definition of symptoms alone can result in differing levels of impairment. According to the current *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM–IV–TR*; American Psychiatric Association, 2000), anhedonia is characterized as diminished enjoyment and interest in pleasant experiences. However, a recent review of assessment techniques (see Horan et al., 2006) suggests that distinctions between internal states of lowered hedonic experience (i.e., subjective reports of pleasure) and behavioral manifestations resulting from anhedonic states (e.g., failure to pursue pleasurable experiences) are critical. Similarly, avolition has been characterized by reductions in internal drive and overt behaviors such as goal-driven behavior (Blanchard, Kring, Horan, & Gur, 2010). Observational reports from caregivers and clinicians are thought to be biased by the presence of other negative symptoms (e.g. affective flattening) and lowered opportunity to engage in pleasurable experiences.
As such, assessment of internal states and related neural mechanisms may be more reflective of underlying pathology.

There is growing consensus that anhedonia and avolition do not result from fundamental impairments in experiencing pleasure. Rather, individuals with schizophrenia (SZ) report intact hedonic capacity for immediate experiences of pleasure and display specific deficits only when anticipating future states of pleasurable affect (Gard, Kring, Gard, Horan, & Green, 2007). Evidence for preservation of normative in-the-moment response has been further supported by self reports of arousal to emotionally valenced stimuli (Herbener, Song, Khine, & Sweeney, 2008), hedonic response to food and film clips (Horan et al., 2006; Waltz et al., 2009), and physiological arousal (Kring & Neale, 1996). Despite these findings, evidence suggests that other components of affective processing are altered in the disorder. Notably, people with schizophrenia have difficulty remembering emotionally salient (Hall, Harris, McKirdy, Johnstone & Lawrie, 2007), and positive stimuli (Herbener, Rosen, Khine, & Sweeney, 2007) material over longer periods. Given that anticipation of future states of pleasure also relies on representational systems, diminished engagement in pleasurable activities may be related to deficits in neural systems responsible for processing and maintaining hedonic information. As such, aberrances in neural reward systems may play a critical role in chronic anhedonia, reduced motivation, and a lack of goal directed activity.

Current conceptualizations of reward processing propose distinct behavioral responses and separable neural processes depending on the nature of the reward. In a model articulated by Berridge and Robinson (2003), reward is thought to involve three processes wherein the individual experiences an initial hedonic response to rewarding stimuli, learns associations between stimuli or behaviors that produce rewards, and as a result, is motivated to pursue rewards in the future. The process underlying immediate hedonic/affective response, termed “liking”, is thought to be analogous to consummatory pleasure (Barch & Dowd, 2010; Berridge & Robinson 2003; Berridge, 2004). Motivation to engage in behaviors that reproduce rewards (or
to seek associated stimuli) is considered “wanting” because the individual is driven to reinstate the initial hedonic experience. However, this state of wanting depends upon successful learning of actions or stimuli that produce rewarding consequences. Integration of hedonic and affective experience into long-term memory, driven by successful learning processes, may potentially explain the connection between states of liking and wanting. If these learning mechanisms are ineffective or impermanent, seemingly intact “liking” responses would be accompanied by attenuated “wanting” responses and lowered pursuit of pleasurable experiences, a pattern found in previous studies (Heerey & Gold, 2007).

Examination of reward learning processes in schizophrenia has resulted in somewhat disparate findings depending on experimental design and task difficulty. While immediate sensitivity to rewarding stimuli appears to be intact, failures to adapt responses to maximize rewards in the long term and in the face of changing demands are consistently found (Gold, Waltz, Prentice, Morris, & Heerey, 2008). For example, impairments in weighing rewards and punishments (Koch et al., 2010), predicting future outcomes (Heerey, Bell-Warren, & Gold, 2008), and reversal learning (Waltz & Gold, 2007), have been found in the context of reward processing deficits. However, the complex mental operations required to perform these tasks require adequate executive functioning which is a cardinal neuropsychological impairment in the disorder. Given this potential confound, tasks employing associative learning with tangible (i.e., monetary) rewards and low cognitive demand (e.g. implicit conditioning and/or low memory load) can provide a more direct and parsimonious approach to assess reward learning. The application of such paradigms has revealed intact associative learning in schizophrenia (e.g., Heerey et al., 2008). However, if individuals with schizophrenia are responsive to reward and are capable of associative learning when cognitive demands are low, what is the exact nature of reward processing deficits? Evidence from behavioral paradigms suggests this learning may be transient as people with schizophrenia are able to acquire stimulus-reward associations during preference conditioning tasks, yet fail to retain associations after a 24 hour retention phase.
(Herbener, 2009). Deficits in the maintenance and implementation of learning may explain why immediate hedonic responses do not translate to motivated behavioral change. Examination of neural components underlying these processes may explain inconsistencies in associative learning and the relationship with negative symptoms.

Associative reward (contingency) learning is dependent on accurate prediction of reward and fluctuations in phasic dopamine release within the basal ganglia and mesolimbic pathways (Schultz, 2002). When rewards are unexpected, phasic bursts of dopamine (DA) in the ventral striatum serve to strengthen behavioral reward contingencies, while unexpected omission of reward results in decreases in phasic DA. These unexpected events in the delivery of reward, known as prediction errors, facilitate associative learning such that cues conferring reward will be selectively strengthened while non-adaptive cues are extinguished over time (Frank, 2005). Results from several reinforcement learning paradigms suggest these neural processes are altered in schizophrenia. For instance, positive prediction errors (unexpected delivery of reward) were associated with hypoactivation in ventral striatal and mesolimbic regions using both primary (Waltz et al., 2009) and secondary rewards (Koch et al., 2010). Similarly, suppression of phasic DA with pharmacological agents (e.g., pramipexole) has been shown to temporarily impair associative reward learning in healthy individuals (Pizzagalli et al., 2008a), while mesolimbic lesions in neonatal rats can result in behavior that is analogous to negative symptoms (Le Pen, Gaudet, Mortas, Mory, & Moreau, 2002). It has been suggested by many that attenuated neural responses are confounded by neuroleptic medications which block D2 receptors in striatal regions; however, hypoactivation of the ventral striatum during reward anticipation has been associated with severity of negative symptoms in unmedicated patients (Juckel et al., 2006a). Similarly, typical classes of antipsychotics (i.e., haloperidol) appear to have a more detrimental effect on neural response than more commonly prescribed atypicals (i.e., olanzapine) (Juckel et al., 2006b). Taken together, these studies suggest a shared
etiology for deficits in reinforcement learning, neural reward systems, and negative symptoms despite the presence of neuroleptic medication.

Another important component of this trial-and-error learning (i.e., contingency learning) involves control of motor responses which are adaptive (vs. non-adaptive) to obtaining desired rewards. Computational modeling of this circuitry suggests that control of motor responses is mediated by dopaminergic signaling between the striatum and basal ganglia through selective responding of DA receptors (Frank, 2005). In this model, cortical efferents to the striatum selectively excite D1 or D2 dopamine receptors which provide inhibitory control over the internal (GPI) and external (GPe) segments of the globus pallidus. In the absence of cortical signaling, the GPi provides inhibitory control over the thalamus, thus preventing unnecessary voluntary movement. When a motor response is required, excitation of D1 receptors (via phasic DA release to the striatum) inhibit the GPi, preventing inhibitory input to the thalamus and allowing excitatory motor signals to be transmitted through the thalamus and onto the cortex. In contrast, decreases in phasic dopamine suppress behavioral responses via D2 receptor stimulation in the striatum. Selective activation of these D2 cells allows for the normal inhibitory control of the GPi on the thalamus to operate, thus preventing execution of motor movements. These complementary D1/D2 cells in the striatum are said to comprise the “direct” and “indirect” pathways of motor signals and are related to adaptive responses to reward as mediated by fluctuations in phasic DA to the striatum. Execution of motor movements via D1 cells in the direct pathway, termed “Go” learning, facilitate responses leading to reward while avoidance of responses carrying low reward value or punishment as mediated by D2 cells in the indirect pathway comprise “No-Go” learning (Frank, 2005; Gold et al., 2008). Deficits found in schizophrenia are restricted to impaired Go responding despite intact No-Go performance (Strauss et al., 2011; Waltz, Frank, Robinson, & Gold, 2007) and are thought to result from high levels of tonic DA in the basal ganglia which dampen phasic DA bursts signaling reward (Waltz, Frank, Wiecki, & Gold, 2011).
Given the pattern of behavioral and neural impairments identified in reward based learning, along with evidence suggesting that memory for emotional information is altered, examining the interaction of these processes may provide additional insight into the nature of hedonic and motivational deficits. The neuroscience literature supports the notion that affective experience, reward processing, and memory may be tied to common neural mechanisms. For instance, ventral striatal activity in healthy controls was associated with enhanced memory for positively valenced images presented as part of a monetary rewards task (Wittman, Schiltz, Boehler, & Düzel, 2008). One potential mechanism underlying successful associative learning involves neural plasticity at corticostriatal synapses. Long term potentiation (LTP) and long term depression (LTD), cellular processes said to selectively strengthen and weaken synaptic connectivity, are thought necessary for memory formation and have been associated with fluctuations in phasic DA at corticostriatal synapses involved in reward learning (Di Filippo, et al., 2009). In support of this, coordinated reactivation between hippocampal and ventral striatal cells have been observed in rats following conditioned place preference (Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009). Abnormalities in these cellular processes may potentially explain poor retention of reward contingencies following associative learning. While accurate identification of such processes will likely require more advanced neuroimaging and neurobiological techniques, the stability of reward learning and associated memory processes in relation to anhedonia and goal directed activity has yet to be fully addressed in behavioral studies.

B. **Purpose**

Given these findings, the present investigation aims to explore associative learning deficits in relation to approach behaviors involved in hedonic and motivational experience. To accomplish this goal, a signal detection task previously studied in SZ (Heerey et al., 2008) and found to be associated with anhedonic deficits in major depression and bipolar disorder (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008; Pizzagalli, Iosifescu, Hallett, Ratner, &
Fava, 2009; Pizzagalli, Jahn, & O’Shea, 2005) will be implemented in a 2 phase trial. Specifically, we will test the hypothesis that the initial acquisition of response contingencies (day 1) will be indistinguishable between SZ and HC. Given that SZ and HC were comparable in acquiring implicit response contingencies with this task previously (Heerey et al., 2008) we expect to obtain similar results. Measures of general task performance (i.e., correct discrimination of stimuli) will be taken to ensure engagement and understanding of the task while measures of response contingency or bias will be indicative of acquisition of reward contingencies. Additional evidence for preferential responding will come from comparisons of accuracy (i.e., percent correct) and automaticity (i.e., reaction time) between the more and less frequently rewarded stimuli; that is, participants will respond more quickly and will be more likely to be correct on the stimuli that is more frequently rewarded. Given that behavior is impacted by reinforcement history, we predict bias and preferential responding to increase from the beginning to the end of the learning phase in both groups.

Testing completed after a 24 hour delay will test the hypothesis that response contingencies will be retained from the learning phase. However, in line with findings that implicit associative learning is diminished in SZ following a 24 hour retention phase (Herbener, 2009), we aim to test the hypothesis that retention of response contingencies is transient in schizophrenia. Drawing from the literature relating performance deficits to impaired sleep cycles in schizophrenia (Manoach et al., 2010), and findings supporting the facilitative effect of sleep on reward based learning in healthy samples (e.g., Fischer et al., 2009; Hsieh, Li, & Tasi, 2010), we expect improvements in response bias and preferential responding to the more frequently rewarded stimulus for HC. We predict SZ will demonstrate declines in these indices following a 24 hour delay despite equivalent performance during the initial learning phase (day 1). Finally, we aim to investigate the relationship between impaired reward learning (e.g., weaker retention of response contingencies over time) and behaviors impacted by approach related deficits including goal directed behavior and self reported anhedonic traits. The
application of a task (Pizzagalli et al., 2005) measuring learning of implicit stimulus-response associations, with low cognitive demand, over a 2 day period will help accomplish these aims. Given the presumed role of the phasic learning system in this task, and the previous application with schizophrenia samples, this paradigm is particularly well suited to study the effects of associative reward learning in schizophrenia.
II. METHOD

A. Participants

Thirty individuals diagnosed with DSM-IV criteria for schizophrenia or schizoaffective disorder (SZ) were recruited at the University of Illinois at Chicago Medical Center, Department of Psychiatry by physician referral and advertisements. In addition, 30 healthy control participants (HC) were recruited through the community with advertisements. All SZ were clinically stable outpatients meeting criteria for schizophrenia or schizoaffective disorder with no recent changes in diagnostic status or medication regimen. All participants were excluded for history of head trauma resulting in loss of conscious, history of neurological injury or impairment, and current substance abuse. HC were screened for lifetime history of Axis I disorder and family history of schizophrenia in first degree relatives and were excluded accordingly. Clinicians blind to individuals’ task performance made diagnoses according to the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002). Participants with an IQ <70 were excluded. Participants with missing or incomplete data were omitted from analyses resulting in a final sample of 22 SZ and 25 HC.

B. Assessments and Measures

Neuropsychological Assessment. The Wechsler Abbreviated Scale of Intelligence, 2 subtest version (WASI) was administered to assess cognitive ability while premorbid IQ was estimated using the Wide Range Achievement Test, Reading Subscale (WRAT-3).

Clinical Symptom Measures. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay, Fiszbein, & Opler, 1987). Depressive symptoms were assessed with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

Measures of Anhedonia. To assess anhedonia participants completed the Physical and Social Anhedonia Scales (Chapman et al., 1976) a true/false self report measure with 2 domains measuring anhedonia towards various pleasurable experiences. Fifty-eight items
related to physical anhedonia assessed attitudes towards sensory experiences, such as smelling bread baking, or watching a sunset. Forty-three items assessing social anhedonia involved experiences with people such as talking, expressing feelings, loving, and various other interactions. Total composite score was a summation of responses from both domains and ranged from 0 - 101 with higher scores indicating greater levels of impairment. An additional 13 items designed to measure untruthful and/or biased responding were assessed as part of a ‘lie’ scale but were not included in the composite score.

**Measures of Goal Directed Activity.** The Heinrich’s Quality of Life Scale (HQLS) was used to assess pursuit of occupational and recreational activities, functional outcome, interpersonal relationships, intrapsychic factors, and participation in activities required for daily living in the SZ sample (Heinrichs, Hanlon, & Carpenter, 1984). The intrapsychic subscale reflects aspects of cognition and affectivity often impaired in the disorder (i.e., sense of purpose, motivation, curiosity, empathy, hedonic capacity, time utilization, and emotional engagement).

**Implicit Reward Task.** To study implicit reward conditioning, a signal detection task designed by Pizzagalli et al. (2005) was implemented. Participants were tested over the course of 2 days to assess retention of learning. Study day 1 was the learning phase of the task. Participants were told they would be playing a game for monetary rewards (5 cent reward per correct response) and to maximize their winnings. Participants were not informed of the response contingency for correct responses, nor were they informed they would repeating this particular task the following day. Upon completion, participants were paid for the monetary bonus they earned. After a 24 hour retention phase, participants returned for day 2 of testing (retention phase) and completed a brief form of the task to assess retention of response contingencies. Participants did not receive monetary rewards in this phase.

The learning phase was comprised of 240 trials (3 blocks of 80 trials). Stimuli were presented on a 19” PC desktop computer using Eprime software (version 2.0; Psychology Software Tools, Inc, Pittsburgh, Pennsylvania). Participants were first exposed to a fixation
point in the center of the screen for 500ms. Next, a mouthless face was presented for 500ms and participants were instructed to view this face but to not make any button response. Next, a face with a long (13 mm) or short (11.5 mm) mouth was presented for 100ms. Mouth type was distinguished by the length of the line depicting the mouth. Participants were instructed to make a judgment about which type of mouth the face had (V key for long mouth and M key for short mouth; this was counterbalanced across participants and remained stable throughout the task). Participants were informed that not all correct responses were rewarded; as such, participants were rewarded for 40 correct trials each block with a brief written message (“Correct!! You won 5 cents”) which was displayed for 1750 ms following the correct response. Incorrect responses were not indicated to participants. The number of short and long mouths was presented an equal number of times for each block. An asymmetrical reinforcement ratio was implemented (correct responses to the long or short mouths were differentially reinforced) to create a response bias to one of the 2 types of stimuli. Reinforcement to long vs. short mouth was randomized across subjects for the learning phase. For half of the participants, correct identification of the long mouth was associated with 3 times (60 of 80 trials) more positive feedback than correct identification of the short mouth (20 of 80 trials); for the remaining participants, reward contingencies were reversed such that correct identification of the short mouth were associated with more frequent rewards. This resulted in 75% of the more frequently rewarded (“rich”) stimuli being rewarded while 25% of less frequently rewarded (“lean”) stimuli receiving rewards. Rewarded trials were pseudo-randomized such that no more than 3 correct trials in a row were rewarded. If a trial with a scheduled reward received an incorrect response, the reward was delayed until the next correct identification of the same stimulus (Pizzagalli et al., 2005). The maximum monetary reward for the entire learning phase was $6. Each 80 trial block was followed by a 10 second break.

Participants completed a similar task intended to measure the retention of response bias after a 24 hour delay. Because this portion of testing was designed to measure retention of
response contingencies (bias), feedback for correct trials was eliminated. Stimuli presentation was identical to the learning phase; however testing consisted of 1 block with 80 trials, lasting approximately 5 minutes. Participants were informed they would not receive monetary rewards for their performance.

C. **Data Collection and Reduction**

General task performance was analyzed for accuracy (percent correct) and reaction time for each condition type (i.e., rich & lean) however these measures were not of primary interest to the hypotheses. To measure differences in the acquisition and maintenance of response contingencies, biased responding to the more frequently rewarded (rich) stimulus was calculated according to signal detection theory (Tripp & Alsop, 1999) which estimates the probability of selecting the rich (i.e., the more frequently rewarded stimuli) when uncertain. According to this model, discriminability (d’) estimates ability to perceptually discriminate between stimuli and is thus a measure of general task performance. It is defined as:

\[
\log d = \frac{1}{2} \log \left( \frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{correct}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{incorrect}}} \right)
\]

where Rich\text{correct} and Lean\text{correct} are the proportion of correct responses to each type of stimuli.

Calculations of response bias (b’) estimate acquisition of response contingencies:

\[
\log b = \frac{1}{2} \log \left( \frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{incorrect}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{correct}}} \right)
\]

where rich and lean are determined by the type of stimuli (i.e., long vs. short) that is more frequently rewarded for individual participants. High response bias (b’) results when the proportion of correct identification of the rich stimulus and the proportion of incorrect responses to the lean stimulus (e.g., choosing ‘rich’ to a ‘lean’ stimulus) are both high.

Reaction time (RT) was analyzed with respect to condition type to assess response related speeding to the more frequently rewarded stimuli. Trials with reaction times ≤ 150 ms and ≥ 2500 ms, were excluded as these are considered outside the normal response range for this task (Pizzagalli et al., 2005). The mean RT for individual participants was calculated and trials exceeding ± 3 SD following logarithmic transformation were excluded from analyses.
Participants missing 10% or more of trials due to response times outside of the normal response range were excluded from analyses. This resulted in a final sample of 22 individuals with schizophrenia and 25 healthy controls.

D. **Statistical Analyses**

To test for group differences in sociodemographic variables, One-way ANOVAs were conducted for age, years of education, premorbid IQ and current IQ. To determine group differences in self reported levels of anhedonic symptoms, One-way ANOVAs were conducted for both domains of the Physical and Social Anhedonia Scales and for a composite of these domains (total score).

To determine if premorbid IQ (WRAT-3 Reading) and current IQ (WASI) impacted performance, bivariate correlations were conducted for each performance measure (discriminability, response bias, bias change scores, accuracy, and RT). If statistically significant correlations between IQ and performance were found, IQ was included as a covariate in subsequent ANOVAs.

Repeated measures analyses of variance (ANOVA) were conducted for discriminability ($d'$), bias ($b'$), bias change scores ($\Delta b'$), accuracy (percentage of correct responses), and RT. In each analysis, diagnostic group (SZ, HC) was the between-subjects factor and Condition (rich, lean) and/or Block (1, 2, 3) were within-subjects factors. The Greenhouse-Geisser correction was used when applicable.

To determine if response bias and patterns of preferential responding were maintained over the 24 hour retention phase, performance measured at the end of the learning phase (block 3) was compared to performance during the 80 trials of the retention phase using a series of repeated measures ANOVAs with Phase as the within-subjects factor and Group as the between-subjects factor.

Finally, to determine if severity of hedonic capacity is related to impairments in reward learning in both groups, correlational analyses were conducted with Chapman scores and
performance measures (e.g., accuracy, response bias, and discriminability). To determine if clinical symptoms (i.e., PANSS, HDRS) and level of functioning (HQLS) impacted performance within the SZ sample, correlational analyses were conducted with all performance measures.
III. Results

A. Demographic Characteristics

Participants did not significantly differ in age, education, premorbid or current IQ, total anhedonia, social anhedonia, or physical anhedonia (see Table I).

B. Learning Phase

IQ was correlated with discriminability and accuracy during the retention phase in both groups, and thus were included as covariates in analyses for these variables.

Discriminability ($d'$). Groups did not differ in their ability to perceptually discriminate between stimuli, $F (1, 44) = .73, \text{ ns}, \eta^2 = .02$. Similar results were obtained when IQ was included as a covariate (see Figure 1).

Response Bias ($b'$). As predicted, groups did not differ in their acquisition of response bias developed during the learning phase, $F (1, 44) = .75, \text{ ns}, \eta^2 = .02$. Both groups increased their response bias from the beginning to the end of the task, $F (2, 88) = 5.93, p < .005, \eta^2 = .12$ (see Figure 2).

Bias change scores ($\Delta b'$). To test if groups differed in the magnitude of response bias change, difference scores between blocks of the learning phase were calculated and entered in a Group x Phase (block 3-1, block 2-1, block 3-2) ANOVA. Groups did not differ in their magnitude of response bias change, $F (1, 44) = .27, \text{ ns}, \eta^2 = .01$, and change among the 3 phases, $F (2, 88) = 1.62, \text{ ns}, \eta^2 = .04$, was not different.

Accuracy. Initial analyses indicated, as hypothesized, that participants were more accurate in response to rich than lean trials, $F (1, 45) = 13.19, p < .005, \eta^2 = .23$; however, a Block x Condition interaction, $F (2, 90) = 3.35, p < .05, \eta^2 = .07$, indicated this was not present until the second block. SZ and HC participants did not differ, $F (1, 45) = .34, \text{ ns}, \eta^2 = .01$. When IQ was included as a covariate, the difference in accuracy for rich and lean trials was no longer significant.
**Supplementary Analyses: Accuracy.** Exploratory analyses were conducted to determine if groups differed in their speed of learning. Accuracy was calculated in 40 trial increments and examined within each group. For HC, accuracy for rich stimuli was higher than lean stimuli after 80 trials of the learning phase, $F(1, 24) = 6.41, p < .05, \eta^2 = .23$ (see Figure 3), while SZ did not evidence this pattern until the latter half of the task (after 160 trials) (see Figure 4). Thus, both groups evidenced preferential responding however schizophrenia participants were slower in developing this pattern of response. When IQ was included as a covariate, the difference in accuracy for rich and lean trials was no longer significant.

**Reaction Time.** Consistent with hypotheses, all participants were quicker to respond to rich than lean trials, $F(1, 44) = 12.64, p < .005, \eta^2 = .22$.

**Summary of Learning Phase Results.** Groups did not differ on any of the test variables during the learning phase. In addition, data for both groups indicated the expected response biases to rich and lean stimuli. However supplementary analysis indicated schizophrenia participants were slower to develop patterns of preferential responding to the stimuli.
**TABLE I.**

DEMOGRAPHIC CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SZ (n = 22)</th>
<th></th>
<th>HC (n = 25)</th>
<th></th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.36</td>
<td>11.83</td>
<td>34.84</td>
<td>12.64</td>
<td>ns</td>
</tr>
<tr>
<td>Premorbid Intelligence</td>
<td>97.45</td>
<td>9.95</td>
<td>95.32</td>
<td>11.33</td>
<td>ns</td>
</tr>
<tr>
<td>IQ (WASI)</td>
<td>102.5</td>
<td>13.34</td>
<td>100.1</td>
<td>12.94</td>
<td>ns</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.91</td>
<td>3.28</td>
<td>13.40</td>
<td>1.53</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td></td>
<td>50%</td>
<td></td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Social Anhedonia</td>
<td>10.86</td>
<td>7.19</td>
<td>8.84</td>
<td>4.35</td>
<td></td>
</tr>
<tr>
<td>Physical Anhedonia</td>
<td>16.32</td>
<td>9.26</td>
<td>14.80</td>
<td>6.67</td>
<td>ns</td>
</tr>
<tr>
<td>Total Anhedonia</td>
<td>27.18</td>
<td>14.76</td>
<td>23.64</td>
<td>9.40</td>
<td>ns</td>
</tr>
<tr>
<td>Antipsychotic Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Typical</td>
<td></td>
<td>9.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Atypical</td>
<td></td>
<td>68.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDRS</td>
<td>10.62</td>
<td>7.88</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18.14</td>
<td>4.79</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Negative</td>
<td>18.95</td>
<td>6.12</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>General</td>
<td>40.33</td>
<td>6.64</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Total</td>
<td>77.43</td>
<td>14.57</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>HQLS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpersonal Relations</td>
<td>22.86</td>
<td>16.40</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Instrumental Role</td>
<td>15.67</td>
<td>4.45</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Intrapsychic Foundations</td>
<td>22.14</td>
<td>7.11</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Common Objects &amp; Activities</td>
<td>9.00</td>
<td>4.89</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Total</td>
<td>66.29</td>
<td>18.67</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

HDRS = Hamilton Depression Rating Inventory.

HQLS = Heinrich’s Quality of Life Scale.

PANSS = Positive and Negative Assessment Scale for Schizophrenia.
Figure 1. Mean discriminability (log d') during the learning phase (blocks 1-3) as seen by schizophrenia and healthy participants. Error bars depict standard error.
Figure 2. Mean bias (log b') during the learning phase (blocks 1-3) as seen by schizophrenia and healthy participants. Error bars depict standard error.
Figure 3. Mean accuracy for rich and lean stimuli during the learning phase (40 trial increments) as seen by healthy participants. Error bars depict standard error.
Figure 4. Mean accuracy for rich and lean stimuli during the learning phase (40 trial increments) as seen by schizophrenia participants. Error bars depict standard error.
C. **Relationship between Learning and Retention Performance**

**Discriminability.** Participants had lower discriminability scores at the end of the learning phase compared to discrimination during each of the four blocks of the retention phase (all $p's < .005$). This difference was not found when indices of IQ were included as covariates. In all analyses, discriminability did not differ between groups.

**Response Bias ($b'$).** Analyses revealed that bias during the 1st block of the retention phase, $F(1, 45) = .14$, $ns$, $\eta^2 = 0$, was not significantly lower than performance at the end of the learning phase. In contrast, response bias during the 2nd, $F(1, 45) = 4.56$, $p < .05$, $\eta^2 = .09$, 3rd, $F(1, 45) = 10.52$, $p < .005$, $\eta^2 = .19$, and 4th blocks of the retention phase, $F(1, 45) = 7.00$, $p < .05$, $\eta^2 = .14$, were significantly lower than bias during the learning phase.

Groups were analyzed separately to determine if bias retention was different between schizophrenia and healthy participants. As shown in Figure 5, HC and SZ demonstrated response bias scores at the end of the learning phase that did not significantly differ from bias during the 1st block of the retention phase. However, for healthy participants bias scores during the 3rd and 4th blocks of retention phase were significantly lower than the learning phase ($p's < .01$), and, in addition, indicated a reversal in the response bias. This is consistent with a gradual extinction of the response bias in the absence of continued reinforcement. In contrast, although schizophrenia participants demonstrated a significant response bias at the end of the learning phase and a trend for a reduced bias in the 2nd block of the retention phase, $F(1, 21) = 3.96$, $p = .06$, $\eta^2 = .16$, their bias during the 3rd-4th blocks did not significantly differ from the end of the learning phase. When IQ was included as a covariate, differences in bias between phases of testing were not found.

**Accuracy.** Participants had significantly higher accuracy for rich than lean stimuli at the end of the learning phase, $F(1, 45) = 21.03$, $p < .001$, $\eta^2 = .32$, while accuracy to rich and lean stimuli did not differ during the retention phase, $F(1, 45) = 14$, $ns$, $\eta^2 = 0$, (Phase x
Condition interaction, $F(1, 45) = 15.78, p < .001, \eta^2 = .26$) (see Figure 6). Exploratory analyses confirmed that accuracy for rich and lean trials did not differ in any of the 4 blocks of the retention phase. When cognitive ability measures were included as covariates, effects of condition and phase were not found.

**Reaction Time (RT).** Reaction time did not differ between the two phases of testing, $F(1, 46) = .01, ns, \eta^2 = 0$, or between the Groups, $F(1, 46) = .46, ns, \eta^2 = .01$ (see Figure 7). Exploratory analyses revealed that reaction times were significantly quicker for rich than lean trials in both groups, but only in the 1st block of the retention phase trials, $F(1, 45) = 6.16, p < .05, \eta^2 = .12$.

**Summary of Retention Performance.** Performance during the retention phase was characterized by improvements in discriminability and accuracy. Groups evidenced differences in retention of response bias. Healthy controls demonstrated a gradual extinction of response bias in the latter half of the retention phase while schizophrenia participants failed to adapt their responses. For both groups, patterns of preferential responding evidenced during the learning phase (i.e., faster and more accurate responses to rich stimuli) were not found during the retention phase.
Figure 5. Mean response bias (log b’) at the end of the learning phase (block 3) and bias during each block (20 trials each) of the retention phase for healthy and schizophrenia participants. Error bars depict standard error.
Figure 6. Mean accuracy for rich and lean stimuli at the end of the learning phase (block 3), and the first and last 40 trials of the retention phase for schizophrenia and healthy participants. Error bars depict standard error.
Figure 7. Mean reaction time for rich and lean stimuli at the end of the learning phase (block 3), and the first and second blocks of the retention phase for schizophrenia and healthy participants. Error bars depict standard error.
D. **Clinical Correlates of Performance**

To determine if cognitive ability, trait anhedonia, and symptom severity was associated with task performance, a series of bivariate correlations were conducted within each diagnostic group. Performance variables included total measures of discrimination, response bias, total accuracy and reaction time during the learning and retention phases.

**Cognitive Ability.** IQ was positively correlated with total accuracy, $r (47) = .34, p < .05$, and discriminability, $r (47) = .37, p < .05$, during the retention phase.

**Anhedonia.** Higher levels of physical anhedonia were negatively correlated with RT during the learning phase at trend, $r (21) = -.42, p = .05$, among schizophrenia participants. Higher levels of social, $r (25) = -.39, p = .05$, and total anhedonia, $r (25) = -.38, p = .06$, were negatively correlated with discriminability during the retention phase among healthy participants.

**PANSS.** PANSS positive scores were associated with smaller improvements in bias from the beginning to the end of the learning phase, $r (21) = -.58, p < .05$, (see Figure 8), and with lower accuracy during the retention phase, $r (21) = -.53, p < .05$ (see Table II). PANSS general and total scores were associated with lower accuracy during the learning phase, $r (21) = -.45, p < .05$, $r (21) = -.42, p = .06$. Additionally, PANSS general and total scores were associated with lower accuracy during the retention phase (for all correlations, $r (21) = -.50$ to $-.52, p < .05$).

**Goal Directed Behavior.** In schizophrenia participants, higher total, interpersonal, instrumental, and intrapsychic functioning on the HQLS were associated with larger improvements in bias from the beginning to the end of the learning phase (for all correlations, $r (21) = .46$ to $.60, p < .05$) (see Figure 9). Additionally, higher total and interpersonal functioning on the HQLS were associated with higher accuracy during the retention phase, (for all correlations, $r (21) = .45$ to $.59, p < .05$).

Because the intrapsychic subscale reflects aspects of both goal directed activity and...
hedonic capacity, correlations between individual items on the subscale and performance measures were conducted. Higher motivation was associated with larger improvements in bias from the 1st to 2nd blocks of the learning phase, $r(21) = .50, p < .05$. Better time utilization (i.e. less time spent in aimless inactivity) was associated with larger improvements in bias from the beginning to the end of the learning phase, $r(21) = .45, p < .05$. Higher empathy scores were associated with higher accuracy during the learning, $r(21) = .47, p < .05$, and retention phases, $r(21) = .61, p < .01$. Sense of purpose, curiosity, anhedonia, and emotional engagement with the interviewer were not associated with any performance variables.

Thus, more severe levels of psychopathology were associated with general performance deficits while indices of goal directed activity had a unique relationship with the development of response bias. Contrary to predictions, anhedonia was not consistently correlated with measures of reward acquisition or retention in either group.
Table II.

**Intercorrelations of Clinical and Performance Variables**

<table>
<thead>
<tr>
<th></th>
<th>Learning Phase</th>
<th></th>
<th>Retention Phase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Accuracy</td>
<td>Total d'</td>
<td>Bias3</td>
<td>Bias31</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>-.34</td>
<td>-.27</td>
<td>0.04</td>
<td>.00</td>
</tr>
<tr>
<td>HQLS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpersonal</td>
<td>.33</td>
<td>.23</td>
<td>.52*</td>
<td>.51*</td>
</tr>
<tr>
<td>Instrumental</td>
<td>.11</td>
<td>.01</td>
<td>.24</td>
<td>.54*</td>
</tr>
<tr>
<td>Intrapsychic</td>
<td>.13</td>
<td>.02</td>
<td>.42</td>
<td>.46*</td>
</tr>
<tr>
<td>Total</td>
<td>.28</td>
<td>.14</td>
<td>.54*</td>
<td>.60**</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>-.31</td>
<td>-.19</td>
<td>-.40</td>
<td>-.48*</td>
</tr>
<tr>
<td>Negative</td>
<td>-.26</td>
<td>-.18</td>
<td>-.05</td>
<td>-.16</td>
</tr>
<tr>
<td>General</td>
<td>-.45*</td>
<td>-.35</td>
<td>-.08</td>
<td>-.27</td>
</tr>
<tr>
<td>Total</td>
<td>-.42</td>
<td>-.30</td>
<td>-.19</td>
<td>-.35</td>
</tr>
</tbody>
</table>

*Note.* Anhedonia = total score from the Physical and Social Anhedonia Scales; Total d' = total discriminability; bias3 = bias achieved at the end of the learning phase, Bias31 = improvement in response bias during the learning phase (block3 – block 1); Bias32 = (block3 – block 2); Retain b' 1-40 = response bias during the first 40 trials of the retention phase; Retain 41-80 b' = response bias during the last 40 trials of the retention phase. *p < .05, **p < .01.
Figure 8. Scatter plot depicting relationship between PANSS Positive Symptoms and improvement in response bias during the learning phase for schizophrenia participants.
Figure 9. Scatter plot depicting relationship between total quality of life (HQLS) and improvement in response bias during the learning phase for schizophrenia participants.
IV. Discussion

This study is the first to examine the long-term retention of response contingencies using a signal detection paradigm in individuals with schizophrenia. Consistent with hypotheses, initial acquisition of response contingencies was quite similar among schizophrenia and control participants. After a 24 hour delay, all groups retained response bias scores equivalent to those acquired at the end of the learning phase; however, only healthy individuals adapted their responses in the absence of reward. Predictions regarding the clinical correlates of performance in schizophrenia participants were partially supported. Indices of goal directed activity were related to the acquisition of response contingencies, while anhedonia was not related to reward acquisition or retention in either group. Implications and limitations of these findings are addressed below.

A. Learning Phase Results

During the learning phase, groups did not differ in general task performance (i.e., discriminability) or in the development of a response bias. These results are consistent with similar studies comparing implicit reinforcement learning among schizophrenia and healthy individuals (Heerey et al. 2008, Herbener, 2009). Thus, individuals with schizophrenia demonstrate intact sensitivity to reward contingencies and can effectively modulate behavior to maximize rewards when cognitive demands are low. Generally, SZ show intact performance on tasks with 1-2 stimuli contingencies (Murray et al., 2008; Somlai, Moustafa, Kéri, Myers, & Gluck, 2011; Weickert et al., 2002; Weickert et al., 2009), that are acquired implicitly and gradually (Gold, Hahn, Strauss, & Waltz, 2009), as was true of paradigm in the present study. These results add to the body of literature showing spared associative reward learning in the disorder.

Also evident were patterns of preferential response. Performance among both groups was characterized by faster and more accurate responses to the more frequently rewarded stimulus. Reinforcement related speeding in probabilistic tasks has been reported
elsewhere (Murray et al., 2008; O’Doherty, 2004; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006) and is often used as an index of successful acquisition of contingencies. Both groups also demonstrated a robust pattern of differential accuracy; however, results from supplementary analyses suggest this preferential responding develops more slowly in schizophrenia. Studies of procedural learning also show that people with schizophrenia evidence slower rates of learning than healthy individuals (Weiler, Bellebaum, Brüne, Juckel, & Daum, 2009).

B. **Retention Phase Results**

We did not find evidence for a specific impairment in the retention of response bias in schizophrenia. Additionally, healthy individuals did not show a strengthening of response bias after the 24 hour retention phase. Rather, all participants successfully encoded response contingencies into long-term memory which were present during the initial portions of the retention phase. This is inconsistent with previous studies (i.e., Herbener, 2009) showing schizophrenia participants fail to retain implicitly learned contingencies following a 24 hour delay period. However this previous study implemented a Pavlovian conditioning paradigm wherein stimuli, rather than behavioral responses, were associated with rewards. In contrast, the present paradigm employed operant/instrumental conditioning and behavior (i.e., button presses) was directly tied to monetary outcomes. Therefore, it is likely that increased behavioral engagement and an implicit understanding that behavior impacts reward delivery improved retention of response contingencies. Given that schizophrenia participants required more time to develop preferential responding (i.e., higher rates of accuracy to rich stimuli) during the learning phase, it is also possible that participants required extended training to achieve stable gains in learning.

During the latter half of the task, groups evidenced differences in their retention of response bias. Healthy controls demonstrated a gradual extinction of response bias that is consistent with a lack of reward delivered during this phase. Results suggest that
participants shifted from an automatic style of response (facilitated by learned response contingencies) to a more careful approach, evidenced by improved accuracy to both rich and lean stimuli. In contrast, schizophrenia participants failed to adapt their responses during the retention phase. Other studies have similarly found that while SZ are able to gradually acquire response contingencies, they are unable to modify their responses when contingencies are reversed (Waltz & Gold, 2007), and show impairments in trial-to-trial adjustments (Gold et al., 2008; Koch et al., 2010; Waltz et al., 2011). Such deficits have been linked to the orbital prefrontal cortex (OFC) which is thought critical to updating reinforcement contingencies and reward value over time (Frank & Claus, 2006). Specially, the OFC is thought to exert top-down control of regions involved in instrumental learning (i.e. the basal ganglia) when weighing losses and gains or changing strategy. Results of computational modeling (i.e., Frank & Claus, 2006) and animal studies (Reekie, Braesicke, Man, & Roberts, 2008), suggest that habitual responding to devalued stimuli are related to OFC dysfunction. It has also been demonstrated that individuals with high levels of negative symptoms are over-reliant on learning from basal ganglia driven prediction errors rather than using on-line representations of value facilitated by the OFC to maximize rewards (Gold et al., 2012). Consistent with this, the present study suggests intact basal ganglia driven learning with specific impairments in the ability to flexibly adapt behavior.

C. **Clinical Correlates**

Hypotheses regarding the relationship between approach related deficits and reward learning were partially supported. Specially, severity of trait anhedonia was not associated with reward retention in either group. This may be attributable to the use of a measure which confounds hedonic capacity, motivational processes, and attitudes towards pleasurable experiences (Treadway & Zald, 2011). Additionally, distinctions between anticipatory and consummatory pleasure are not made. Therefore it is possible we did not find any associations because the Chapman elicits explicit representations of hedonic
experience (e.g., memory for previous experiences of pleasure, affective forecasting, attitudes about experiences) while the reward paradigm reflects implicit aspects of hedonic experience which may reflect distinct cognitive mechanisms.

While goal directed activity was not related to reward retention, it was strongly associated with the ability to acquire response contingencies. Schizophrenia participants with greater engagement in goal directed activities (i.e., instrumental and interpersonal activities), better intrapsychic functioning, and better global functional outcome, evidenced larger improvements in bias from the beginning to the end of the learning phase. This is consistent with associations found between psychosocial functioning and learning on a probabilistic classification task in schizophrenia (Somali et al., 2011). While it could be argued that better functional outcome relates to general improvements in performance (evidenced by correlations with accuracy), we found specific associations between approach behavior and acquisition of response contingencies. Specifically, individuals with high levels of motivation and low levels of aimless inactivity evidenced greater improvement in response during the learning phase. Taken together, this suggests that the capacity to learn from experience and modulate behavior to receive rewards is directly related to successful pursuit of goal directed activities.

We also found that PANSS positive symptoms were associated with smaller improvements in bias from the beginning to the end of the learning phase. While this was not central to hypotheses, associations between psychotic symptoms and abnormal ventral striatal response during rewarding learning have also been identified in first episode patients (i.e., Murray et al., 2008), which is consistent with the notion that psychotic symptoms stem from a misattribution of salience to benign stimuli (Kapur, 2003). It is unclear if our data support this notion however, future studies may benefit from examining potential dissociations between positive and negative symptoms in relation to reward learning deficits.
D. **Implications for Liking and Wanting**

As suggested elsewhere (e.g., Barch & Dowd, 2010; Foussias & Remington, 2010; Gard et al., 2007), anhedonic traits do not appear related to deficits in the immediate experience of pleasure (i.e., “liking”). Rather, reductions in approach related behavior stem from difficulties translating hedonic and motivational drives into goal-driven behavior. Data from this paradigm suggest that impairments in “wanting” are not related to difficulties retaining behavioral reward contingencies. Instead, the disorder can be characterized in part by difficulties effectively modulating behavior to obtain rewards.

We also found that successful acquisition of response contingencies was related to approach behaviors including motivation and success in goal directed behaviors (e.g., social and occupational pursuits). This suggests that instrumental reward learning may index an ability contributing to functional performance, or the ability to take action to pursue goals, rather than internal states such as liking.

E. **Limitations**

Of primary concern is the association of task performance with general cognitive ability. Current and premorbid IQ was negatively correlated with discrimination and accuracy on both days of testing. When learning phase analyses were repeated with cognitive measures entered as covariates, patterns of preferential responding including the development of response bias were no longer significant. Heerey et al. (2008) reported a similar relationship between working memory and discriminability on this paradigm. This suggests performance on this task is highly related to general cognitive ability.

Another issue is that the ability to determine rate of learning was limited by the experimental task and data analyses. While changes in bias and preferential responding over the three blocks of learning phase provided some insight into learning rate, we could not evaluate trial-to-trial adjustments in performance.
F. **Future Directions**

Future efforts to understand and treat negative symptoms will benefit from greater consensus in defining hedonic and motivational deficits and identifying their underlying cognitive and neural substrates. While results are supportive of previous distinctions between hedonic and motivational drives (e.g., Barch & Dowd, 2010), further examination of cognitive and affective processes underlying goal-driven behavior is needed. Given the complex nature of goal-driven behavior, it will be useful to understand how individual difference variables and environmental constraints impact hedonic and motivational pursuits. Additionally, research which examines goals that are personally relevant and ecologically valid may have the greatest capacity to inform clinical intervention strategies.
CITED LITERATURE


March 9, 2011

Ellen S. Herbener, PhD
Psychiatry
912 S. Wood St.
136 N.P.I.-S, M/C 913
Chicago, IL 60612
Phone: (312) 413-2638 / Fax: (312) 413-4122

RE: Protocol # 2004-0785
“Affective Systems and Deficits in Individuals with Psychopathology and Controls”

Dear Dr. Herbener:

Your Continuing Review submission was reviewed and approved by members of IRB #1 under the Expedited review process on February 11, 2011. You may now continue your research.

Please note the following information about your approved research protocol:

**Protocol Approval Period:** March 11, 2011 - March 9, 2012

**Approved Subject Enrollment #:** 250 – 122 enrolled to date

**Performance Sites:**
- UIC, University of Maryland
- a) National Institute of Mental Health;
- b) National Institute of Mental Health

**PAF#:**
- a) 2003-04409
- b) 2006-06459

**Grant/Contract No:**
- a) 1 K23 MH067223
- b) Not available (subcontract)

**Grant/Contract Title:**
- a) Affective Deficits in Schizophrenia
- b) Clinical and Computational Studies of Dopamine Function in Schizophrenia

**Research Protocol:**
- a) Investigator Protocol: Affective systems and deficits in individuals with psychopathology and controls, Version #6, 11/28/2010

**Recruitment Materials:**
- a) UIC Telephone Script, Affective systems and deficits, Version #2, 01/06/2006
- b) E-mail notice: "We are currently recruiting...", Affective systems and deficits, Web Ad HC, Version #5, 05/06/2010
c) Recruitment, Student Version 1 10/18/2010

d) Screening, Student Version 1 10/18/2010

e) Debrief Student Version 1 10/18/2010

f) Recruitment Pamphlet: Patient Participants Needed for Medical Research Study, Version #4, 05/06/2010

g) Affective systems and deficits, Web Ad PT, Version #4, 02/01/2011

**Informed Consents:**

a) Affective Systems and deficits-version 2 student, 11/28/2010

b) UIC Adult Consent: Affective systems and deficits, version 15, 11/28/2010

**HIPAA Authorization:**

a) "Affective Systems and Deficits in Individuals with Psychopathology and Controls: Authorization", Version #1, 01/26/2007

(Please continue to use the current Authorization form, approved and stamped February 21, 2007.)

**Additional Determinations for Research Involving Minors:**

The Board determined that this research satisfies 45 CFR 46.404, research not involving greater than minimal risk. Therefore, in accordance with 45 CFR 46.408, the IRB determined that only one parent's/legal guardian's permission/signature is needed. Wards of the State may not be enrolled unless the IRB grants specific approval and assures inclusion of additional protections in the research required under 45 CFR 46.409. If you wish to enroll Wards of the State contact OPRS and refer to the tip sheet.

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

**Please Note:** The following individuals require Investigator Continuing Education: Scott K. Hill and Michael Frank. This training must be completed prior to any further participation on this study. Please refer to the OPRS website for information regarding continuing education requirements and opportunities:

http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/education/2-2-2/ce_requirements.shtml

Additionally, please be sure to include a complete copy of Appendix P, with all current research personnel listed, at the time of Continuing Review, as well as the most recently approved versions of the consent/recruitment materials. Several of the required documents were not provided in the submission and had to be obtained administratively.

**Please note the Review History of this submission:**

<table>
<thead>
<tr>
<th>Receipt Date</th>
<th>Submission Type</th>
<th>Review Process</th>
<th>Review Date</th>
<th>Review Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/04/2011</td>
<td>Continuing Review</td>
<td>Expedited</td>
<td>02/11/2011</td>
<td>Approved</td>
</tr>
</tbody>
</table>
Please remember to:

→ Use your research protocol number (#2004-0785) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3202. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Teresa D. Johnston, B.S., C.I.P.
Assistant Director, IRB # 1
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. Informed Consent Documents:
   a) Affective Systems and deficits-version 2 student, 11/28/2010
   b) UIC Adult Consent: Affective systems and deficits, version 15, 11/28/2010
3. Recruiting Materials:
   a) UIC Telephone Script, Affective systems and deficits, Version #2, 01/06/2006
   b) E-mail notice: "We are currently recruiting...", Affective systems and deficits, Web Ad HC, Version #5, 05/06/2010
   c) Recruitment, Student Version 1 10/18/2010
   d) Screening, Student Version 1 10/18/2010
   e) Debrief Student Version 1 10/18/2010
   f) Recruitment Pamphlet: Patient Participants Needed for Medical Research Study, Version #4, 05/06/2010
   g) Affective systems and deficits, Web Ad PT, Version #4, 02/01/2011

cc: Anand Kumar, Psychiatry, M/C 912
OVCRC Administration, M/C 672
VITA

NAME: Emily Kristina Olsen

EDUCATION: B.S., Psychology, University of California, Davis, 2005

RESEARCH POSITIONS: Graduate Student Researcher, University of Illinois, Chicago, Department of Psychiatry, Neuropsychiatric Institute. PI: Ellen Herbener, Ph.D. (2009 - 2012)

Study Coordinator, UC Davis, Department of Psychiatry, Imaging Research Center. PI: Cameron Carter, MD. (2005 - 2009)


TEACHING: Teaching Assistant, University of Illinois, Chicago, Department of Psychology (2009 – 2012).

PROFESSIONAL MEMBERSHIP: PSI CHI, National Psychology Honor Society


