Running head: WITHDRAWAL TREATMENT ON ATTENTIONAL BIASES IN OPIOID

ADDICTION

The Effects of Withdrawal Treatment on Attentional Biases towards Drug Cues in Opioid

Addiction

Haijing Wu

Under the Direction of Dr. David Zald

Thesis completed in partial fulfillment of the requirements of the Honors Program in

Psychological Sciences

Vanderbilt University

March 2012

ABSTRACT

To investigate attentional biases in drug addiction, the Emotional Blink of Attention paradigm was used to study opioid-dependent patients undergoing inpatient withdrawal treatment at the Vanderbilt Psychiatric Hospital. In multiple trials, participants identified a target photo which appeared in an RSVP stream 200 or 800 msec after an erotic, neutral, or opioid-related (pill) distractor photo. Patients generally performed worse at the task than controls, which may reflect cognitive impairment from withdrawal symptoms. Patients exhibited an attentional blink after the presentation of pill distractors which, although greater than that shown by controls, was not differentially greater relative to their overall poorer performance. Task accuracy for pill distractors at lag 2 was modulated by the implementation of treatment in patients, whereas accuracy remained consistent across time in controls. Interestingly, task accuracy for pill distractors at lag 8 did not improve in patients, which may suggest prolonged problems disengaging from drug stimuli even after treatment.

INTRODUCTION

Approximately 15.6% (29 million) of the adult population in the United States will engage in illicit drug use at some point in their lives, and approximately 2.9% (5.4 million) become addicted to these illicit drugs (Grant & Dawson, 1998; Grant, Dawson, Stinson, Chou, Dufour, & Pickering, 2004). Those that seek addiction treatment, or otherwise try to discontinue their drug use, are faced with a major challenge—the likelihood of relapse. To understand drug relapse, one must understand the neurobiological and cognitive mechanisms underlying drug addiction. A direct causal effect becomes evident, in which addiction sets the stage for future relapse through significant long-term changes that occur in the brain.

Due to its role in motivation and reward, the dopamine system is strongly implicated in addiction (Koob & Volkow, 2009). Neuroplasticity from addiction begins with changes in the ventral tegmental area (the site of dopamine production), which leads to a cascade of neuroadaptations from the ventral striatum to dorsal striatum and orbitofrontal cortex and results in dysregulation of the prefrontal cortex, cingulate gyrus, and extended amygdala. One can deduce the overall impact of addiction from the sheer number of neural structures involved. In fact, it is the persistence of these altered structures that make addicts vulnerable to relapse, according to Robinson and Berridge (2000). Their incentive-sensitization theory of addiction proposes that addictive drugs produce long-lasting changes in the brain through dopamine, particularly in brain systems involved in motivation and reward. The neuroadaptations that take place render these brain systems hypersensitive to drugs and drug-related stimuli, and produce symptoms of "drug-wanting" (craving) that lead to drug-seeking and drug-taking behavior.

Garavan and Hester (2007) describe the cognitive processes that contribute to a person's drug-seeking behavior. A wide spectrum of processes may become dysfunctional and exacerbate

a person's dependence on drugs. These processes include Pavlovian and instrumental reinforcement, attentional processing of environmental stimuli, reward motivation in decision-making, learning and memory, and the monitoring and inhibiting of one's behavior. Accordingly, cocaine addicts show attentional biases towards drug-related stimuli, poor performance in tests of inhibitory control, and compromised monitoring and evaluation of behavior. Out of the cognitive processes underlying addiction, this study focuses on attentional bias towards drug-related stimuli, as assessed by the Emotional Blink of Attention (EBA) paradigm. According to Franken, Booij, and van den Brink (2005), attentional bias towards drug cues may contribute to addictive behavior in several ways. First, enhanced perception of drug stimuli can result in feelings of craving that trigger drug use. Second, once a drug cue is detected, it is more difficult to disengage attention away from it, which may further perpetuate drug use. Lastly, the automatic focusing on drug cues overcomes competing stimuli that could lead to alternative non-drug-taking behavior.

The EBA paradigm has emerged from decades of research on rapid serial visual presentation (RSVP) streams, in which stimuli such as letters, words, and pictures are presented in rapid succession in the same spatial location. Raymond, Shapiro, and Arnell (1992) first coined the term "attentional blink" in their paper on the temporary suppression of visual processing. In one of their four experiments, RSVP streams of letters were presented; all of the letters were black except for one white letter (Target 1, or T1). Participants were either asked to identify the white letter and indicate whether they saw a black X (Target 2, or T2) presented after the white letter, or to ignore the color of the white letter and solely indicate whether they saw the black X. Task accuracy significantly dropped when participants also had to identify the white letter, when the black X was presented 180-450 msec after the white letter. Raymond et al. (1992)

attributed the decrease in performance to the allocation of attention in processing T1 (the white letter) so much so that there were no resources left to process T2 (the black X) in this time span—a phenomenon they called the attentional blink.

Introduced by Most, Chun, Widders, and Zald (2005), the EBA task incorporates photos instead of letters in its RSVP streams. T1 is replaced with an emotional photo, which contrasts with neutral photos in the rest of the stream and serves as a critical distractor in finding T2, a rotated neutral photo. Most et al. (2005) presented this task to participants in order to investigate the degree to which emotional stimuli attract attention at the cost of processing other stimuli. Participants were asked to identify the rotated photo among a rapid stream of 17 upright photos, each presented for 100 msec. They had to specify whether this target was rotated 90° to the left or to the right. All photos in the stream, including the rotated photo, were pictures of landscapes or buildings—with the exception of the distractor photo. The distractor was a neutral, scrambled-negative, or emotionally negative photo shown either two or eight items before the rotated photo (lag 2 and lag 8, respectively). Emotionally negative photos included photos of violence, distress, and medical trauma in people or animals. Most et al. (2005) found that participants had significant difficulty detecting the direction the target was rotated if the distractor was a negative photo shown at lag 2. Task accuracy was not affected for the neutral and scrambled-negative distractors at lag 2, nor was it affected for presentations of any distractor type at lag 8. Attentional biases to negative photos resulted in a temporary inability to process targets that participants actively searched for; they experienced an attentional blink after the presentation of negative stimuli.

Furthermore, Most et al. (2005) hypothesized that individual differences related to trait anxiety would affect the extent to which a person would be able to reduce his or her attentional

blink. To test their hypothesis, they took the highest scorers and lowest scorers on the harm avoidance section of the Tridimensional Personality Questionnaire. Low harm avoidance scores corresponded to carefree and confident personalities, while high harm avoidance scores corresponded to anxious and tense personalities. Though a significant correlation was not found between harm avoidance and the magnitudes of attentional blinks in this experiment, a subsequent experiment did reveal a correlation. In the second experiment, a specific attentional set was introduced; participants were informed that the target photo would be of a building. In the nonspecific attentional set, participants were informed that the target photo could be a building or a landscape without a building. The specific attentional set helped participants ignore the negative distractors and find the target photo, and as a result, individual differences of harm avoidance were brought to the surface. Indeed, people who scored lower in harm avoidance did significantly better at reducing the magnitudes of their attentional blinks than people who scored higher in harm avoidance did.

The same EBA task has been utilized to test aversively-conditioned stimuli as well. In another study, Smith, Most, Newsome, and Zald (2006) found that participants displayed an attentional bias to aversively-conditioned photos even when the associations were only recently learned. Half of the participants were conditioned against car photos when the car photos were paired with an unpleasant noise, while the other half of the participants were conditioned against bird photos when the bird photos were paired with unpleasant noise. Photos of cars and birds were then used as distractors in the EBA task. Participants were less likely to identify the target photo after presentation of the distractor they were aversively conditioned against. The aversively-conditioned stimuli were able to cause participants to exhibit an attentional blink.

The EBA paradigm is by no means limited to negative stimuli, as positive stimuli have also elicited an attentional blink, as discovered in a study by Most, Smith, Cooter, Levy, and Zald (2007). Male and female participants were allowed to adopt a specific attentional set, similar to the procedure in the 2005 study involving negative stimuli. Erotic photos (of couples engaging in sexual activity) and negative photos were used as distractors. Under the specific attentional set, men and women had improved accuracy identifying target photos after negative distractors but not after erotic distractors. While attending to both erotic and aversive stimuli has evolutionary value (for example, in alerting one of a potential mate or potential danger), these results point towards the possibility that the two classes of stimuli are processed through different cognitive pathways. Emotional effects on attention seem to arise from arousal independent of whether something is considered positive or negative, though the effects may in fact be stronger for erotic stimuli than other stimulus types, an outcome supported by Arnell, Killman, and Fijavz (2007) in their RSVP experiment with various types of emotional words.

Piech, Pastorino, and Zald (2010) tested the attentional capture of food stimuli using the EBA task and found that hunger biases attention towards food stimuli. Participants completed the EBA task in two separate sessions, one in which they were hungry and the other in which they were sated. In both sessions, they were told that the target photo would always be a landscape. Participants performed significantly worse after food distractors in the hungry session than in the sated session. However, hunger did not impact task accuracy after presentation of romantic distractors; an attentional blink was observed for romantic distractors in both the hungry and sated sessions. Piech et al. (2010) demonstrated a unique effect in which participants must be in a specific physical state to show an attentional blink towards distractors associated with that state. Similar results are anticipated in the present study involving drug-dependent patients.

Given that attention is limited in capacity, why are certain stimuli chosen over others to occupy our mental resources? After reviewing these EBA experiments, we can begin to answer this question. One idea is that potentially dangerous stimuli are given priority because they are highly relevant to our survival (Blake, Yang, & Zald, 2007). This was true when the EBA task was first conducted with aversive stimuli, though researchers later proved that conditioned stimuli, erotic stimuli, and food stimuli also had preferential access to attention (Most, 2006; Smith, 2007; Piech, 2010). To be fully inclusive of these, it is best to modify the previous statement and say that people are more sensitive to and preoccupied with stimuli in their environment that represent their psychological concerns (Rosenberg, 2009). The variety of stimuli used in the EBA task indicates that the task effectively assesses attention and provides useful information about psychological concerns when evaluated closely.

In the present study, the EBA task was used to examine whether opioid-related stimuli elicit an attentional blink in opioid-dependent patients undergoing inpatient withdrawal treatment at the Vanderbilt Psychiatric Hospital. Opioids refer to the class of drugs derived from the opium plant and include codeine, oxycodone, hydrocodone, morphine, and heroin. Most of these drugs are μ receptor agonists and, upon μ receptor activation, produce an intense euphoric sensation followed by a longer-lasting high. Though effective for the treatment of pain, opioids are highly addictive. Opioid-dependent users are those who are unable to stop using opioids even in the face of difficulties that are caused by the opiate use itself. The 2006 National Survey on Drug Use and Health (NSDUH) revealed that, between 1999 and 2006, the number of people illicitly using prescription pain relievers doubled from 2.2 million to 5.2 million. In fact, the abundance and frequency of opioid use is one reason we chose to test opioid-dependent patients. The other

reason is that the opioid-dependent patients follow a very discrete protocol at the Vanderbilt

Psychiatric Hospital, known as the Clinical Opiate Withdrawal Symptom (COWS) protocol.

Under the COWS protocol, Clonidine is first administered and is followed by

Buprenorphine if a patient's withdrawal symptoms persist. Withdrawal symptoms include:

anxiety, depression, nausea, diarrhea, and leg and abdominal cramps, as well as strong drug

cravings. This method of opioid detoxification is known as short-term substitution therapy, in

which the physician prescribes these substitute medications for opioids and gradually tapers the

dosage down during a time span of one to two weeks. According to Schatzberg and Nemeroff

(2004), Buprenorphine works by acting as a partial agonist of the μ opiate receptor and is a

clinically effective analgesic agent with an estimated potency of 25-40 times that of morphine (p.

1018). However, due to Buprenorphine's potential addictive effects, many physicians first

administer or exclusively rely on Clonidine, an α-adrenergic agonist that inhibits norepinephrine

release by engaging inhibitory autoreceptors in the locus coeruleus (p. 1015).

The inhibition of the locus coeruleus by Clonidine is particularly interesting, since this

brain structure is hypothesized to be the source of the attentional blink (Nieuwenhuis, Gilzenrat,

Holmes, & Cohen, 2005). According to Aston-Jones and Cohen (2005), the locus coeruleus

operates in context of two different modes of activity—the phasic and tonic modes. In the phasic

mode, a task-oriented event produces a widespread but temporally specific release of

norepinephrine, enhancing processing of motivationally relevant stimuli. In the tonic mode,

neurons in the locus coeruleus fail to respond phasically to task events due to postactivation

inhibition. The locus coeruleus is unavailable to process the information for a brief period of

about 500 msec; it is during this time that an attentional blink occurs (Nieuwenhuis et al., 2005).

It is fitting that brain regions involved in attentional processing, such as the parietal cortex,

pulvinar nucleus, and superior colliculus, receive particularly dense innervation from the locus coeruleus (Foote & Morrison, 1987). Moreover, Aston-Jones and Cohen (2005) propose that the norepinephrine system helps to regulate the reinforcement learning mechanisms implemented by the dopamine system. Disturbances of the two systems are implicated in many psychiatric disorders, including drug addiction (Weinshenker & Schroeder, 2007).

The amygdala can enhance processing of motivationally salient cues and direct attention towards emotional stimuli, as observed in a study by Anderson and Phelps (2001). In a task involving RSVP streams of neutral words in black color, participants were asked to identify two green words that serve as T1 and T2. Healthy participants showed a decreased attentional blink towards T1 if T2 was a negative word. In contrast, participants with bilateral damage to the amygdala or unilateral lesions to the left amygdala did not show enhanced processing of negative words in the task. It suggests that the function of the left amygdala is necessary for breaking through an attentional blink caused by the neutral target at T1. A subsequent study by Piech et al. (2011) revealed that participants with unilateral damage to the amygdala on either side performed no differently than healthy controls in an EBA task involving neutral, aversive, and erotic distractors. All participants regardless of amygdala damage exhibited attentional blinks after the presentation of aversive and erotic distractors. Thus, the amygdala may not always be critical for the emotional modulation of attention, and its role in the EBA paradigm needs to be further investigated. Researchers have begun to study other structures such as the anterior cingulate, insula, and orbitofrontal cortices and how they may contribute to the EBA (Schwabe et al., 2011).

Field, Munafo, and Franken (2009) conclude that there is a modest but statistically significant correlation between subjective craving and attentional bias in cognitive science

experiments. Their analysis suggests a combination of conditions that are expected to induce a larger correlation between craving and attentional bias: studying users of illicit drugs, using direct rather than indirect measures to infer attentional processing, and studying individuals whose current level of craving is high rather than low. The design of my experiment fits two out of three of the preceding criteria, since opioids are illicit drugs when not prescribed, and patients who have not yet received withdrawal treatment should have high craving levels. Direct measures of attentional bias involve eye movement monitoring and the measurement of event related potentials; indirect measures involve assessing task performance. Though the EBA task falls into the latter category, its employment across a diverse range of stimuli has produced consistent results. Additionally, the EBA task stands out from previous studies that primarily use reaction times as a measure of attentional bias, through demonstrating that stimuli can capture attention to the extent of not even perceiving subsequent stimuli. At the very least, results from tasks assessing implicit cognitive biases, such as the EBA task, should have better predictive utility than those from self-report methods of introspection (McCusker, 2001).

Though the EBA paradigm has begun to be employed in clinical settings involving patients with generalized anxiety disorder and obsessive-compulsive disorder (Olatunji, Ciesielski, Armstrong, Zhao, & Zald, 2011; Olatunji, Ciesielski, & Zald, 2011), no published studies to date have used the paradigm to study drug-dependent patients undergoing withdrawal treatment. The present project serves as a pilot study in addressing the feasibility of performing cognitive science research in the addictions unit at the Vanderbilt Psychiatric Hospital. We investigated the following questions: 1) Do opioid-dependent patients exhibit an attentional blink towards opioid-related stimuli that healthy participants do not exhibit? 2) When patients complete the EBA task at each stage of withdrawal treatment, do Clonidine and Buprenorphine

modulate the levels of attentional bias towards the opioid stimuli? 3) Finally, do patients'

subjective ratings of craving and pain correlate with their level of withdrawal symptoms

throughout treatment? We hypothesized that: opioid-dependent patients would exhibit an

attentional blink towards the opioid stimuli whereas healthy participants would not, and the

magnitude of the blink would decrease through the course of treatment with Clonidine and

Buprenorphine, along with a decrease in craving and pain ratings and withdrawal symptoms.

METHOD

Participants

Eight patients undergoing inpatient opioid withdrawal treatment at the Vanderbilt

Psychiatric Hospital participated, as well as eight healthy people matched in age, gender, and

education who served as controls. The majority of participants were female—five patients and

five controls. Patients ranged from ages 20 to 38, and controls ranged from ages 18 to 46.

Patients had between 9 and 15 years of education, and controls had between 11 and 16 years of

education. Patients received a diagnosis of opioid dependence upon their psychiatric admission

evaluation. All patients were dependent on opioids in pill form, which included Lortab, Percocet,

and Oxycontin.

Symptom Assessment

Patients were assessed by nurses using the Clinical Opiate Withdrawal Symptom (COWS)

protocol to determine the need for treatment with Clonidine and Buprenorphine (Wesson & Ling,

2003). They were given a score of 0 to 4 for the following seven criteria: resting pulse rate,

sweating over 30 minutes, bone or joint aches, runny nose or tearing, tremor, yawning, and

anxiety or irritability. They were given a score of 0 to 5 for the following four criteria:

restlessness, pupil size, gastrointestinal upset, and gooseflesh skin. The maximum score possible

was 48. For a score of 5 or greater, 0.1 mg of Clonidine was administered every hour, for up to

0.4 mg in a span of 8 hours. If a patient received 0.4 mg of Clonidine in 8 hours or scored a 15 or

greater on COWS prior to receiving 0.4 mg of Clonidine in 8 hours, Buprenorphine injections

were administered on a rigid schedule of 0.3 mg per dose every 8 hours for 9 consecutive doses.

Clonidine continued to be administered for scores 5 or greater, for up to 0.4 mg within an 8 hour

period. Vital signs and COWS scores were obtained prior to each dose of Clonidine and

Buprenorphine.

Stimuli

Stimuli were color photographs—256 upright landscape/architectural, 84 target (42

landscape/architectural photos rotated 90 degrees to the left or right), 30 neutral, 30 erotic, 30

opioid-related (photos of pills)—presented on a Dell desktop with a 38.5x31cm display and

measuring 320 by 240 pixels. The neutral, erotic, and pill photos were used as distractors.

Neutral photos, of flowers and rocks, were taken from the International Affective Picture System

(IAPS; Lang, Bradley, & Cuthbert, 2001). Erotic photos, of couples engaging in sexual activity,

were taken from photos used in previous studies by our lab. Pill photos were taken from the

Internet. Pill photos were chosen instead of injection and smoking photos because it is the most

common route of opioid administration among patients at the psychiatric hospital.

Design

Primary task

Patients were tested at three stages in their withdrawal treatment: before receiving

Clonidine and Buprenorphine, during Clonidine and Buprenorphine (usually after the fourth or

fifth Buprenorphine injection), and after Clonidine and Buprenorphine (at least 12 hours after

receiving the last Clonidine and Buprenorphine). The healthy controls were also tested three

times on a similar schedule to control for practice effects. These three testings correspond to Session 1, Session 2, and Session 3.

At each session, participants completed trials of an RSVP stream of 17 photos, each presented for 100 msec. All photos were upright landscape/architectural photos except for two (see Figure 1). One photo was the target, of a landscape rotated 90 degrees to the left or right. One photo was the critical distractor, which was a neutral, erotic, or pill photo. The distractor photo was positioned as either the 4th, 5th, 6th, 7th, or 8th photo within the stream and was followed by the target photo two positions later, or the distractor photo was positioned as either the 3rd, 4th, 5th, or 6th photo within the stream and was followed by the target photo eight positions later (lag 2 and lag 8, respectively). The computer randomized which photos are paired with which lag and also randomized the order of trials.

Participants were asked if they saw a rotated photo and, if they did, to specify which direction it was rotated. Both answers had to be correct to count towards our measure of task accuracy. They were also told: 1) the rotated photo will always be of a landscape, 2) photos of other objects may appear but should be ignored, and 3) not all trials will contain a rotated photo. Participants completed an 8-trial practice session (with photos shown at 150 msec and without erotic and pill distractors), followed by 76 "real" trials (with photos shown at 100 msec and with all three types of distractors). Six of these trials were catch trials, which did not contain a target photo. Lastly, participants rated their current drug craving and pain level from a scale of 1 to 7, corresponding to "Not at All" through "Most Imaginable."

Rating task

After completing the primary task, participants rated how positive or negative they found the erotic and pill photos, on a scale of 1 to 5. Each photo was shown briefly for 100 msec and presented in random order. This rating task was completed only once, at the final testing.

RESULTS

Participant Characteristics

Out of the eight patients tested in this study, six patients experienced severe enough withdrawal symptoms to receive Buprenorphine shots. At the beginning of treatment, they received COWS scores ranging from 0 to 13 and then each progressed to a score of 15 or greater (up to a score of 25). Two patients received only Clonidine and did not advance to the Buprenorphine shots. Even though they experienced milder withdrawal, these two patients still showed symptom improvement because their COWS scores were higher at the beginning of treatment (scores of 8 and 9) than at the end of treatment (scores of 4 and 5). They are included in the analyses for this reason. It should be noted that seven out of the eight patients were tested for Session 1 in the middle of withdrawal treatment for benzodiazepines. Shown in Table 1, opioid-dependent patients and healthy controls were well-matched on gender, age, and education level with no significant differences between the two groups (Ps>.05).

RSVP Task Accuracy

Means and standard deviations of task accuracy for all conditions

Means and standard deviations of task accuracy on the RSVP by distractor, lag, and session are presented for patients and controls in Table 2. It should be noted that two patients could not be tested for Session 3, and their matched controls were not tested for Session 3 either.

The means for patients and controls in Sessions 1 and 2 come from a sample size of eight, while

the means for patients and controls in Session 3 come from a sample size of six.

Patient and control accuracy at Session 1

To examine whether patients (N=8) and controls (N=8) perform at the task differently, a 2

(Group: patients, controls) x 3 (Distractor: erotic, neutral, pill) x 2 (Lag: 2, 8) mixed model

Analysis of Variance (ANOVA) was performed for task accuracy at Session 1. This ANOVA

included one between-subjects factor of Group and two repeated-measures factors of Distractor

and Lag. The ANOVA revealed a significant main effect of Group [$F(1,14) = 18.40$, P=.001,

partial $\eta^2 = .57$], reflecting higher accuracy for controls relative to patients, Distractor [$F(2,28) =$

39.55, P=.000, partial $\eta^2 = .74$], reflecting differential performance across distractor types, and

Lag [$F(1,14) = 119.92$, P=.000, partial $\eta^2 = .90$], reflecting higher accuracy at lag 8 than at lag 2.

These main effects were qualified by a significant Distractor x Lag interaction [$F(2,28) = 11.09$,

P=.000, partial $\eta^2 = .44$].

Paired t-tests showed similar significant effects in patient and control accuracy at Session

1. For patients, task accuracy was significantly higher at lag 8 than at lag 2 after presentation of

erotic [$t(7) = -4.66$, P=.002] and pill distractors [$t(7) = -5.53$, P=.001] but not after neutral

distractors [$t(7) = -1.55$, P=.164], indicating an attentional blink towards erotic and pill

distractors. At lag 2, patients performed significantly better after neutral distractors than after pill

distractors [$t(7) = 2.53$, P=.039], after neutral distractors than after erotic distractors [$t(7) = -4.28$,

P=.004], and after pill distractors than after erotic distractors [$t(7) = -3.25$, P=.014]. At lag 8,

patients performed significantly better after neutral distractors than after erotic distractors [$t(7) =$

-3.00, P=.020]. All other comparisons of task accuracy at different lags and distractors were not

significant (Ps>.05). Controls showed similar effects in Session 1: they exhibited an attentional

blink towards erotic and pill distractors, with the highest performance at lag 2 after presentation

of neutral distractors, followed by performance after presentation of pill distractors, and the

lowest performance after presentation of erotic distractors (Ps<.05). Furthermore, the lack of a

significant Group x Distractor interaction signifies that the attentional blinks experienced by the

two groups were not significantly different in magnitude for either type of distractor. In contrast

to patients, controls did not perform significantly better after neutral distractors than after erotic

distractors at lag 8 [$t(7)$ = -1.43, P=.195].

Independent sample t-tests revealed that patients performed significantly worse than

controls at the task for erotic distractors at lag 8 [$t(14)$ = -2.65, P=.019], for neutral distractors at

lag 2 [$t(14)$ = -2.52, P=.025], and for pill distractors both at lag 2 [$t(8.88)$ = -4.35, P=.002] and at

lag 8 [$t(14)$ = -2.50, P=.026]. These data indicate that, while patients and controls both exhibit

attentional blinks towards erotic and pill distractors and also have similar differential

performance for the three distractor types, patients generally perform worse than controls at the

task—significantly so for erotic distractors at lag 8, neutral distractors at lag 2, and pill

distractors at both lags. The results for patients are depicted in Figure 2, and the results for

controls are depicted in Figure 3.

Patient and control accuracy at Session 1 and Session 2

To investigate whether the attentional blink changes when treatment is implemented, task

accuracy of patients (*N*=8) and controls (*N*=8) was compared at Sessions 1 and 2. A 2 (Group:

patients, controls) x 2 (Session: Session 1, Session 2) x 3 (Distractor: erotic, neutral, pill) x 2

(Lag: 2, 8) mixed model ANOVA was performed for task accuracy. This ANOVA included one

between-subjects factor of Group and three repeated-measures factors of Session, Distractor, and

Lag. The ANOVA revealed a significant main effect of Group [$F(1,14)$ = 11.30, P=.005, partial

$\eta^2 = .48$], reflecting higher accuracy for controls relative to patients, Session [$F(1,14) = 18.68$, $P=.001$, partial $\eta^2 = .57$], reflecting overall better performance during Session 2, Distractor [$F(2,28) = 50.42$, $P=.000$, partial $\eta^2 = .78$], reflecting differential performance across distractor types, and Lag [$F(1,14) = 144.00$, $P=.000$, partial $\eta^2 = .91$], reflecting higher accuracy at Lag 8 than at Lag 2. These main effects were qualified by significant Session x Distractor [$F(2,28) = 5.56$, $P=.009$, partial $\eta^2 = .28$] and Distractor x Lag [$F(2,28) = 20.33$, $P=.000$, partial $\eta^2 = .59$] interactions.

To examine the significant effects in patients more closely, a 2 (Session: Session 1, Session 2) x 3 (Distractor: erotic, neutral, pill) x 2 (Lag: 2, 8) repeated measures ANOVA was performed separately for task accuracy in patients and controls. Similar to the mixed model ANOVA, the ANOVA for patients revealed significant main effects for Distractor [$F(2,14) = 25.30$, $P=.000$, partial $\eta^2 = .78$] and Lag [$F(1,7) = 58.45$, $P=.000$, partial $\eta^2 = .89$], as well as a significant Distractor x Lag interaction [$F(2,14) = 5.27$, $P=.020$, partial $\eta^2 = .43$]. Likewise, the ANOVA for controls showed significant main effects for Distractor [$F(2,14) = 25.32$, $P=.000$, partial $\eta^2 = .78$] and Lag [$F(1,7) = 96.44$, $P=.000$, partial $\eta^2 = .93$], and a significant Distractor x Lag interaction [$F(2,14) = 20.27$, $P=.000$, partial $\eta^2 = .74$]. However, only the ANOVA for patients revealed a significant main effect of Session [$F(1,7) = 20.02$, $P=.003$, partial $\eta^2 = .74$] and a Session x Distractor interaction that trended towards significance [$F(2,14) =3.29$, $P=.068$, partial $\eta^2 = .32$], which suggests that the significant main effect of Session and the significant Session x Distractor interaction in the mixed model ANOVA were driven by patient accuracy.

Paired t-tests showed identical significant effects in patient and control accuracy at Session 2. Similar to Session 1, task accuracy for patients was higher at lag 8 than at lag 2 after presentation of erotic [$t(7) = -5.29$, $P=.001$] and pill distractors [$t(7) = -5.09$, $P=.001$] but not

after neutral distractors [$t(7) = -.22$, $P=.834$], indicating an attentional blink towards erotic and

pill distractors. At lag 2, patients performed significantly better after neutral distractors than after

pill distractors [$t(7) = 6.95$, $P=.000$] and also performed significantly better after neutral

distractors than after erotic distractors [$t(7) = -5.46$, $P=.001$]. Unlike Session 1, task accuracy at

lag 2 was not significantly higher after pill distractors than after erotic distractors [$t(7) = -1.24$,

$P=.255$]. Also unlike Session 1, task accuracy at lag 8 was not significantly higher after neutral

distractors than after erotic distractors [$t(7) = -.08$, $P=.941$]. No comparisons of task accuracy at

lag 8, or for any other lags and distractors were significant (Ps>.05). Controls showed identical

effects in Session 1: they exhibited an attentional blink towards erotic and pill distractors and, at

lag 2, performed significantly better after neutral distractors than after pill distractors and also

after neutral distractors than after erotic distractors (Ps<.05).

As shown in Figure 2 and Figure 3, further analyses revealed that the two groups

performed differently across the two sessions. Paired sample t-tests showed that patients had

significant improved task accuracy from Session 1 to Session 2 for erotic distractors presented at

both lag 2 [$t(7) = -2.97$, $P=.021$] and lag 8 [$t(7) = -4.51$, $P=.003$]. An improvement in task

accuracy trended towards significance for pill distractors presented at lag 2 [$t(7) = -2.18$, $P=.066$].

No other comparisons between Session 1 and Session 2 were significant (Ps>.05). For controls,

there were no significant differences in task accuracy between the two sessions (Ps>.05), but

there was a trend towards significant improvement for erotic distractors presented at lag 8 [$t(7) =$

-2.28, $P=.057$]. Independent sample t-tests revealed that, similar to Session 1, patients at Session

2 performed significantly worse than controls for neutral distractors at lag 2 [$t(14) = -3.00$,

$P=.010$] and pill distractors at lag 8 [$t(14) = -2.46$, $P=.027$]. Unlike Session 1, patients no longer

performed significantly worse for erotic distractors at lag 8 and pill distractors at lag 2 (Ps>.05).

These data indicate that, in Session 2, patients more closely matched the task accuracy of controls for erotic distractors at lag 8 and for pill distractors at lag 2, because patients improved significantly in task accuracy from Session 1 to Session 2 for erotic distractors at lag 8, and improvement trended towards significance for pill distractors at lag 2.

Buprenorphine patient accuracy at Session 1 and Session 2

Out of the eight patients in this study, six patients received both Clonidine and Buprenorphine while two patients received only Clonidine. An additional repeated measures ANOVA was performed for the six patients who advanced to Buprenorphine shots to see if excluding the two Clonidine-only patients alter the results. A 2 (Session: Session 1, Session 2) x 3 (Distractor: erotic, neutral, pill) x 2 (Lag: 2, 8) ANOVA revealed significant main effects of Session [$F(1,5) = 16.36$, $P=.010$, partial $\eta^2 = .77$], Distractor [$F(2,10) = 23.40$, $P=.000$, partial $\eta^2 = .82$], and Lag [$F(1,5) = 33.45$, $P=.002$, partial $\eta^2 = .87$], similar to the main effects in the ANOVA performed for all patients. However, unlike the results for all patients, in which there was a significant Distractor x Lag interaction and a Session x Distractor interaction trending towards significance, there were no significant interactions (Ps>.05) and the Distractor x Lag interaction only trended towards significance [$F(2,10) = 3.00$, $P=.096$, partial $\eta^2 = .38$].

Independent sample t-tests revealed that there were no significant differences (Ps>.05) in task accuracy at any lag or distractor combination between Buprenorphine patients and all patients, as depicted in Figure 4. Paired t-tests for Buprenorphine patients at Session 1 showed an attentional blink for erotic distractors [$t(5) = -4.34$, $P=.007$] and pill distractors [$t(5) = -4.65$, $P=.006$]. At lag 2, Buprenorphine patients performed significantly better after neutral distractors than after erotic distractors [$t(5) = -3.87$, $P=.012$], and at lag 8, performed significantly better after neutral distractors than after erotic distractors [$t(5) = -4.11$, $P=.009$]. These significant

effects were also found in the t-tests including the Clonidine-only patients. However, in contrast to all of the patients, Buprenorphine patients did not perform significantly better after neutral distractors than after pill distractors [$t(5) = 2.48$, $P=.056$], nor after pill distractors than after erotic distractors [$t(5) = -2.12$, $P=.087$]; rather, these effects trended towards significance. The exact same significant effects were found for Buprenorphine patients and all the patients in Session 2. Paired t-tests for Buprenorphine patients at Session 2 revealed an attentional blink for erotic [$t(5) = -3.91$, $P=.011$] and pill distractors [$t(5) = -4.37$, $P=.007$], higher task accuracy at lag 2 after neutral distractors than after erotic distractors [$t(5) = -4.63$, $P=.006$] and after neutral distractors than after pill distractors [$t(5) = 8.14$, $P=.000$], and no significant effects at lag 8 (Ps>.05). Lastly, paired t-tests for Buprenorphine patients across the two sessions showed that they had improved task accuracy from Session 1 to Session 2 for erotic distractors presented at lag 8 [$t(5) = -5.93$, $P=.002$], whereas all patients showed significant improvement across sessions for erotic distractors at both lag 2 and lag 8. These data indicate that excluding the two Clonidine-only patients slightly altered the results in Session 1 but not in Session 2, but the differences were not large enough to be considered significant between the two groups.

Patient accuracy at Session 2 and Session 3

To investigate whether the attentional blink changes when treatment has concluded, task accuracy of patients was compared at Sessions 2 and 3. A total of six patients were tested for Session 3—five of which received both Clonidine and Buprenorphine, while one received only Clonidine. A 2 (Session: Session 2, Session 3) x 3 (Distractor: erotic, neutral, pill) x 2 (Lag: 2, 8) repeated measures ANOVA revealed main effects of Distractor [$F(2,10) = 9.15$, $P=.006$, partial $\eta^2 = .65$], reflecting differential performance across distractor types, and Lag [$F(1,5) = 19.37$, $P=.007$, partial $\eta^2 = .80$], reflecting higher accuracy at Lag 8 than at Lag 2. These main effects

were qualified by a significant Distractor x Lag interaction [$F(2,10) = 8.92$, $P=.006$, partial η^2 = .64]. Main effects of Distractor and Lag and a Distractor x Lag interaction were also found for patient accuracy when comparing Session 1 and Session 2. However, unlike Sessions 1 and 2, there was no significant main effect of Session [$F(1,5) = .17$, $P=.699$, partial η^2 = .033] for task accuracy in Session 2 and 3, indicating no significant differences in task accuracy across these two sessions. The results for patients are depicted in Figure 2.

Paired t-tests revealed similar task accuracy in Session 2 and Session 3, with one key difference in attentional blinks. Task accuracy in Session 3 was significantly higher at lag 8 than at lag 2 after presentation of pill distractors [$t(5) = -4.49$, $P=.006$], but only trended towards significance after erotic distractors [$t(5) = -2.24$, $P=.076$], and was not significant after neutral distractors [$t(5) = -.52$, $P=.625$], indicating an attentional blink towards pill distractors only. In contrast, patients in the Session 2 exhibited significant blinks towards both erotic and pill distractors. Similar to Session 2, patients in Session 3 performed significantly better at lag 2 after neutral distractors than after erotic distractors [$t(5) = -3.02$, $P=.029$] and after neutral distractors than after pill distractors [$t(5) = 3.07$, $P=.028$, and they did not show significant differences in task accuracy at lag 8 (Ps>.05). Lastly, paired t-tests for patients across Sessions 2 and 3 did not show significant differences in task accuracy at any lag or distractor type (Ps>.05), which fits accordingly with the lack of a main effect of Session. These data indicate that, from Session 2 to Session 3, the attentional blink after pill distractors persisted while the blink after erotic distractors only trended towards significance; this difference is likely due to the smaller sample size of six patients.

Valence Ratings for Distractors in the RSVP Task

Means and standard deviations of valence ratings for erotic and pill distractors are presented in Table 3. Independent sample t-tests revealed that none of the patient and control means were significantly different from each other ($Ps>.05$).

DISCUSSION

This study investigated the extent to which emotional stimuli capture the attention of opioid-dependent patients as they progressed through inpatient withdrawal treatment at the Vanderbilt Psychiatric Hospital. As hypothesized, patients exhibited an attentional blink in the RSVP task after the presentation of pill distractors. However, controls also exhibited an attentional blink after pill distractors were presented. Critically, the magnitude of this blink was not differentially greater in patients than in controls, as revealed by the lack of a Group x Distractor interaction. Thus, task accuracy on the EBA task does not appear to provide a robust discriminative measure of bias towards opioid pill cues in the context of opioid addiction. Had only patients shown the attentional blink, the EBA task could have potentially been employed as an objective assessment to highlight individual differences and differential responses to treatment, and perhaps even predict patients who are most vulnerable to relapse. We did not find support for its use in this population.

Both patients and controls exhibited an attentional blink after presentation of erotic distractors, which was more robust than the blink associated with pill distractors across all three sessions. The attentional capture of erotic stimuli was so powerful that it exceeded that of pill stimuli for opioid-dependent patients. This finding is consistent with the Most et al. (2007) and Arnell et al. (2007) studies that show erotic stimuli have a unique advantage in occupying attentional resources. On the other hand, the pill distractors may be much more ambiguous

stimuli. Given that healthy controls exhibited a blink after the pill distractors, these findings indicate that pill stimuli are not clinically selective distractors during the RSVP task. The problem does not appear to lie in the image characteristics, as the pill distractors were no higher in measures of luminance and contrast than the erotic distractors were. Rather, the pill stimuli may not be specific enough to opioid addiction. Many people are familiar with taking pills to treat short-term illness or may even take them to manage chronic disease. Interestingly, there was no significant difference in the valence ratings of pill distractors between patients and controls; it is unclear why both groups rated the pills as slightly negative.

Though both patients and controls exhibited a blink after the presentation of erotic and pill distractors, the two groups executed the task with different levels of performance. Across all three sessions and at both lags, patients generally performed worse at the task in comparison to controls. These findings may reflect a generalized attentional control deficit in this clinical population, as it did in patients with generalized anxiety disorder in Olatunji et al.'s study (2011), who also performed with lower task accuracy at both lags 2 and 8. Additionally, opioid-dependent patients performed consistently worse than controls after neutral distractors at lag 2; patients with generalized anxiety disorder also had impaired task accuracy for neutral distractors. However, it is important to take into consideration that the opioid-dependent patients in this study were tested as they endured severe withdrawal symptoms, which provides an alternative explanation for their impaired task accuracy relative to controls. Patients could have been preoccupied with their physical symptoms of withdrawal, drawing their attention away from the task, and could have also experienced an overall decrease in their ability to concentrate. It is not possible to know how much this factor contributes to task accuracy unless a study is performed with opioid-dependent participants in a non-treatment setting.

Since patients and controls exhibited a blink after the presentation of pill distractors that was not significantly different in magnitude, it becomes crucial to look at whether patients experienced an additional amount of blink over controls—that is, the degree to which the blink from patients might exceed the blink from controls. One way to evaluate this is to examine patient and control accuracy at lag 2 for the erotic and pill distractors that elicited a blink. In Session 1, patients performed significantly worse than controls at the task after pill distractors shown at lag 2, but not after erotic distractors shown at lag 2. Although it did not reach a point of significance, patients experienced an attentional blink for pill distractors that was greater in magnitude than the blink controls experienced. This finding fits well with the hypothesis, because patients should be more preoccupied with pill stimuli in their environments given their dependence on opioids and their inability to take opioids during their hospitalization. These data leave open the possibility that patients are indeed more sensitive to drug-related distractors, but suggest the magnitude of the difference is relatively subtle. A larger sample might allow this difference to reach statistical significance, but a differential effect is likely to be relatively modest given these initial observations.

The finding regarding group differences in the attentional blink towards pills also seems to be unique to Session 1. In Session 2, patients no longer performed worse than controls after pill distractors shown at lag 2. Furthermore, from Session 1 to Session 2, patients showed improvement that trended towards significance for pill distractors at lag 2, and showed significant improvement for erotic distractors at lags 2 and 8. In contrast to patients, controls did not show significant improvement at any lag and distractor combination but showed an improvement that trended towards significance for erotic distractors at lag 8. The greater number of conditions in which patients showed improvement can be attributed to the implementation of

withdrawal treatment. It appears that receiving Clonidine and Buprenorphine not only reduced the degree of attentional capture that pill distractors at lag 2 had on patients but also reduced the degree of attentional capture for erotic distractors at both lags. This supports the notion that patients generally performed worse at the task than controls did because patients could not focus well as a result of their withdrawal symptoms. Accordingly, these symptoms were most exacerbated in Session 1 when they had not yet begun to receive treatment. However, one possible confounding factor must be considered closely in this regard. Seven out of the eight patients were tested for Session 1 in the middle of withdrawal treatment for benzodiazepines, which takes place before withdrawal treatment for opioids. In benzodiazepine treatment, Phenobarbitol is administered hourly until patients become drowsy and eventually fall asleep, and the medication could have contributed to decreased cognitive performance at Session 1.

While the implementation of treatment modulated the effect of pill distractors at lag 2, it did not modulate the effect of pill distractors at lag 8. In both Sessions 1 and 2, patients performed significantly worse than controls at the task after pill distractors were presented at lag 8. Furthermore, patients did not show significant signs of improvement for pill distractors at lag 8 between the two sessions. Olatunji et al. (2011) described the task impairment at lag 2 as reflecting sensitivity to attentional capture, whereas impairment at lag 8 reflects problems with the disengagement of attention. In this study, opioid-dependent patients showed worse performance for pill distractors at lags 2 and 8, but only the impaired performance at lag 8 persisted through the course of treatment. This indicates that this clinical population may suffer from a prolonged problem in disengaging from pill stimuli, rather than in selectively attending to pill stimuli, and that withdrawal treatment does not effectively modulate their disengagement of attention.

Excluding the two patients who only received Clonidine from the analyses altered the findings in Session 1 but did not alter them enough to the point of significance. In Session 1, the patients who went on to Buprenorphine shots did not perform significantly better after pill distractors than after erotic distractors at lag 2; rather this effect only trended towards significance. The Buprenorphine patients also did not show significant improvement from Session 1 to Session 2 for erotic distractors at lag 2 and did not show improvement that trended towards significance for pill distractors at lag 2. The lower task accuracy for pill distractors at lag 2 may highlight the greater severity of withdrawal in these patients before receiving treatment; the lack of improvement for erotic and pill distractors at lag 2 may point towards a resistance towards the attention-modulating effects of treatment. These findings, again, were not significant when comparing the Buprenorphine patients to all patients. Research must be done with additional patients to reach conclusive results about these trends.

Implementing treatment appears to be the critical factor in decreasing the attentional capture of pill distractors in patients, because concluding treatment did not affect patient accuracy from Session 2 to Session 3. Patients did not show signs of significant improvement at any lag and distractor combination between the two sessions. Interestingly, in Session 3, patients only exhibited a significant attentional blink after pill distractors; the blink after erotic distractors trended towards significance. This is likely due to the smaller sample size of six patients when comparing Sessions 2 and 3, as opposed to the sample size of eight patients when comparing Sessions 1 and 2. It was hypothesized that, as they progressed through withdrawal treatment, patients would show a steady decline in the magnitude of their blink associated with pill distractors. These findings show that this is not the case; rather, patients experienced an initial

decrease in their attentional capture from pill stimuli when treatment began, and this decrease did not change significantly when treatment concluded.

It was also predicted that patients' subjective ratings of craving and pain would correlate with their withdrawal symptoms, but we were unable to test this hypothesis due to the inadequate timing of symptom assessment. We had planned on using a patient's COWS scores as an assessment of withdrawal symptoms but failed to realize until after data collection that COWS scores were not collected at the time of the three experimental sessions. COWS scores were not available for several patients at Session 1, because they had not yet been placed on the COWS protocol. COWS scores were not available for several patients at Session 3, because patients were no longer being assessed on the protocol after completion of Buprenorphine shots. For a few patients at Session 2, the last COWS score was not assessed close enough to the time of testing; it was usually several hours beforehand. This issue could be remedied by asking a nurse to assess each patient's score on COWS immediately before the patient completes the RSVP task and rates craving and pain levels at each session.

This study served as a pilot study in addressing the feasibility of performing cognitive science research in the addictions unit at the Vanderbilt Psychiatric Hospital. The main barrier we encountered was in patient recruitment. Out of all the patients seeking opioid withdrawal treatment at the hospital, we were only able to introduce the study to about half of them. We were not able to reach out to the other half in time. Due to severe withdrawal, these patients received Clonidine, and sometimes Buprenorphine, within a matter of hours upon admission to the hospital, which rendered them ineligible for the study since the first testing must be done prior to receiving treatment. Out of the patients who were asked to participate in the study, only about half of them agreed to. Many opted not to participate because they were not feeling well,

which was not unreasonable given their state of withdrawal. Out of the patients willing to

participate, about half were mentally unable to perform the RSVP task due to drowsiness from

withdrawal treatment for benzodiazepines. Indeed, we encountered a high comorbidity rate for

benzodiazepine and opioid addiction, which is evident in the majority of the patients we were

able to test. With this logic, we were ultimately only able to recruit a rough estimate of 12.5% of

the opioid-dependent patients receiving treatment at the psychiatric hospital.

Several measures were undertaken in an effort to improve patient recruitment. The most

effective measure was to obtain remote access to StarPanel, Vanderbilt's electronic medical

records system, which allowed for us to check daily for new patients at the addictions unit. The

other measures involved being notified when potential candidates were admitted. All patients

admitted to the psychiatric hospital must first go through an initial assessment by a team called

Respond. The staff at Respond was briefed on the criteria we looked for in patients and asked to

call us to notify us of candidates. The staff members on the unit, including nurses and mental

health specialists, were also asked to call us to notify us of candidates. However, both groups of

staff members only did so intermittently. It was not that they did not want to help, for many of

them were enthusiastic to; rather, they were just unable to add these responsibilities onto their

already demanding clinical duties. On top of difficulty with patient recruitment, computer issues

that interfered with the rapid graphic processing necessary for the RSVP task rendered a year's

worth of data unusable. Despite our best efforts, a small sample size remained an extreme

limitation in this study, and we conclude that it is not feasible to efficiently conduct behavioral

research at the addictions unit for this reason.

Our small sample size has two main implications for the interpretations of the results.

First, a small sample size is unfavorable in detecting between-group differences. We had

originally aimed to test a total of 30 patients; the greater statistical power with this larger sample would have helped to detect the extent to which patients exhibited a larger attentional blink after pill distractors in comparison to controls. Even with the smaller sample size, it is promising to already see that patients performed worse than controls for pill distractors at lag 2 in Session 1, which signals that patients exhibited a larger blink for pill stimuli before they received treatment. Second, a small sample size is not as disadvantageous in detecting within-group effects but may overlook effects that eventually become significant with a larger sample. It would be interesting to see how an increase in sample size would impact patient accuracy across the three experimental sessions. Patients already showed improvement that trended towards significance from Session 1 to Session 2 for pill distractors at lag 2; testing additional patients could very well push this trend into a level of statistical significance in a more adequately powered sample.

It is essential for future research to address the difficulty of patient recruitment for studies of cognitive science at the Vanderbilt Psychiatric Hospital. One way recruitment could substantially be improved is to integrate research protocols with standard protocol at the hospital. This has recently been proposed by Dr. David Zald and Dr. Peter Martin, who aim to introduce a research assessment program that requires the participation of all patients receiving treatment at the addictions unit. The program would provide a thorough and comprehensive assessment of behavioral and neurobiological dimensions that may help inform long-term course and treatment outcomes for patients who struggle with drug addiction. Along with personality questionnaires, neuroimaging scans, and genotyping measures, behavioral tasks such as the EBA task used in this study would be included in the assessment. With this task, researchers could continue to use the same pill distractors to investigate the additional attentional blink elicited by patients over controls.

Researchers could also pilot a different set of stimuli in hopes of finding stimuli more specific to opioid addiction. With the heightened ability to catch patients before they begin to receive treatment, it would be possible to study the effects of injection-related distractors on heroin and IV morphine users, who typically receive treatment very quickly after admission to the hospital. This subset of opioid-dependent patients would be an ideal population to study, as they would surely experience severe withdrawal symptoms, and healthy controls would not have as much previous exposure to injection-related stimuli. It would also be possible to recruit opioid-dependent patients exclusively and eliminate the confounding factor of benzodiazepine dependency. Regardless of which stimuli are ultimately tested, it would be highly informative to include a control group of people dependent on opioids who do not wish to seek treatment. This control group would help determine whether impaired task accuracy in patients is due to a general deficit in attentional control or due to the withdrawal symptoms themselves.

REFERENCES

Anderson, A. & Phelps, E. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*, *411*, 305-308.

Arnell, K., Killman, K., & Fijavz, D. (2007). Blinded by Emotion: Target Misses Follow Attention Capture by Arousing Distractors in RSVP. *Emotion*, *7*(3), 465-477.

Aston-Jones, G. & Cohen, J. (2005). An Integrative Theory of Locus Coeruleus-Norepinephrine Function: Adaptive Gain and Optimal Performance. *Annual Review of Neuroscience*, *28*, 403-450.

Blake, R., Yang, E., & Zald, D. (2007). Fearful Expressions Gain Preferential Access to Awareness During Continuous Flash Suppression. *Emotion*, *7*(4), 882-886.

Field, M., Munafo, M., & Franken, I. (2009). A Meta-Analytic Investigation of the Relationship Between Attentional Bias and Subjective Craving in Substance Abuse. *Psychological Bulletin*, *135*(4), 589-607.

Foote, S. & Morrison, J. (1987). Extrathalamic modulation of cortical function. *Annual Review of Neuroscience*, *10*, 67-95.

Franken, I., Booij, J., & van den Brink W. (2005). The role of dopamine in human addiction: From reward to motivated attention. *European Journal of Pharmacology*, *526*, 199-206.

Garavan, H. & Hester, R. (2007). The role of cognitive control in cocaine dependence. *Neuropsychology Review*, *17*(3), 337-345.

Grant, B. & Dawson, D. (1998). Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse*, *10*, 163–173.

Grant, B., Dawson, D., Stinson, F., Chou, S., Dufour, M., & Pickering, R. (2004). The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991– 1992 and 2001–2002. *Drug and Alcohol Dependence*, *74*, 223–234.

Koob, G. & Volkow, N. (2009). Neurocircuitry of Addiction. *Neuropsychopharmacology Reviews*, 1-22.

Lang, P., Bradley, M., & Cuthbert, B. (2001). *International Affective Picture System (IAPS): Instruction manual and affective ratings* (Tech. Rep. No. A-5). Gainesville: University of Florida, Center for Research in Psychophysiology.

McCusker, C. (2001). Cognitive biases and addiction: an evolution in theory and method. *Addiction*, *96*, 47-56.

Most, S., Chun, M., Widders, D., & Zald, D. (2005). Attentional rubbernecking: Cognitive control and personality in emotion-induced blindness. *Psychonomic Bulletin and Review, 12*(4), 654.

Most, S., Smith, S., Cooter, A., Levy, B., & Zald, D. (2007). The naked truth: Positive, arousing distractors impair rapid target perception. *Cognition & Emotion, 21*(5), 964-981.

Nieuwenhuis, S., Gilzenrat, M., Holmes, B., & Cohen, D. (2005). The role of the locus coeruleus in mediating the attentional blink: a neurocomputational theory. *Journal of Experimental Psychology: General*, *134*(3), 291-307.

Olatunji, B., Ciesielski, B., Armstrong, T., Zhao, M., & Zald, D. (2011). Making something out of nothing: neutral content modulates attention in generalized anxiety disorder. *Depression and Anxiety*, *28*, 427-434.

Olatunji, B., Ciesielski, B., & Zald, D. (2011). A selective impairment in attentional

    disengagement from erotica in obsessive-compulsive disorder. *Progress in Neuro-*

    Psychopharmacology & Biological Psychiatry, *35*, 1977-1982.

Piech, R., Pastorino, M., & Zald, D. (2010). All I saw was the cake. Hunger effects on attentional

    capture by visual food cues. *Appetite*, *54*, 579-582.

Piech, R., McHugo, M., Smith, S., Dukic, S., Van Der Meer, J., Abou-Khalil, B., Most, S., &

    Zald, D. Attentional capture by emotional stimuli is preserved in patients with amygdala

    lesions. *Neuropsychologia* (2011), doi:10.1016/j.neuropsychologia.2011.08.004.

Raymond, S., Shapiro, K., & Arnell, K. (1992). Temporary Suppression of Visual Processing in

    an RSVP Task: An Attentional Blink? *Journal of Experimental Psychology, 18*(3), 849-

    860.

Robinson, T. & Berridge K. (2000). The psychology and neurobiology of addiction: an

    incentive-sensitization view. *Addiction*, *95*(2), 91-117.

Rosenberg, H. (2009). Clinical and laboratory assessment of the subjective experience of drug

    craving. *Clinical Psychology Review*, *29*, 519-534.

Schatzberg, A. & Nemeroff, C. (2004). *Textbook of Psychopharmacology* (3rd ed.). Washington,

    DC: American Psychiatric Publishing, Inc.

Schwabe, L., Merz, C., Walter, B., Vaitl, D., Wolf, O., & Stark, R. (2011). Emotional

    modulation of the attentional blink: The neural structures involved in capturing and

    holding attention. *Neuropsychologia*, *49*(3), 416-425.

Smith, S., Most, S., Newsome, L., & Zald, D. (2006). An Emotion-Induced Attentional Blink

    Elicited by Aversively Conditioned Stimuli. *Emotion*, *6*(3), 523-527.

Weinshenker, D. & Schroeder, J. (2007). There and Back Again: A Tale of Norepinephrine and

Drug Addiction. *Neuropsychopharmacology*, *32*, 1433-1451.

Wesson, D. & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *Journal of

Psychoactive Drugs*, *35*(2), 253-259.

Table 1. Demographic information by diagnostic group.

	Patients	Controls
N	8	8
N female	5	5
Age *M*(*SD*)	32.38 (9.12)	31.62 (10.11)
Education in years *M*(*SD*)	11.38 (1.85)	13.00 (1.60)

Table 2. RSVP task means and standard deviations of accuracy percentage by distractor, lag, and session for patients and controls.

Lag	Patients									Controls								
	Erotic M (SD)			Neutral M (SD)			Pill M (SD)			Erotic M (SD)			Neutral M (SD)			Pill M (SD)		
	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
2	18.75 (14.58)	40.63 (17.61)	36.67 (19.66)	63.75 (19.96)	74.38 (9.80)	63.33 (10.33)	36.88 (16.02)	49.06 (14.94)	40.00 (10.95)	35.00 (18.52)	45.63 (30.41)	48.33 (27.14)	85.00 (13.09)	90.00 (11.02)	85.00 (13.78)	63.13 (5.94)	61.56 (12.46)	64.17 (11.14)
8	55.00 (20.70)	75.63 (18.21)	61.67 (23.17)	77.50 (7.07)	76.25 (20.31)	70.00 (29.67)	72.50 (15.81)	75.63 (10.50)	81.67 (21.37)	78.75 (14.58)	89.38 (14.25)	91.67 (11.69)	87.50 (18.32)	88.13 (11.93)	95.00 (8.37)	90.00 (11.95)	89.38 (11.78)	90.00 (12.65)

Table 3. Patient and control mean valence ratings for erotic and pill distractors.

	Patients	Controls
Erotic *M*(*SD*)	3.15 (1.12)	3.15 (.38)
Pill *M*(*SD*)	2.03 (.80)	2.54 (.45)

Figure Captions

Figure 1. The trial procedure for the emotional blink of attention paradigm. Note that the distractor consisted of three distinct

categories (erotic, neutral, and pill) presented at 200 and 800ms lags.

Figure 2. Task accuracy for patients at Lag 2 and Lag 8 by distractor and session.

Figure 3. Task accuracy for controls at Lag 2 and Lag 8 by distractor and session.

Figure 4. Task accuracy for Buprenorphine patients and all patients at Sessions 1 and 2 by distractor and lag.
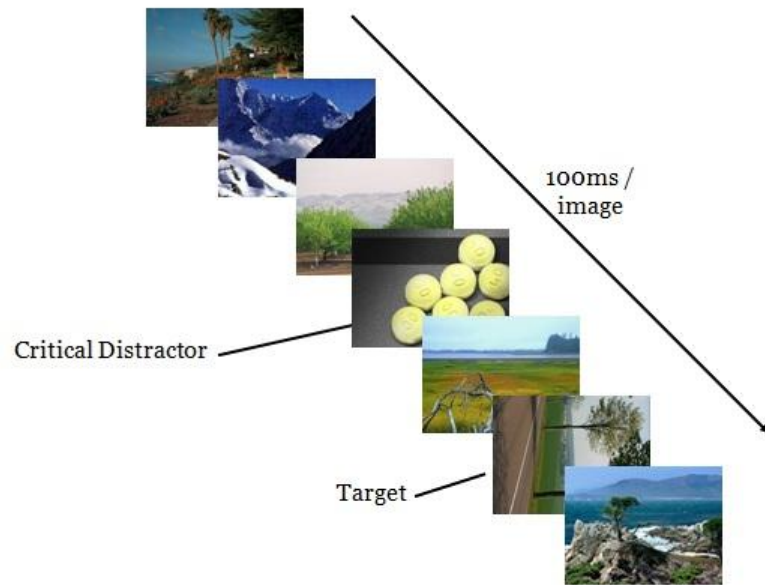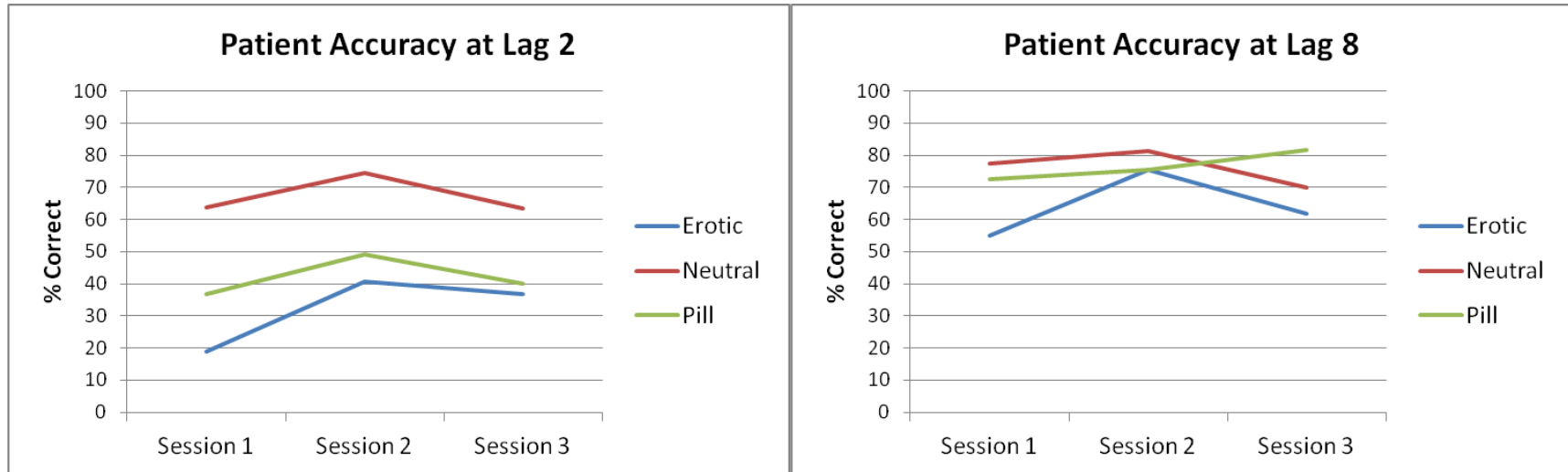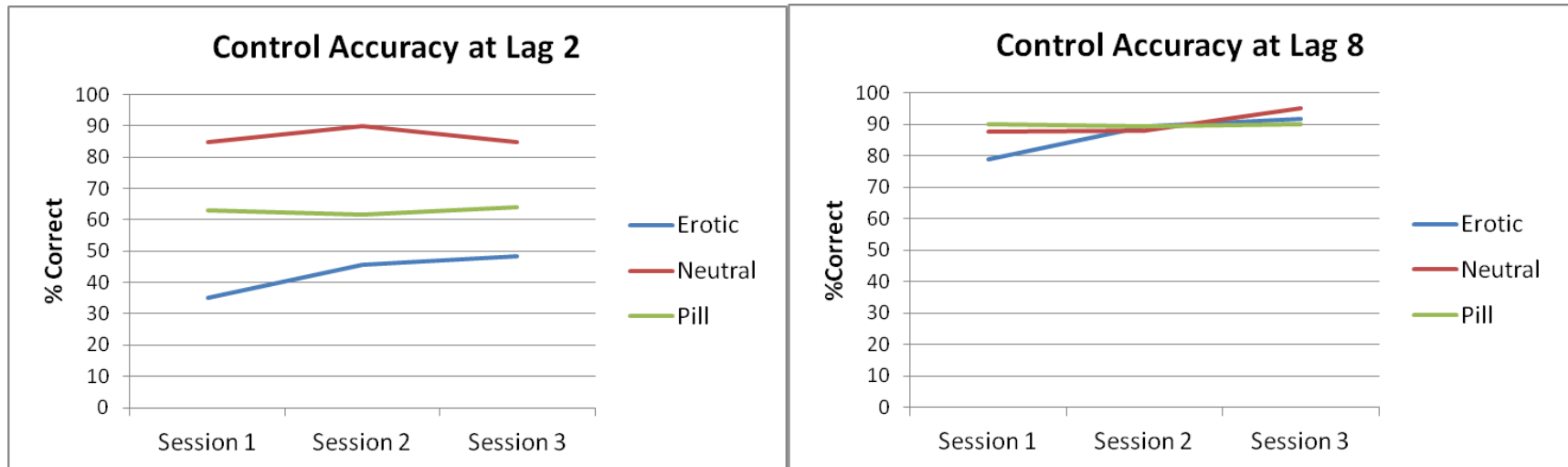
Figure 1.

100ms / image

Critical Distractor

Target

Figure 2.

Figure 3.

Figure 4.

Task Accuracy at Session 1 for Buprenorphine Patients and All Patients

Task Accuracy at Session 2 for Buprenorphine Patients and All Patients